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Faktory ovlivňující distribuci a eliminaci léčiv a jejich využití v personalizované farmakoterapii

Factors affecting drug distribution and elimination and their application in personalized pharmacotherapy

DIZERTAČNÍ PRÁCE

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Abstrakt

Cílem předkládané dizertační práce bylo studium faktorů ovlivňujících distribuci a eliminaci léčiv a možností využití těchto faktorů k individualizaci dávkování. Práce je složena ze tří tematických okruhů: odhad distribučního objemu a následně dávkování vybraných léčiv (vankomycin, amikacin, fenobarbital) pomocí deskriptorů velikosti těla; odhad clearance a následně dávkování vybraných léčiv (vankomycin, amikacin, fenobarbital, perindopril) pomocí ukazatelů funkčního stavu ledvin; a vliv lékových interakcí na distribuci a eliminaci fenobarbitalu. Dizertační práce shrnuje vlastní originální publikace z těchto oblastí.

Individuální farmakokinetické parametry byly spočítány pro každého pacienta na základě jeho demografické a klinické charakteristiky, údajů o dávkování a naměřených sérových hladin léčiva. Vztahy mezi distribučním objemem/clearance léčiv a deskriptory velikosti těla/ukazateli funkčního stavu ledvin byly prověřeny pomocí regresní analýzy.

Distribuční objem vankomycinu nejlépe predikovala celková tělesná hmotnost. Jako optimální se při podávání vankomycinu kontinuální infuzí jevila nasycovací dávka 10,7 mg/kg, která zkrátila dobu do dosažení terapeutických hladin ze 17 na 1 hod. Naproti tomu, distribuční objem amikacinu byl nejvíce asociován s povrchem těla, i když korigovaná tělesná hmotnost byla prakticky stejně vhodným prediktorem. Optimální jednotlivá dávka amikacinu byla 517 mg/m^2, respektive 14 mg/kg korigované tělesné hmotnosti. Distribuční objem fenobarbitalu u asfyktických novorozenců byl závislý na hmotnosti, povrchu těla a celkové tělesné délce. Optimální nasycovací dávka byla u této kohorty 15 mg/kg.

Clearance vankomycinu i amikacinu nejvíce odpovídala odhadu glomerulární filtrace pomocí CKD-EPI rovnice. Navrhli jsme nomogramy pro odhad optimální udržovací dávky vankomycinu podávaného kontinuální infuzí a pro odhad optimálního dávkovacího intervalu amikacinu pomocí rovnice CKD-EPI. Clearance fenobarbitalu podávaného asfyktickým novorozencům nebyla závislá na žádné ze sledovaných charakteristik. Proto se jako optimální jevila fixní udržovací dávka 9 mg/den, což odpovídá normalizované dávce 3 mg/kg/den. Clearance perindoprilátu byla lépe predikována cystatinem C než kreatininem. Rozdíly v predikční schopnosti jednotlivých rovnic využívajících cystatin C byly minimální.

Běžně používaná komedikace (vazoaktivní látky, furosemid, fenytoin, tramadol, sufentanyl, midazolam) neměla v reálných klinických podmínkách vliv na farmakokinetiku fenobarbitalu u asfyktických novorozenců.

Klíčová slova:
Personalizovaná farmakoterapie, terapeutické monitorování léčiv, optimalizace dávkování, farmakokinetika, distribuční objem, clearance, deskriptory tělesné hmotnosti, odhad glomerulární filtrace.

Abstract

The aim of this dissertation thesis was to study the factors affecting drug distribution and elimination and to use these factors to individualize dosing. The work consists of three thematic areas: estimation of the volume of distribution and subsequent dosing of selected drugs (vancomycin, amikacin, phenobarbital) using body size descriptors; estimation of clearance and subsequent dosing of selected drugs (vancomycin, amikacin, phenobarbital, perindopril) using renal function status markers; and the impact of drug interactions on the distribution and elimination of phenobarbital. The thesis summarizes original papers on these topics.

Individual pharmacokinetic parameters were calculated for each patient based on their demographic and clinical characteristics, dosing records and measured serum drug levels. The relationships between distribution volume/drug clearance and body size descriptors/renal functional status markers were examined by regression analysis.

Vancomycin volume of distribution was best predicted by the total body weight. Loading dose of 10.7 mg/kg of total body weight was optimal in patients taking continuous vancomycin and would lead to reducing of median time to reach target concentrations from 17 to 1 hour. On the contrary, amikacin volume of distribution was most associated with the body surface area, although the adjusted body weight was practically just as good predictor. The optimal single dose of amikacin was 517 mg/m^2 and 14 mg/kg of adjusted body weight, respectively. The distribution volume of phenobarbital in asphyxiated newborns was related with weight, body surface area and length. The optimal loading dose for this cohort was 15 mg/kg.

The clearance of both vancomycin and amikacin most closely corresponded to the estimation of glomerular filtration rate using the CKD-EPI equation. We designed nomograms for estimation of the optimal continuous vancomycin maintenance dose and for estimation of the optimal amikacin dosing interval using the CKD-EPI equation. Phenobarbital clearance did not relate with any of the examined characteristics in asphyxiated newborns. Therefore, a fixed maintenance dose of 9 mg/day appeared to be optimal, corresponding to a weight-normalized dose of 3 mg/kg/day. Perindoprilat clearance related better with cystatin C than with creatinine. Differences in prediction performance of the individual equations using cystatin C were minimal.

Frequently used co-medication (vasoactive drugs, furosemide, phenytoin, tramadol, sufentanyl, midazolam) did not affect phenobarbital pharmacokinetics in asphyxiated newborns in real clinical settings.

Key worlds:
Personalized pharmacotherapy, therapeutic drug monitoring, dosing optimization, pharmacokinetics, volume of distribution, clearance, body weight descriptors, glomerular filtration rate estimation.

Obsah

Seznam zkratek

ABW	Korigovaná tělesná hmotnost (adjusted body weight)
ALT	Alaninaminotransferáza
AST	Aspartátaminotransferáza
AUC_{24}	Plocha pod křivkou průběhu plazmatických koncentrací léčiva za 24 hodin
BMI	Index tělesné hmotnosti (Body-mass index)
BSA	Povrch těla (body surface area)
CAR	Konstitutivní androstanový receptor
CKD-EPI	Rovnice pro odhad glomerulární filtrace (Chronic Kidney Disease Epidemiology Collaboration)
CL	Clearance
CL-CR	Clearance kreatininu
CL-VAN	Clearance vankomycinu
C_{max}	Maximální plazmatická koncentrace
Css	Sérová koncentrace léku v ustáleném stavu
CYP	Cytochom P450
FD	Farmakodynamika
FK	Farmakokinetika
GF	Glomerulární filtrace
IBW	Ideální tělesná hmotnost (ideal body weight)
INR	Mezinárodní normalizovaný poměr (International Normalized Ratio)
JIP	Jednotka intenzivní péče
LBW	Tukuprostá tělesná hmotnost (lean body weight)
LD	Nasycovací dávka
MD	Udržovací dávka
MDRD	Rovnice pro odhad glomerulární filtrace (Modification of Diet in Renal Disease)
MIC	Minimální inhibiční koncentrace
PXR	Pregnanový xenobiotický receptor
SPC	Souhrn údajů o přípravku
TDM	Terapeutické monitorování hladin léčiv (therapeutic drug monitoring)
Vd	Distribuční objem

Seznam vlastních publikací

Sumární IF = 13,586

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Abstrakty, postery a přednášky na odborných konferencích:

1. POKORNÁ, P., **ŠÍMA, M.**, ČERNÁ, O., ALLEGAERT, K. & TIBBOEL, D. 2017. Kinetically guided dosing of vancomycin in critical ill neonates and young infants treated for sepsis. 16th European Society for Developmental Perinatal and Paediatric Pharmacology Congress.
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Poděkování

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1. Literární úvod

Většina léčiv je v současné době vyvíjena, schvalována a uváděna na trh na základě jejich účinku ve většině populace. Koncept jednotné dávky léčiva pro všechny pacienty se stejným onemocněním však vzhledem k interindividuální variabilitě farmakokinetiky a farmakodynamiky nemusí vést ke kýženým výsledkům. Zvláště u léčiv s úzkým terapeutickým indexem může stejná dávka vést u některých pacientů k projevům toxicity a u jiných může být neúčinná. Personalizovaná farmakoterapie je obor, zabývající se individualizací medikamentózní léčby pro konkrétního pacienta. Ve své práci jsem se zabýval faktory ovlivňujícími distribuci a eliminaci léčiv a možnostmi individualizace dávkování léčiv pomocí těchto faktorů. Konkrétně se jednalo o následující oblasti:

- odhad distribučního objemu a následně dávkování léčiv podle velikosti těla,
- odhad clearance a následně dávkování renálně vylučovaných léčiv podle funkčního stavu ledvin,
- vliv lékových interakcí na distribuci a eliminaci léčiva.

Jako modelová léčiva pro studium těchto vztahů byly vybrány především látky s úzkým terapeutickým indexem, u nichž může být individualizace dávkování klinicky významná:

- vankomycin,
- amikacin,
- fenobarbital,

a dále

- perindopril,

kde byl vztah mezi clearance perindoprilátu a funkčním stavem ledvin sledován z důvodu posouzení compliance pacientů k antihypertenzní medikaci.

1.1. Dávkování léčiv podle velikosti těla

Tento způsob individualizace dávkování je založen na předpokladu, že se farmakokinetické parametry léčiva mění proporcionálně s rostoucí velikostí těla. Základní antropometrické parametry, pomocí nichž můžeme definovat velikost těla, jsou hmotnost a výška. Z nich pak byly vyvinuty další – odvozené deskriptory, které, byť většinou neměly primárně sloužit pro účely individualizace dávkování, mohou lépe korelovat se skutečným distribučním objemem léků. V praxi se jedná nejčastěji o index tělesné hmotnosti (BMI),

povrch těla (BSA), ideální tělesnou hmotnost (IBW), korigovanou tělesnou hmotnost (ABW) a tukuprostou tělesnou hmotnost (LBW). Výpočty alternativních deskriptorů uvádí tabulka 1.

Tabulka 1: Výpočty alternativních deskriptorů velikosti těla. Převzato z (Pai, 2012).

Deskriptor	**Vzorec pro výpočet**
BMI (kg/m^2)	= hmotnost (kg) ÷ výška $(m)^2$
BSA (m^2)	= 0,007184 × hmotnost $(kg)^{0,425}$ × výška $(cm)^{0,725}$; Du Bois = √[(výška (cm) × hmotnost (kg) ÷ 3600]; Mosteller
IBW (kg)	= 49,9 + {0,89 × [výška (cm) – 152,4]}; muži = 45,4 + {0,89 × [výška (cm) – 152,4]}; ženy
ABW (kg)	= IBW + 0,4 × [hmotnost (kg) – IBW]
LBW (kg)	= [9270 × hmotnost (kg)] ÷ [6680 + 216 × BMI (kg/m^2)]; muži = [9270 × hmotnost (kg)] ÷ [8780 + 244 × BMI (kg/m^2)]; ženy

- **BMI**

Podklady k výpočtu BMI uveřejnil již v devatenáctém století Adolphe Quetelet, který se původně domníval, že objem těla závisí na hmotnosti a výšce umocněné na třetí. Tento koncept byl přezkoumán v roce 1972, kdy poměr mezi hmotností a výškou, výškou^2 a výškou^3 byl sledován ve vztahu k incidenci ischemické srdeční choroby u mužů (Keys et al., 1972). Největší asociace byla pozorována při použití výšky^2, a tak vznikla současná podoba vzorce. Dnes se BMI používá zejména jako indikátor nadváhy a různých stupňů obezity. BMI roste se vzrůstající hmotností, nerozlišuje však, zda je nadváha dána svalovou či tukovou tkání. Tento fakt limituje použití BMI jako univerzálního prediktoru dávkování, neboť složení svalové a tukové tkáně je rozdílné a distribuce do těchto kompartmentů bude záviset na fyzikálně-chemických vlastnostech léčiva – lipofilní léčiva se budou distribuovat přednostně do tukové tkáně, hydrofilní pak do tkáně svalové. Další slabinou je, že vzorec pro výpočet BMI byl vyvinut během experimentu na mužích – je tedy otázkou, nakolik přesné je použití tohoto vzorce u žen.

- **BSA**

Odhad BSA podle Du Boise byl vyvinut v roce 1916 během výzkumu respirace a metabolizmu u obézních pacientů (Green and Duffull, 2004). Du Bois vycházel

z předpokladu, že BSA závisí na tělesné hmotnosti, výšce a neznámé konstantě. Regresní analýzou porovnal kombinace těchto veličin se skutečnou, experimentálně změřenou BSA. Výsledkem byla rovnice uvedená v tabulce 1. V roce 1987 byla publikována Mostellerova adaptace vzorce pro výpočet BSA (Mosteller, 1987). I přes nepatrně menší přesnost odhadu skutečné BSA je tato rovnice pro svoji jednoduchost v klinické praxi rozšířenější. Běžně se využívá pro odhad dávek v pediatrii či onkologii (Kaestner and Sewell, 2007). Vzhledem k tomu, že BSA zahrnuje hmotnost i výšku pacienta, lze předpokládat, že by mohla být přesnějším prediktorem pro odhad dávky než např. samotná hmotnost. Na druhou stranu nebere v potaz pohlaví pacienta a podobně jako BMI nedokáže rozlišit tukovou a svalovou tkáň. Poslední zmiňovaná nevýhoda dává tušit, že odhad optimální dávky pomocí tohoto parametru bude méně přesný u pacientů s nadprůměrnými hodnotami BSA, zatímco u pacientů s průměrnou a podprůměrnou BSA bude predikce optimální dávky spolehlivější.

- **IBW**

V letech 1942 a 1943 uveřejnila Metropolitní životní pojišťovna v New Yorku data, která sledovala relaci mezi tělesnou velikostí a mortalitou zvlášť pro ženy a pro muže. Na základě těchto dat byl vyvinut parametr ideální hmotnosti. Koncept IBW byl několikrát aktualizován, v současnosti je nejčastěji zmiňována rovnice publikovaná Devinem v roce 1974 v kazuistice zabývající se toxicitou gentamicinu (Green and Duffull, 2004). Rovnice nesouvisí se skutečnou hmotností, pouze odhaduje ideální hmotnost ve vztahu k výšce a pohlaví. Možnost jejího využití pro odhad dávky je proto spekulativní. Nezdá se věrohodné, že by podávání jednotné dávky všem stejně vysokým pacientům bylo optimální, a to ani v případě hydrofilních léčiv, která se nedistribuují do tukové tkáně.

- **ABW**

ABW je první deskriptor tělesné hmotnosti, který byl primárně vyvinut pro účely optimalizace dávkování léčiv – konkrétně jako nástroj normalizace distribučního objemu aminoglykosidů (Bauer et al., 1983). ABW vychází z reálné tělesné hmotnosti a IBW, kdy určitá část nadbytku reálné hmotnosti nad IBW (vyjádřená tzv. korekčním faktorem) se přičte k IBW. Hodnota korekčního faktoru ve studii byla stanovena 0,45 pro gentamicin, 0,37 pro tobramycin a 0,42 pro amikacin. Pro jednoduchost se v praxi nejčastěji používá jednotná hodnota korekčního faktoru 0,4. ABW se jeví jako věrohodný parametr pro odhad optimální dávky, neboť ve svém výpočtu zahrnuje hmotnost, výšku i pohlaví. Na druhou

stranu používání jednotného korekčního faktoru může vést k nepřesnostem, uvážíme-li, že drobné rozdíly byly pozorovány i mezi jednotlivými zástupci aminoglykosidů, které mají velmi podobnou farmakokinetiku. ABW s korekčním faktorem 0,4 je tedy možné použít k optimalizaci dávkování léčiv s malým distribučním objemem, odpovídajícím přibližně extracelulární tekutině. Aplikace na širší paletu léčiv by vyžadovala validaci hodnoty korekčního faktoru.

- **LBW**

LBW je odvozen z tzv. frakce tukové hmoty. Tento termín byl zaveden během snah popsat vzrůstající prevalenci obezity ve Spojeném Království (Green and Duffull, 2004). LBW získáme po odečtení součinu frakce tukové hmoty a reálné hmotnosti od reálné hmotnosti. Ačkoliv původní účel tohoto deskriptoru byl popis trendu v morbiditě a mortalitě ve vztahu k velikosti těla, LBW se později uplatnila také při studiu farmakokinetických parametrů léčiv. V roce 2005 byla navržena nová podoba vzorce, vyvinutá na základě měření bioelektrické impedance u 373 pacientů s hmotností 40,7 – 216,5 kg, respektive s BMI 17,1 – 69,9 kg/m^2 (Janmahasatian et al., 2005). LBW v sobě zahrnuje pohlaví, hmotnost i výšku. Lze předpokládat, že – podobně jako ABW – bude dobrým prediktorem pro odhad optimální dávky u hydrofilních léčiv s omezenou distribucí do tukové tkáně.

Distribuci a eliminaci léčiv popisují dva primární farmakokinetické parametry – distribuční objem a clearance.

Distribuční objem je definován jako zdánlivý objem, ve kterém by se muselo veškeré množství léčiva přítomného v těle homogenně rozptýlit, aby v něm bylo dosaženo stejné koncentrace léčiva, jako je v plazmě. Distribuční objem souvisí se strukturálními aspekty těla, jeho hodnota však neumožňuje rozpoznat, zda je léčivo v těle distribuováno rovnoměrně, či zda se kumuluje v nějakém kompartmentu. Green et al. ve své přehledové práci uvádí, že jako nejlepší deskriptor pro odhad distribučního objemu se obecně jeví reálná hmotnost (Green and Duffull, 2004) – největší část (40 %) studií, které porovnávaly asociaci reálné tělesné hmotnosti a dalších deskriptorů s distribučním objemem léčiv uvádí jako nejlepší prediktor reálnou hmotnost. Je ale třeba podotknout, že tento výstup je zobecněním vztahů mezi deskriptory tělesné velikosti a distribučním objemem napříč nejrůznějšími léčivy. Reálná hmotnost bude ve skutečnosti vhodným prediktorem u léčiv

lipofilních a amfifilních, zatímco distribuční objem silně hydrofilních léčiv bude lépe korelovat s deskriptory jako je ABW či LBW.

Clearance je definována jako objem plazmy, která se od daného léčiva zcela očistí za jednotku času, a jako taková souvisí s funkční kapacitou a perfuzí eliminačních orgánů. Nejvíce studií (35 %), které porovnávaly asociaci LBW a dalších deskriptorů s clearance léčiv uvádí jako nejlepší prediktor LBW (Green and Duffull, 2004). Tento závěr se zdá být věrohodný, vycházíme-li z předpokladu, že tuková tkáň nemá vlastní eliminační aktivitu. Na rozdíl od distribučního objemu, clearance léčiv obvykle lépe vystihují jiné kovariáty, než deskriptory tělesné velikosti – např. markery funkčního stavu ledvin u léčiv s primárně renální exkrecí.

1.2. Dávkování renálně eliminovaných léčiv podle funkčního stavu ledvin

Tento princip individualizace dávkování vychází z korelace mezi clearance léčiva a funkčním stavem ledvin. Tento vztah se týká samozřejmě pouze léčiv vylučovaných primárně ledvinami. Dávky léčiv s významnou hepatální exkrecí či léčiv extenzivně metabolizovaných se obvykle pomocí tohoto principu neupravují. K základním metodám vyšetření funkčního stavu ledvin patří vyšetření glomerulární filtrace (GF) (Levin and Stevens, 2014). GF je definována jako objem plazy, který je ledvinami kompletně očištěn od konkrétní látky za jednotku času. V současné době se GF měří pomocí clearance endogenního nebo exogenního markeru filtrace. Metody měření GF jsou ale dosti složité, limitujícím faktorem je často správný sběr moči. Proto je GF v klinické praxi běžně odhadována ze sérové koncentrace kreatininu, popř. cystatinu C. Mezi nejčastěji používané výpočtové metody odhadu GF na podkladu stanovení sérového kreatininu patří rovnice Cockcroft-Gault (Cockcroft and Gault, 1976), MDRD (Modification of Diet in Renal Disease) (Levey et al., 1999) a CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) (Levey et al., 2009). U dětí a mladistvých je doporučeno používat rovnici dle Schwartze (Schwartz et al., 1987). Ze sérového cystatinu C lze pak GF odhadnout CKD-EPI variantou pro cystatin C, kombinovanou CKD-EPI rovnicí pro kreatinin i cystatin C (Inker et al., 2012), případně použitím jednoduššího výpočtu, např. dle Hoeka (Hoek et al., 2003). Všechny uvedené rovnice shrnuje tabulka 2.

Tabulka 2: Rovnice pro odhad GF. Použité zkratky: Skr sérový kreatinin (μmol/L), Scyst sérový cystatin C (mg/L).

Rovnice	**Vzorec pro výpočet**
Cockcroft-Gault (mL/s)	= {[(140 – věk) × hmotnost (kg)] ÷ (48,8 × Skr)} × 0,85 (ženy)
MDRD (mL/s/1,73 m^2)	= 515,3832 × $Skr^{-1,154}$ × $věk^{-0,203}$ × 0,742 (ženy) × 1,21 (černá populace)
CKD-EPI (kreatinin) (mL/s/1,73 m^2)	= 2,4 × $(Skr ÷ 61,9)^{-0,329}$ × $0,993^{věk}$ × 1,159 (černá populace); ženy se Skr ≤ 62 μmol/L = 2,4 × $(Skr ÷ 61,9)^{-1,209}$ × $0,993^{věk}$ × 1,159 (černá populace); ženy se Skr > 62 μmol/L = 2,35 × $(Skr ÷ 79,6)^{-0,411}$ × $0,993^{věk}$ × 1,159 (černá populace); muži se Skr ≤ 80 μmol/L = 2,35 × $(Skr ÷ 79,6)^{-1,209}$ × $0,993^{věk}$ × 1,159 (černá populace); muži se Skr > 80 μmol/L
Schwartz (mL/s/1,73 m^2)	= F × výška (cm) ÷ Skr F = 0,600; vždy při stanovení Skr enzymatickou metodou F = 0,487; stanovení Skr Jaffé metodou, nedonošené děti do 1 roku F = 0,663; stanovení Skr Jaffé metodou, donošené děti do 1 roku F = 0,810; stanovení Skr Jaffé metodou, dívky od 1 roku do 18 let F = 0,810; stanovení Skr Jaffé metodou, chlapci od 1 roku do 12 let F = 0,959; stanovení Skr Jaffé metodou, chlapci od 12 do 18 let
CKD-EPI (cystatin C) (mL/s/1,73 m^2)	= 2,217 × $(Scyst ÷ 0,8)^{-0,499}$ × $0,996^{věk}$ × 0,932 (ženy); Scyst ≤ 0,8 mg/L = 2,217 × $(Scyst ÷ 0,8)^{-1,328}$ × $0,996^{věk}$ × 0,932 (ženy); Scyst > 0,8 mg/L
CKD-EPI (kreatinin + cystatin C) (mL/s/1,73 m^2)	= 2,17 × $(Skr ÷ 61,9)^{-0,248}$ × $(Scyst ÷ 0,8)^{-0,375}$ × $0,995^{věk}$ × 1,08 (černá populace); ženy se Skr ≤ 62 μmol/L a se Scyst ≤ 0,8 mg/L = 2,17 × $(Skr ÷ 61,9)^{-0,248}$ × $(Scyst ÷ 0,8)^{-0,711}$ × $0,995^{věk}$ × 1,08 (černá populace); ženy se Skr ≤ 62 μmol/L a se Scyst > 0,8 mg/L = 2,17 × $(Skr ÷ 61,9)^{-0,601}$ × $(Scyst ÷ 0,8)^{-0,375}$ × $0,995^{věk}$ × 1,08 (černá populace); ženy se Skr > 62 μmol/L a se Scyst ≤ 0,8 mg/L = 2,17 × $(Skr ÷ 61,9)^{-0,601}$ × $(Scyst ÷ 0,8)^{-0,711}$ × $0,995^{věk}$ × 1,08 (černá populace); ženy se Skr > 62 μmol/L a se Scyst > 0,8 mg/L

	= 2,25 × (Skr ÷ 79,6)$^{-0,207}$ × (Scyst ÷ 0,8)$^{-0,375}$ × 0,995^{věk} × 1,08 (černá populace); muži se Skr ≤ 80 μmol/L a se Scyst ≤ 0,8 mg/L = 2,25 × (Skr ÷ 79,6)$^{-0,207}$ × (Scyst ÷ 0,8)$^{-0,711}$ × 0,995^{věk} × 1,08 (černá populace); muži se Skr > 80 μmol/L a se Scyst ≤ 0,8 mg/L = 2,25 × (Skr ÷ 79,6)$^{-0,601}$ × (Scyst ÷ 0,8)$^{-0,375}$ × 0,995^{věk} × 1,08 (černá populace); muži se Skr > 80 μmol/L a se Scyst ≤ 0,8 mg/L = 2,25 × (Skr ÷ 79,6)$^{-0,601}$ × (Scyst ÷ 0,8)$^{-0,711}$ × 0,995^{věk} × 1,08 (černá populace); muži se Skr > 80 μmol/L a se Scyst > 0,8 mg/L
Hoek (mL/s/1,73 m^2)	= 80,35 ÷ Scyst – 4,32

Posouzení GF na podkladě sérové koncentrace kreatininu vychází ze zjištění, že hladina kreatininu v séru exponenciálně vzrůstá s klesající GF (Stevens et al., 2006). Vzhledem k exponenciálnímu vztahu je vzestup sérového kreatininu v počátečních fázích renálního selhávání poměrně malý, počáteční stádium renální insuficience tedy nemusí být na podkladě pouhého sledování hladiny kreatininu rozpoznáno. Samotná hodnota sérového kreatininu je nepřesně prediktivní – je ovlivněna především množstvím svalové hmoty. Výpočtové vzorce se snaží tento vliv korigovat pomocí proměnných jako je věk, pohlaví či rasa.

- **Rovnice Cockcroft-Gault**

Tato rovnice pro odhad clearance kreatininu byla publikována v roce 1976 (Cockcroft and Gault, 1976) a na dlouhou dobu se stala nejrozšířenějším způsobem odhadu GF. Díky tomu je také hojně využívána v různých doporučeních na úpravu dávek léčiv podle funkčního stavu ledvin. Vzhledem k tomu, že tato rovnice odhaduje renální clearance kreatininu (která v sobě zahrnuje i tubulární sekreci), dochází k systematickému nadhodnocování GF (Stevens et al., 2006). Navíc ve svém výpočtu zahrnuje tělesnou hmotnost, takže dochází k dalšímu nadhodnocení GF u obézních osob nebo u pacientů s retencí tekutin. Výpočet Cockcroft-Gault byl také vyvinut s použitím nestandardizované metody stanovení sérového kreatininu. Dle současných doporučení by se proto tento odhad neměl v klinické praxi dále využívat. Data a zkušenosti s dávkováním léčiv podle novějších rovnic jsou však zatím omezené a je otázka nakolik lze dávkovací schémata podle Cockcroft-Gault rovnice extrapolovat.

- **Rovnice MDRD**

V roce 1999 vyšla velká multicentrická studie o vlivu nízkoproteinové diety na rychlost progrese chronických renálních onemocnění (Levey et al., 1999). Na podkladě této studie byl odvozen vzorec MDRD, který byl o pár let později ještě upraven pro použití standardizované metody stanovení kreatininu (Levey et al., 2007). Vzhledem k tomu, že MDRD studie zahrnovala pouze pacienty s chronickým onemocněním ledvin, není validována pro použití u pacientů s normální nebo mírně sníženou funkcí ledvin. Proto byla později stejnými autory vyvinuta nová rovnice (CKD-EPI), která je použitelná i pro zdravou populaci.

- **Rovnice CKD-EPI**

Tato rovnice byla navržena v roce 2009 (Levey et al., 2009). CKD-EPI poskytuje výsledky nejbližší reálné GF. Proto je v současnosti doporučována jako nejvhodnější metoda odhadu GF na podkladě sérové hladiny kreatininu. Dodatečně pak byla vyvinuta CKD-EPI rovnice pro odhad GF z cystatinu C, a také kombinovaná CKD-EPI rovnice využívající jak kreatinin, tak cystatin C (Inker et al., 2012).

Kreatinin vzniká ve svalech ireverzibilní neenzymovou dehydratací a následnou spontánní cyklizací z kreatinu a z kreatinfosfátu. Následně pak přechází do krevního oběhu. Jeho produkce je závislá na množství svalové hmoty, proto je relativně stabilní. Je ale závislá na věku, pohlaví a rase (Laterza et al., 2002). Produkci kreatininu rovněž ovlivňuje intenzita tělesné aktivity a příjem potravy bohaté na aminokyseliny. Kreatinin se neváže na plazmatické bílkoviny a je volně filtrován v glomerulech. Na jeho eliminaci se ale také minoritně podílí tubulární sekrece. U zdravých jedinců je tato frakce zanedbatelná, nabývá však na významu u pacientů se střední a těžkou renální insuficiencí, kdy významně klesá GF (Laterza et al., 2002). Z uvedeného vyplývá, že odhad GF pomocí sérového kreatininu, může v určitých klinických situacích (ztráta svalové hmoty, těžší renální insuficience, atd.) vést k nadhodnocení.

Cystatin C je protein patřící do rodiny inhibitorů cysteinových proteáz. Je produkován všemi jadernými buňkami a vylučován glomerulární filtrací. Na rozdíl od kreatininu nepodléhá tubulární sekreci, ale je reabsorbován buňkami proximálních tubulů. Zde je však kompletně katabolizován, takže nepřechází zpět do krevního oběhu (Laterza et al., 2002). Díky tomu clearance cystatinu C plně odpovídá GF. Řada prací nasvědčuje tomu, že sérové hladiny cystatinu C se zvyšují při malém poklesu GF dříve než hladiny

kreatininu (Čabarkapa, 2015). Proto je cystatin C považován za přesnější marker pro odhad GF. Nicméně, i výpočet GF pomocí hladiny cystatinu C může být zkreslen – např. u pacientů s některými maligními onemocněními, nekompenzovanou hypo/hypertyreózou, či při podávání glukokortikoidů (Čabarkapa, 2015). Další nevýhodou cystatinu C je vyšší cena jeho stanovení.

1.3. Vankomycin

Vancomycin je glykopeptidové antibiotikum, patřící mezi léky volby v terapii závažných nozokomiálních infekcí vyvolaných gram-pozitivními bakteriemi včetně meticilin-rezistentních kmenů *Staphylococcus aureus* (Rybak et al., 2009a). Vykazuje na koncentraci nezávislou baktericidní aktivitu, přičemž poměr plochy pod křivkou průběhu plazmatických koncentrací za 24 hodin (AUC_{24}) nad minimální inhibiční koncentrací (MIC) je považován za farmakokineticko-farmakodynamický (FK/FD) parametr, který nejlépe predikuje úspěšnost léčby (Moise-Broder et al., 2004). Jako cílová hodnota se považuje $AUC_{24}/MIC \geq 400$ (Rybak et al., 2009b). Metaanalýza dat publikovaných v devíti kohortových studiích potvrdila, že dosažení tohoto FK/FD cíle vede k signifikantnímu snížení rizika selhání terapie a snížení mortality (Men et al., 2016).

Vankomycin patří mezi léky s úzkým terapeutickým indexem – nejčastěji bývá zmiňována jeho nefrotoxicita a ototoxicita (Rybak et al., 2009a, Tesfaye et al., 2012). Existuje poměrně málo dat dokládajících přímý vztah mezi konkrétními hladinami vankomycinu a toxicitou. Ta bývá dávána spíše do souvislosti s délkou terapie, nebo s konkomitantním podáváním jiných nefrotoxických/ototoxických léčiv (Rybak et al., 2009a). Nicméně, několik menších studií dokumentuje souvislost mezi toxicitou a vyššími hladinami/dávkami vankomycinu (Lodise et al., 2008, Farber and Moellering, 1983, Jeffres et al., 2007, Spapen et al., 2011).

V klinické praxi se využívají dvě strategie podávání vankomycinu – kontinuální infuze a intermitentní infuze (Martínková, 2015). Teoretická výhoda kontinuálního podávání vychází z předpokladu, že trvalé udržování hladin vankomycinu nad MIC, bez většího kolísání, povede k větší účinnosti a menší toxicitě. Přidanou hodnotou pak je finanční úspora. Existuje dostatečné množství dat dokládajících, že kontinuální podávání vankomycinu je u dospělých pacientů plnohodnotnou alternativou intermitentní aplikace

(Waineo et al., 2015). Nicméně, nadřazenost ve smyslu vyšší účinnosti nebo nižší toxicity se neprokázala (Man et al., 2010).

Zatím co při intermitentním podávání se doporučuje udržovat údolní koncentrace mezi 10 a 20 mg/L (15-20 mg/L v případě závažných infekcí) (Rybak et al., 2009a), pro kontinuální podávání nebyl dosud ustanoven jednotný konsenzus stran terapeutického rozmezí. Některé studie navrhují rozmezí 15-25 mg/L (Saugel et al., 2013, Spadaro et al., 2015), jiné 20-25 mg/L (Wysocki et al., 2001), nebo 20-30 mg/L (Cristallini et al., 2016). Vezmeme-li v úvahu, že hodnota AUC_{24} by měla být minimálně 400 mg.h/L (při MIC = 1 mg/L) (Moise-Broder et al., 2004, Holmes et al., 2013) a maximálně cca 700 mg.h/L (při překročení se předpokládá vyšší riziko nefrotoxicity) (Neely et al., 2014), cílové terapeutické koncentrace mezi 15 a 30 mg/L lze považovat za uspokojivé.

Při výskytu infekce u kriticky nemocných pacientů je třeba bezprostředně zahájit antibiotickou terapii (Leekha et al., 2011, Vincent et al., 2016). Při kontinuálním podání vankomycinu bez aplikace nasycovací dávky (LD) stoupají sérové koncentrace postupně, dokud nedojde k navození ustáleného stavu, kdy se vyrovná rychlost přívodu léčiva s rychlostí jeho eliminace. To znamená, že terapeutických hladin je dosaženo až s určitým zpožděním, které ale může negativně ovlivnit úspěch léčby (Lodise et al., 2003). Aby bylo dosaženo terapeutických hladin co nejdříve, je třeba podat LD (Wang et al., 2001, Mohammedi et al., 2006, Truong et al., 2012). Studie uvádí aplikaci LD 15-20 mg/kg (Wysocki et al., 2001, Vuagnat et al., 2004, Hutschala et al., 2009). Bohužel, v klinických podmínkách není aplikace LD běžnou praxí a ani současně platný souhrn údajů o přípravku (SPC) nedoporučuje tuto dávkovací strategii.

LD může být spočítána z Vd (Wada et al., 1998). Vzhledem k vysoké variabilitě Vd u pacientů na jednotkách intenzivní péče (JIP), LD odhadnuté na základě populačních hodnot Vd nemusí být přesné (Boucher et al., 2006). Vzhledem k tomu, že Vd souvisí se strukturálními aspekty těla, bývá LD nejčastěji individualizována pomocí hmotnosti (Pan et al., 2016). Mohammedi et al. uvádí, že aplikace normalizované LD 15 mg/kg je přesnější než podávání fixní LD 500 mg (Mohammedi et al., 2006).

Tak jako LD může být odhadnuta pomocí Vd, tak udržovací dávky (MD) léku můžeme vypočítat z jeho CL (Janků, 1983). A podobně jako Vd, vykazuje také CL u JIP pacientů značnou inter a intraindividuální variabilitu (Boucher et al., 2006).

Více než 80 % podané dávky vankomycinu je během 24 hodin vyloučeno glomerulární filtrací v nezměněné formě (Matzke et al., 1986). Studie ukazují lineární

vztah mezi CL vankomycinu a CL kreatininu (Matzke et al., 1984, Llopis-Salvia and Jiménez-Torres, 2006, Pea et al., 2009, Kees et al., 2010).

V literatuře můžeme nalézt několik návrhů dávkování kontinuálního vankomycinu pomocí nomogramů. Tyto nomogramy predikují MD z CL kreatininu odhadnuté rovnicí Cockcroft-Gault (Pea et al., 2009, Jeurissen et al., 2011), MDRD (van Maarseveen et al., 2014), nebo na základě měřené CL kreatininu (Baptista et al., 2014). Dosud nebyl navržen žádný nomogram vycházející z CKD-EPI rovnice.

1.4. Amikacin

Amikacin je širokospektré aminoglykosidové antibiotikum, široce využívané především v terapii gram-negativních infekcí u pacientů na JIP.

Aminoglykosidy vykazují účinek závislý na koncentraci, kdy poměr mezi maximální dosaženou koncentrací (C_{max}) a MIC je považován za FK/FD parametr určující úspěšnost léčby. Za cílovou hodnotu se považuje $C_{max}/MIC \geq 8$ (Moore et al., 1987). Aminoglykosidy vykazují významný post-antibiotický efekt, rovněž v závislosti na koncentraci. Délka trvání tohoto efektu se u amikacinu při dodržování terapeutických hladin uvádí přibližně 4 – 6 hodin (Isaksson et al., 1990).

Aminoglykosidy patří mezi léky s úzkým terapeutickým indexem. Nefrotoxicita a ototoxicita jsou nejčastěji zmiňované nežádoucí účinky. Nefrotoxicita bývá obvykle reverzibilní a je způsobena kumulací léku v buňkách proximálních tubulů, zatímco ototoxicita může být ireverzibilní a zdá se, že souvisí s celkovou kumulativní dávkou (Beaubien et al., 1989).

Existují dvě strategie dávkování aminoglykosidů. Konvenční dávkování spočívá v podávání dávek normalizovaných na tělesnou hmotnost 2 – 3 x denně, zatímco moderní, tzv. „once-daily“ strategie je založena na podání celé denní dávky (rovněž normalizované na hmotnost pacienta) naráz s prodlouženým intervalem (24 hodin u pacientů s normální funkcí ledvin). Druhá jmenovaná strategie je v současnosti jednoznačně preferována vzhledem ke stejné (teoreticky možná i vyšší) účinnosti, ale především nižší toxicitě (Nicolau et al., 1995).

Z důvodu jištění účinnosti a prevence toxicity je u aminoglykosidů doporučeno rutinní terapeutické monitorování hladin (TDM) (Begg et al., 2001, Germovsek et al., 2016). Úprava dávky na podkladě TDM je ale možná až po zahájení terapie. Startovací

dávka a dávkovací interval musí tedy být vypočítány pomocí Vd, respektive CL (Wada et al., 1998, Janků, 1983). Jak již bylo uvedeno v předešlé kapitole, patofyziologické změny u kriticky nemocných pacientů mohou vést k alteraci farmakokinetiky léčiv (Wong et al., 2014). Zejména u léčiv s úzkým terapeutickým indexem (jako je amikacin) je proto vhodné nevycházet pouze z populačních dat, ale individualizovat FK parametry pomocí vhodných kovariát.

Amikacin je hydrofilní látka, která se distribuuje do extracelulární tekutiny, čemuž odpovídá jeho Vd přibližně 0.25 L/kg (Dager, 1994). SPC doporučuje denní dávku amikacinu 15 mg/kg hmotnosti pro pacienty s normální funkcí ledvin. U obézních pacientů pak je pak doporučeno vypočítat denní dávku pomocí ABW. Denní dávky uváděné ve studiích se obvykle pohybují od 11 do 30 mg/kg (Freeman et al., 1997).

Vzhledem k tomu, že aminoglykosidy jsou v nezměněné formě vylučovány glomerulární filtrací v ledvinách, je nutná úprava jejich dávkování u pacientů se sníženou funkcí ledvin. Některé studie uvádí redukci dávky odpovídající stupni postižení ledvin, jiné navrhují dávku ponechat a prodlužovat dávkovací interval. Pokud chceme následovat principy „once-daily“ podání aminoglykosidů, ponechání dávky a prodlužování intervalu se jeví jako logičtější postup (Freeman et al., 1997). Mnoho doporučení pro dávkování aminoglykosidů odvozuje délku intervalu u pacientů renální insuficiencí od hodnoty CL kreatininu odhadnuté pomocí rovnice Cockcroft-Gault (Lim et al., 2015). Je ale jen velmi málo dat o možnosti využití novějších rovnic (MDRD, CKD-EPI). Některé studie uvádí lepší predikci dávkování při použití Cockcroft-Gault oproti MDRD (Charhon et al., 2012, Ryzner, 2010). Pai et al. popisují, že CKD-EPI nejlépe predikuje CL aminoglykosidů (Pai et al., 2011), nicméně tato studie zahrnuje pouze pacienty léčené jinými aminoglykosidy (gentamicin, tobramycin). Pouze jedna studie zmiňuje CKD-EPI rovnici jako nejlepší metodu odhadu CL amikacinu (Lim et al., 2015).

1.5. Fenobarbital

Fenobarbital je stále lékem první volby pro kontrolu a terapii křečí u asfyktických novorozenců s hypoxicko-ischemickou encefalopatií (Carmo and Barr, 2005).

Neexistuje jednotný konsenzus k terapeutickému rozmezí. Jalling uvádí, že křeče ustávají přibližně při hladinách 12 – 30 mg/L (Jalling, 1975). Některé studie cílí na rozmezí 10 – 30 mg/L (Touw et al., 2000, Turhan et al., 2010), jiné na 15 – 40 mg/L

(Nahata et al., 1988, Gherpelli et al., 1993, Filippi et al., 2011, Oztekin et al., 2013). Na základě těchto dat lze tedy hodnoty sérových koncentrací fenobarbitalu mezi 10 a 40 mg/L pokládat za uspokojivé. Při hladinách nad 40 mg/L se častěji vyskytují nežádoucí reakce jako např. sedace, letartgie, nebo zvýšená dráždivost. Pokud koncentrace fenobarbitalu překročí 60 mg/L, může dojít k apnoím až zástavě dechu.

Ve snaze maximalizovat účinnost a minimalizovat toxicitu je v průběhu terapie doporučeno TDM (Koren, 1997). Iniciální dávka však musí být, tak jako u výše zmiňovaných antibiotik, vypočtena z FK parametrů – LD z Vd a MD z CL (Anderson and Holford, 2013). Fenobarbital vykazuje značnou interindividuální variabilitu FK parametrů. Kromě toho má na farmakokinetiku zásadní vliv také maturace organizmu a postnatální změny ve složení těla (Alcorn and McNamara, 2003). Proto opět preferujeme individualizaci FK parametrů pomocí dostupných kovariát před použitím populačních dat.

Nejčastěji uváděné kovariáty farmakokinetiky fenobarbitalu jsou hmotnost a gestační stáří (případně postnatální věk) (Touw et al., 2000, Yukawa et al., 2011, Shellhaas et al., 2013). Touw et al. popsali také vztah mezi výškou či BSA a FK parametry fenobarbitalu (Touw et al., 2000). Další studie však přinášejí nekonzistentní závěry, což komplikuje hledání ideálních proměnných umožňujících individualizaci dávkování. Pitlick et al. pozorovali nárůst CL během prvního měsíce po narození, zatímco korelace s Vd se neprokázala (Pitlick et al., 1978). Grasela et al. uvádí, že Vd ani CL nejsou ovlivněny gestačním stářím (Grasela and Donn, 1985). Gilman et al. nenalezli žádný vztah mezi eliminačním poločasem léku a gestačním/postnatálním věkem (Gilman et al., 1983). Byl také zkoumán vliv asfyxie. Zatímco Gal et al. popisují nižší CL u asfyktických novorozenců (Gal et al., 1984, Gal et al., 1982), Grasela et al. nezaznamenali žádný vliv na CL, ale uvádí zvýšení Vd v případě asfyxie (Grasela and Donn, 1985).

V klinické praxi se fenobarbital obvykle dávkuje podle tělesné hmotnosti: zahajuje se intravenózním podáním LD 15 – 20 mg/kg (v případě přetrvávajících křečí je možno sekvenčně podávat další bolusy 5 – 10 mg/kg až do dosažení koncentrace 40 mg/L) (Gilman et al., 1989), poté se podávají MD 3 – 4 mg/kg/den (Fischer et al., 1981). V průběhu terapie se dávky upravují na základě dosažených koncentrací a podle klinické odezvy.

Přibližně 25 % z dávky fenobarbitalu je vyloučeno v nezměněné formě. Majoritní část se metabolizuje oxidací enzymem 2C9 cytochromu P450. V menší míře se pak na metabolické přeměně fenobarbitalu podílí CYP2C19, CYP2E1 a N-glukosidace (Kwan and Brodie, 2004).

V neonatologické intenzivní péči se frekventovaně používá několik léků/lékových skupin, které mohou ovlivnit farmakokinetiku fenobarbitalu. Noradrenalin působí vazokonstrikčně a může tak snížit průtok krve ledvinami, zatímco dopamin v nízkých dávkách působí opačně (Richer et al., 1996). Vazoaktivní medikace by tedy mohla cestou změn v renální perfuzi alterovat clearance fenobarbitalu (Schetz, 2002). Silný diuretický účinek furosemidu ovlivňuje obsah vody v různých kompartmentech (O'Donovan and Bell, 1989), což by se mohlo odrazit v distribuci fenobarbitalu. A konečně současné podávání fenytoinu může alterovat hepatální metabolizmus fenobarbitalu – a to jak ve smyslu inhibice, tak indukce – v závislosti na délce konkomitantní terapie (Encinas et al., 1992). Po zahájení souběžné terapie s fenytoinem může dojít k nárůstu plazmatických hladin fenobarbitalu v důsledku kompetice o stejnou metabolickou cestu (CYP2C9, CYP2C19) (Patsalos et al., 2008). Při delším podávání obou léčiv mohou naopak plazmatické koncentrace fenobarbitalu klesat následkem fenytoinem navozené indukce enzymů cytochromu P450 cestou aktivace nukleárních receptorů (PXR, CAR) (Brodie et al., 2013).

1.6. Perindopril

Hypertenze patří celosvětově mezi nejvýznamnější příčiny morbidity a mortality. Je hlavním rizikovým faktorem srdečního selhání, ischemické choroby srdeční, cévní mozkové příhody či renální insuficience. Inhibitory angiotenzin konvertujícího enzymu (k nimž perindopril náleží) významně snižují kardiovaskulární rizika hypertoniků, proto podle současných doporučení patří mezi antihypertenziva první volby (Sindone et al., 2016).

Rozsáhlá meta-analýza ukázala, že vysoké procento (45,2%) hypertoniků je non-compliantní ke své medikaci (Abegaz et al., 2017). Jako možné vysvětlení se nabízí fakt, že hypertenze bývá dlouho asymptomatická, zatímco antihypertenziva mohou vykazovat nežádoucí účinky – byť obvykle nezávažné. Je zdokumentováno, že míra non-compliance je přímo úměrná komplexnosti léčby (tj. počtu užívaných léků, frekvenci jejich podávání atd.) (Borghi and Tartagni, 2012).

Vyhodnocení non-compliance u konkrétního pacienta může být v klinické praxi obtížné. Byla navržena celá řada metod testování compliance, ale žádnou z nich nelze považovat za „zlatý standard“ (Osterberg and Blaschke, 2005). Pacientské diáře, dotazníky, počítání tablet, záznamy o frekvenci preskripce, elektronické lékovky, či sledování klinické odezvy patří mezi nepřímé metody. Tyto metody mohou být snadno

zkresleny – ať už záměrnou manipulací pacientem, nebo jinými faktory. Oproti tomu, měření sérových koncentrací léčiv představuje přímou a přesnou metodu. I zde však může dojít k falešnému zdání, že pacient je compliantní, např. v důsledku interindividuální variability v eliminaci léčiva, nebo záměrným užitím jedné dávky před kontrolou (tzv. compliance bílého pláště). TDM je považováno za mnohem přesnější metodu individualizace dávkování, než pouhé změření hladiny (Gross, 1998). Proto by FK interpretace sérových hladin antihypertenziv mohla redukovat také výše zmíněné nedostatky při určování compliance.

Perindoprilát je majoritně vylučován do moči a jeho sérové hladiny jsou tak nepřímo úměrné funkčnímu stavu ledvin (Verpooten et al., 1991). Proto lze předpokládat, že odhadnutá míra glomerulární filtrace bude zásadní kovariátou pro predikci CL perindoprilátu.

2. Hypotézy a cíle práce

Během postgraduálního studia jsem se zaměřil na studium faktorů ovlivňujících distribuci a eliminaci léčiv a na možnosti individualizace dávkování léčiv pomocí těchto faktorů.

Stanovené hypotézy:

1. Distribuční objem hydrofilních léčiv (vankomycin, amikacin) bude lépe predikován pomocí odvozených deskriptorů tělesné velikosti (korigovaná hmotnost, tukuprostá hmotnost, povrch těla) než celkovou tělesnou hmotností.
2. Clearance renálně eliminovaných léčiv (vankomycin, amikacin) bude nejlépe predikována současně doporučovanou rovnicí CKD-EPI.
3. Clearance renálně eliminovaných léčiv (perindopril) bude lépe predikovat cystatin C než kreatinin.
4. Farmakokinetické parametry fenobarbitalu u asfyktických novorozenců by mohly být ovlivněny demografickou (hmotnost, délka, gestační stáří) a klinickou (funkční stav eliminačních orgánů, tíže asfyxie) charakteristikou pacienta, ale také současně užívanou medikací.

Cílem práce bylo:

1. Porovnat predikční validitu jednotlivých deskriptorů velikosti těla pro odhad distribučního objemu a následnou optimalizaci dávkování vybraných léčiv (vankomycin, amikacin, fenobarbital).
   - Přílohy 1, 3, 4.
2. Porovnat predikční validitu jednotlivých výpočtů glomerulární filtrace pro odhad clearance a následnou optimalizaci dávkování vybraných léčiv (vankomycin, amikacin, fenobarbital, perindopril).
   - Přílohy 2, 3, 4, 6.
3. Posoudit vliv lékových interakcí na distribuci a eliminaci fenobarbitalu.
   - Příloha 5.

3. Metody

Použité metody jsou *in extenso* popsány v přiložených publikacích.

Farmakokinetické analýzy byly provedeny s využitím softwaru MWPharm^{++} (MediWare, Praha, Česká republika). Používal jsem jednokompartmentové modely s eliminační kinetikou 1. řádu. Populační farmakokinetický model byl v první fázi individualizován pomocí demografických (hmotnost, výška, věk, pohlaví) a klinických (funkční stav ledvin) dat, ve druhé fázi pak následovala individualizace pomocí změřených hladin léčiva – cílem bylo „fitovat“ model z první fáze tak, aby průběh simulovaných plazmatických koncentrací v čase co nejvíce protínal reálně naměřené koncentrace. Z takto individualizovaného farmakokinetického modelu pak byly u každého pacienta spočítány farmakokinetické parametry.

Vztahy mezi farmakokinetickými parametry a jejich potencionálními kovariátami byly prověřeny pomocí regresních modelů v programu GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

4. Výsledky

Získané výsledky jsou *in extenso* popsány v přiložených publikacích.

Zde uvádím stručný výčet hlavních výsledků a některé nepublikované analýzy.

Predikční schopnost deskriptorů velikosti těla pro odhad distribučního objemu a následnou optimalizaci dávkování léčiva jsem testoval ve studiích popsaných v přílohách 1, 3 a 4.

Do studie v příloze 1 bylo zařazeno 30 pacientů, kterým byl podáván vankomycin kontinuální infuzí. Medián (IQR) distribučního objemu vankomycinu byl 0,45 (0,39-0,61) L/kg. Medián (IQR) optimální simulované nasycovací dávky pak byl 10,7 (8,8-14,2) mg/kg (pro snadnou aplikaci v reálných podmínkách klinické praxe bylo zaokrouhleno na 10 mg/kg). Po aplikaci této LD normalizované na celkovou tělesnou hmotnost, ideální tělesnou hmotnost a korigovanou tělesnou hmotnost by 71,4 %, respektive 57,1 %, respektive 60,7 % pacientů mělo sérové koncentrace v terapeutickém rozmezí (15-30 mg/L). Výsledky této analýzy korespondují s regresní analýzou vztahů mezi Vd vankomycinu a tělesnou hmotností, IBW a ABW vyjádřených regresními koeficienty 0,4553, respektive 0,1025, respektive 0,3722. Při simulaci podání optimální LD 10 mg/kg celkové hmotnosti došlo k výraznému zkrácení mediánu (IQR) času do dosažení hladiny 20 mg/L ze 17 (11-24) h na 1 (1-4) h.

Do studie v příloze 3 bylo zařazeno 53 pacientů, kterým byl podáván amikacin. Medián (IQR) distribučního objemu amikacinu byl 0,26 (0,23-0,29) L/kg. Lineární regresí byly prověřeny vztahy mezi Vd amikacinu a vybranými deskriptory tělesné velikosti (celková hmotnost, ABW, LBW, BSA). Predikční schopnost klesala v pořadí BSA, ABW, celková hmotnost, LBW (odpovídající regresní koeficienty byly 0,2758, 0,2688, 0,2517 a 0,2403). Medián optimální normalizované dávky byl 13 mg/kg celkové hmotnosti, 14 mg/kg ABW, 19 mg/kg LBW a 517 mg/m^2 BSA. Cílové vrcholové koncentrace (35 – 65 mg/L) byly dosaženy u 83,0 % pacientů při dávkování na celkovou hmotnost a u 90,6 % pacientů při dávkování na ABW, LBW a BSA. V porovnání s tím byly při podání fixní dávky 1000 mg cílové vrcholové koncentrace dosaženy u 81,1 % pacientů.

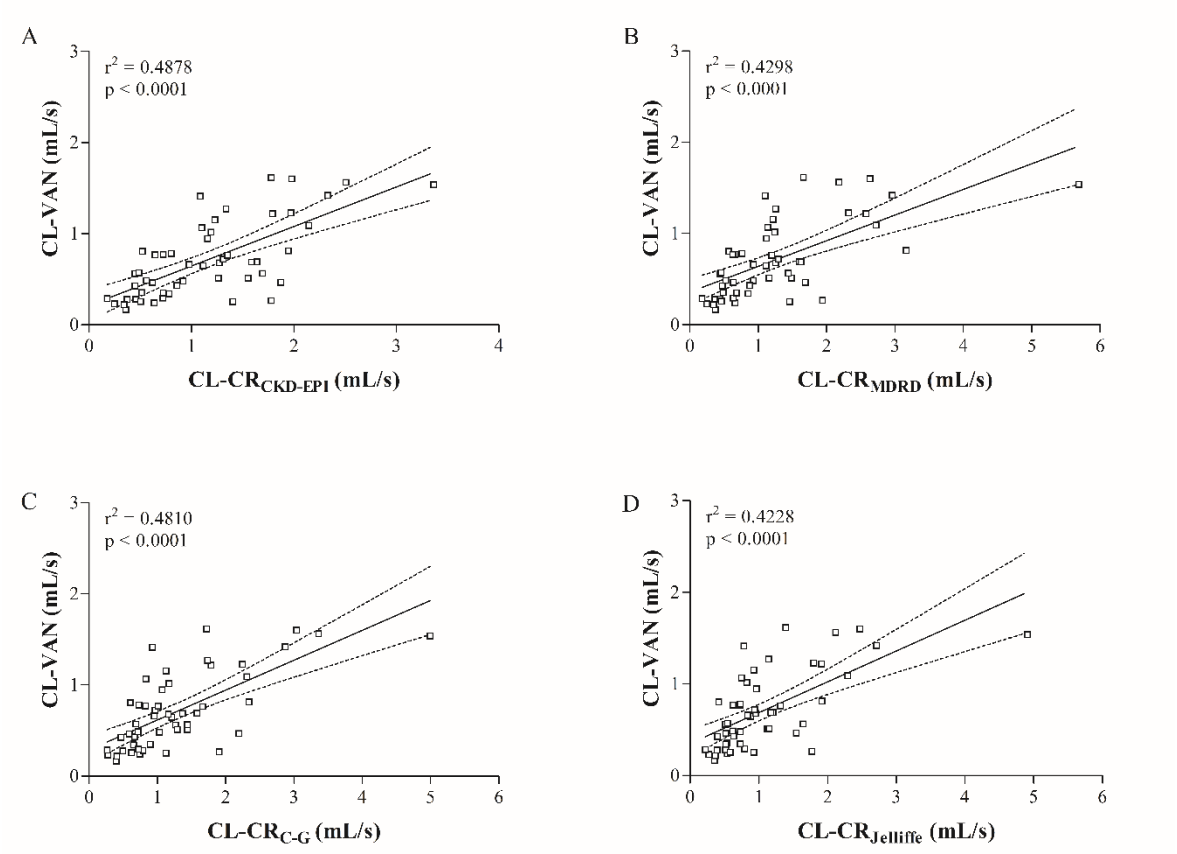
Do studie v příloze 4 bylo zařazeno 36 asfyktických novorozenců s hypoxicko-ischemickou encefalopatií. Medián (IQR) distribučního objemu fenobarbitalu byl 0,49

(0,38-0,59) L/kg. Lineární regrese ukázala signifikantní vztah mezi Vd fenobarbitalu a hmotností, délkou a BSA (odpovídající regresní koeficienty byly 0,3097, 0,1593 a 0,3112). Medián optimální LD fenobarbitalu byl 44,9 mg respektive 14,7 mg/kg hmotnosti (zaokrouhleno na 45 mg a 15 mg/kg). Cílové vrcholové koncentrace fenobarbitalu (20 – 40 mg/L) bylo dosaženo u 58 % pacientů po podání fixní LD a u 72 % po podání normalizované LD.

Predikční schopnost jednotlivých výpočtů glomerulární filtrace pro odhad clearance a následnou optimalizaci dávkování léčiv jsem testoval ve studiích popsaných v přílohách 2, 3, 4 a 6.

Do studie v příloze 2 bylo zařazeno 51 pacientů, kterým byl podáván vankomycin kontinuální infuzí. Medián (IQR) clearance vankomycinu byl 0,026 (0,016-0,044) L/h/kg. Obrázek 1. a tabulka 3 znázorňují výsledky regresní analýzy hodnotící vztah mezi CL vankomycinu z FK analýzy a CL kreatininu odhadnuté podle jednotlivých výpočtů.

Obr. 1: Závislost clearance vankomycinu (CL-VAN) na clearance kreatininu (CL-CR) odhadnuté pomocí výpočtu CKD-EPI, MDRD, Cockcroft-Gault (C-G) a Jelliffe.



Tab. 3: Regresní analýza vztahu mezi clearance vankomycinu a clearance kreatininu vypočítané podle jednotlivých rovnic (CKD-EPI, MDRD, Cockcroft-Gault, Jelliffe).

	Směrnice přímky (95% CI)	Posun po ose Y (95% CI)
CKD-EPI CL-CR	0,433 (0,306-0,561)	0,213 (0,043-0,383)
MDRD CL-CR	0,281 (0,188-0,375)	0,358 (0,211-0,505)
Cockcroft-Gault CL-CR	0,327 (0,230-0,425)	0,291 (0,139-0,443)
Jelliffe CL-CR	0,336 (0,224-0,449)	0,350 (0,199-0,501)

Další analýza pracovala kromě hodnoty CL vankomycinu získané z FK analýzy (tuto hodnotu jsem považoval za reálnou) ještě s hodnotami CL vankomycinu vypočítanými z jednotlivých odhadů CL kreatininu. Tyto výpočty byly provedeny na základě vztahů, které poskytla regresní analýza (viz. tab. 3), tedy:

CL vankomycinu vypočítaná z CL kreatininu dle rovnice CKD-EPI (mL/s)
= 0,433 × CKD-EPI CL-CR (mL/s) + 0,213.
CL vankomycinu vypočítaná z CL kreatininu dle rovnice MDRD (mL/s)
= 0,281 × MDRD CL-CR (mL/s) + 0,358.
CL vankomycinu vypočítaná z CL kreatininu dle rovnice Cockcroft-Gault (mL/s)
= 0,327 × Cockcroft-Gault CL-CR (mL/s) + 0,291.
CL vankomycinu vypočítaná z CL kreatininu dle rovnice Jelliffe (mL/s)
= 0,336 × Jelliffe CL-CR (mL/s) + 0,350.

Z každé jednotlivé hodnoty CL vankomycinu pak byla vypočítána optimální udržovací dávka vankomycinu:

MD (mg/den) = 24 (hod) × CL vankomycinu (L/hod) × 22,5 mg/L.

Hodnota 22,5 mg/L byla zvolena jako střed doporučovaného terapeutického rozmezí pro vankomycin podávaný kontinuální infuzí (15 – 30 mg/L). Výsledkem tedy byly odhady optimální MD odvozené z rovnic CKD-EPI, MDRD, Cockcroft-Gault a Jelliffe.

Následně pak byla vypočítána koncentrace vankomycinu v ustáleném stavu (Css), která by byla navozena při podávání takovýchto MD:

Css (mg/L) = MD (mg/den) ÷ 24 ÷ CL vankomycinu (L/hod).

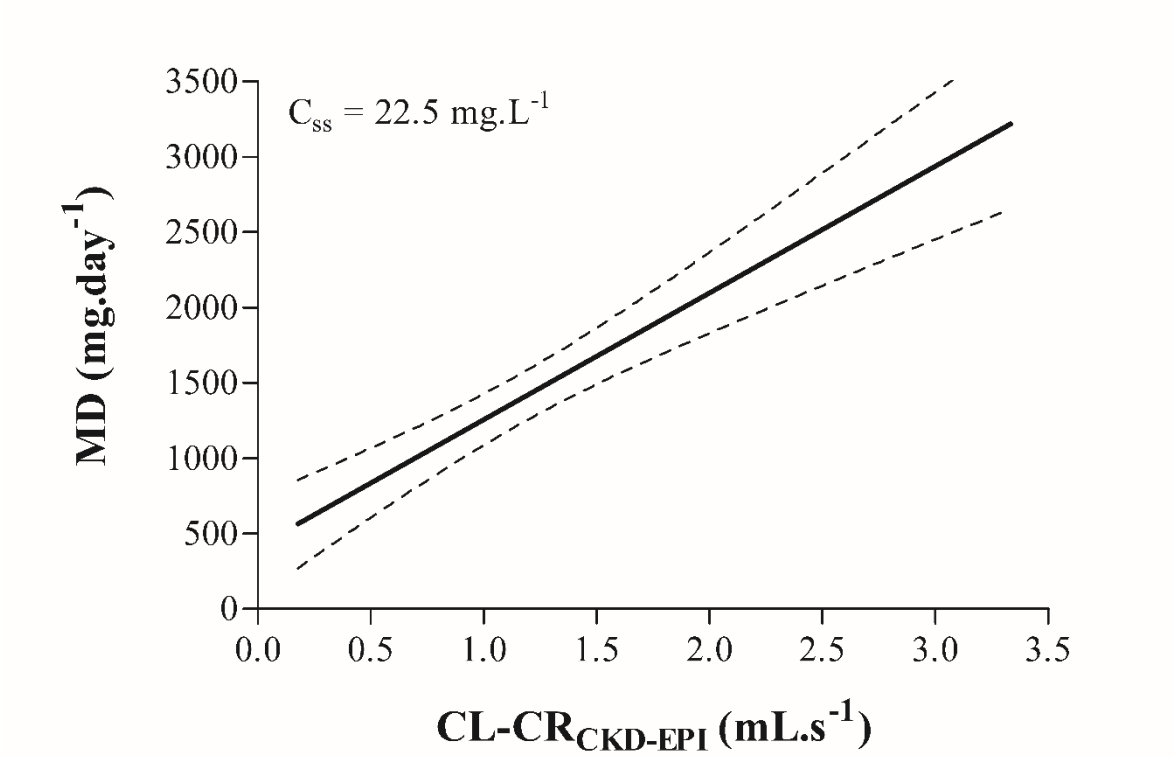
V tomto výpočtu byla zahrnuta MD odvozená z CL kreatininu a potažmo tedy CL vankomycinu podle rovnic CKD-EPI, MDRD, Cockcroft-Gault a Jelliffe, ale také reálná hodnota CL vankomycinu spočítaná na podkladě FK analýzy. Pokud by tedy CL vankomycinu odhadnutá a spočítaná si byly vždy rovny, byly by Css vždy 22,5 mg/L. Odhady CL vankomycinu ale byly více či méně přesné, proto se i Css lišily. Tabulka 4 uvádí zastoupení pacientů (absolutní i procentuální), kteří by měli Css v/pod/nad akceptovatelným terapeutickým rozmezím (15 – 30 mg/L) při podávání MD odvozených z jednotlivých rovnic pro odhad CL kreatininu/GF. Dále uvádí medián a 95% konfidenční interval Css.

Tab. 4: Zastoupení pacientů, kteří měli Css v/pod/nad akceptovatelným terapeutickým rozmezím (15-30 mg/L) a medián Css při podávání MD odvozených z rovnic CKD-EPI, MDRD, Cockcroft-Gault a Jelliffe.

	n (%); N = 51			Medián (95% CI) (mg/L)
	15-30 mg/L	< 15 mg/L	> 30 mg/L	
$MD_{CKD-EPI}$	32 (63)	3 (6)	16 (31)	24 (20-28)
MD_{MDRD}	26 (51)	7 (14)	18 (35)	26 (21-31)
MD_{C-G}	30 (59)	5 (10)	16 (31)	24 (20-29)
$MD_{Jelliffe}$	26 (51)	7 (14)	18 (35)	25 (20-29)

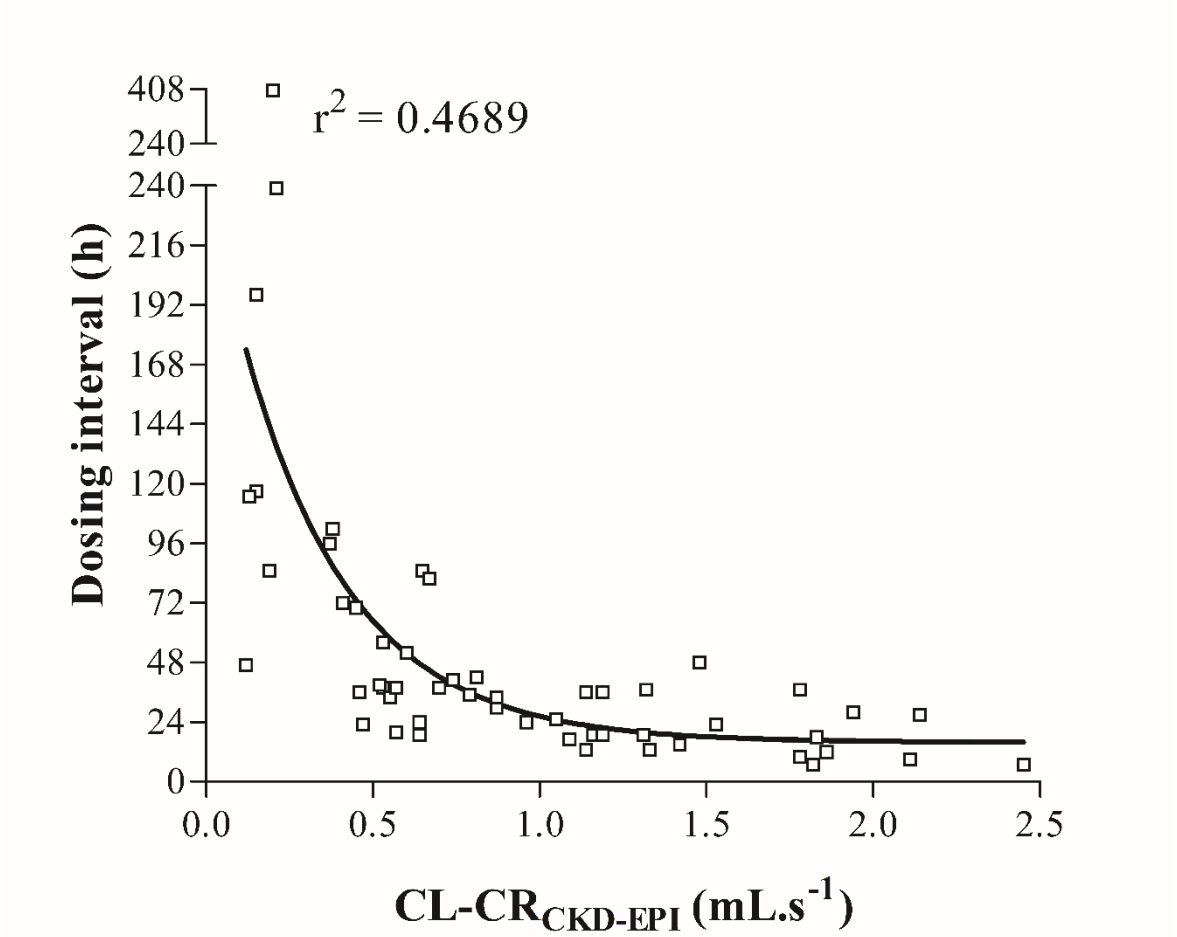
Na základě regresního modelu, který vykazoval nejlepší predikční schopnost (CKD-EPI) byla stanovena optimální denní udržovací dávka 842 × CKD-EPI CL-CR (mL/s) + 414 mg. Pro snadnou aplikaci v reálných podmínkách klinické praxe jsme vypracovali nomogram (obr. 2).

Obr. 2: Nomogram pro odhad optimální denní udržovací dávky vankomycinu (MD) podávaného kontinuální infuzí pomocí CKD-EPI clearance kreatininu (CL-CR$_{CKD-EPI}$). Cílová koncentrace v ustáleném stavu je 22,5 mg/L.



Medián (IQR) clearance amikacinu u pacientů ve studii v příloze 3 (n = 53) byl 0,024 (0,014-0,040) L/h/kg. Odvozené FK parametry T1/2 a eliminační konstanta pak byly 8,5 (4,5-12,0) h a 0,082 (0,058-0,154) h^{-1}. Lineární regresí byly prověřeny vztahy mezi CL amikacinu a CL kreatininu odhadnutou pomocí CKD-EPI, MDRD a Cockcroft-Gault rovnice. Predikční schopnost klesala v pořadí CKD-EPI, MDRD a Cockcroft-Gault (odpovídající regresní koeficienty byly 0,5818, 0,5548 a 0,5415). Optimální dávkovací interval (vypočítaný pomocí individuálních hodnot eliminační konstanty) se pohyboval od 7 do 403 h a rostl exponenciálně s klesající clearance kreatininu dle CKD-EPI. Regresní křivka měla předpis: dávkovací interval (h) = 228,7 × e$^{-3,08 \times \text{CKD-EPI CL-CR (mL/s)}}$ + 15,84. Pro možnost použití v praxi jsme vypracovali nomogram pro odečet optimálního dávkovacího intervalu z hodnoty CKD-EPI CL-CR (obr. 3).

Obr. 3: Nomogram pro odhad optimálního dávkovacího intervalu po podání 1000 mg amikacinu pomocí CKD-EPI clearance kreatininu (CL-CR$_{CKD-EPI}$). Cílová údolní koncentrace je 0-5 mg/L.



Medián (IQR) clearance fenobarbitalu u asfyktických novorozenců s hypoxicko-ischemickou encefalopatií ve studii v příloze 4 (n = 36) byl 0,0045 (0,0034-0,0055) L/h/kg. Lineární regrese neukázala žádný signifikantní vztah (P < 0,05) mezi clearance fenobarbitalu a sledovanými parametry (hmotnost, délka, BSA, sérový kreatinin, CL-CR dle Schwartze, celkový bilirubin, ALT, AST, INR, skóre podle Apgarové, pH pupečníkové krve, přebytek bazí). Medián optimální MD fenobarbitalu byl 8,5 mg respektive 2,7 mg/kg hmotnosti (zaokrouhleno na 9 mg a 3 mg/kg). Cílové koncentrace v ustáleném stavu (15 – 35 mg/L) bylo dosaženo u 86 % pacientů po podání fixní MD a u 72 % po podání normalizované MD.

Do studie v příloze 6 bylo zařazeno 23 pacientů užívajících perindopril. Na základě naměřených hladin perindoprilátu a jejich interpretace bylo 6 pacientů (26,1 %) označeno za zcela non-compliantní (nedetekovatelné hladiny perindoprilátu), 5 pacientů (21,7 %) za

částečně non-compliantní (naměřená hladina perindoprilátu byla méně než 25 % oproti hladině odhadnuté z populačního modelu) a 12 pacientů (52,2 %) bylo compliantních. FK analýza zahrnuje pouze pacienty, které považujeme za compliantní: medián (IQR) clearance perindoprilátu byl 10,1 (4,9-17,0) L/h. Modely lineární regrese ukázaly, že CL perindoprilátu lze predikovat jak pomocí kreatininu tak cystatinu C, ale odhady pomocí cystatinu C se ukázaly jako přesnější.

Vliv případných lékových interakcí na distribuci a eliminaci léčiva jsem testoval ve studii popsané v příloze 5.

Do této studie bylo zařazeno 37 asfyktických novorozenců s hypoxicko-ischemickou encefalopatií. Mediány (IQR) FK parametrů fenobarbitalu byly následující: Vd = 0,48 (0,36-0,62) L/kg, CL = 0,0034 (0,0025-0,0050) L/h/kg. Lineární regrese mezi FK parametry fenobarbitalu a kumulativními dávkami (na dávce závislá analýza) současně podávaných léčiv (noradrenalin, dopamin, dobutamin, furosemid, fenytoin, midazolam, sufentanyl, tramadol) neukázala žádnou interakci. Na dávce nezávislá analýza – porovnání mediánů FK parametrů fenobarbitalu ve skupině s a bez daného konkomitantně podávaného léčiva ukázala signifikantní pokles CL fenobarbitalu u pacientů léčených dopaminem ve srovnání s pacienty, kteří dopamin neužívali (P = 0,0246).

5. Diskuze

Výsledky předkládané dizertační práce jsou *in extenso* diskutovány v přiložených publikacích.

V prvním tematickém okruhu této práce, který je zpracován v publikacích v přílohách 1, 3 a 4, jsem se zabýval možnostmi odhadu distribučního objemu a následně dávkování léčiv pomocí deskriptorů velikosti těla.

Pro odhad dávkování lipofilních látek, které se extenzivně distribuují do tukové tkáně, se zdá být nejvhodnější celková tělesná hmotnost, zatímco ABW nebo LBW jsou navrženy pro dávkování hydrofilních látek, jejichž distribuce do tukové tkáně je omezená (Alobaid et al., 2016). Uvádí se, že relativní obsah vody v tukové tkáni je přibližně 30 % oproti obsahu vody v jiných tkáních. To znamená, že i rozsah distribuce hydrofilních léčiv v tukové tkáni by měl být asi třetinový oproti jiným kompartmentům (Wurtz et al., 1997). Tuto aproximaci však významně ovlivňuje vysoká variabilita obsahu vody v tukové tkáni, pokles obsahu vody s věkem, případně další faktory (Alobaid et al., 2016).

Naše práce ukázala, že Vd vakomycinu nejlépe koreluje s celkovou tělesnou hmotností. Je ale třeba uvést, že z naší analýzy byli vyloučeni pacienti s morbidní obezitou (BMI > 40 kg/m^2) u nichž by dávkování na celkovou hmotnost vedlo k toxickým hladinám. Jako optimální se ukázala být nasycovací dávka 10,7 mg/kg. To je sice méně, než bývá uváděno, nicméně to koresponduje s nižší pozorovanou hodnotou distribučního objemu (medián 0,45 L/kg odpovídá spodní hranici v literatuře uváděného rozmezí) (Rybak et al., 2009a). Jako možné vysvětlení se nabízí variabilita funkčního stavu ledvin i obecné klinické charakteristiky pacientů v naší studii. Vyšší hodnoty Vd lze očekávat především u kriticky nemocných v sepsi (Roberts et al., 2011). Přestože nebyla přímo popsána žádná souvislost mezi Vd vankomycinu a CL kreatininu (Matzke et al., 1984), Vd hydrofilních léčiv by mohlo teoreticky vzrůstat u pacientů s renální insuficiencí z důvodu retence tekutin. Dalším možným důvodem nižšího Vd v naší studii může být použití jednokompartmentového modelu. Obvykle se uvádí, že dvoukompratmentový model poskytuje přesnější FK simulace průběhu plazmatických hladin vankomycinu (Rotschafer et al., 1982). Vícekompartmentové modely však vyžadují větší počet změřených koncentrací, což v klinické praxi není často možné naplnit.

Na rozdíl od vankomycinu, Vd amikacinu nejlépe odpovídaly BSA a ABW. BSA predikovala Vd numericky jen nepatrně lépe než ABW, deskriptor vyvinutý speciálně pro dávkování aminoglykosidů. Signifikantní vztah (i když numericky o něco méně intenzivní) vykázaly i celková tělesná hmotnost a LBW. Tyto vztahy se odrazily i v analýze počtu pacientů, kteří měli vrcholové plazmatické hladiny amikacinu v/mimo terapeutické rozmezí – dávkování normalizované na BSA, ABW i LBW vedlo ke stejným výsledkům. Za optimální lze tedy považovat dávku 517 mg/m^2 BSA (popř. 14 mg/kg ABW, či 19 mg/kg LBW). Nicméně, je třeba dodat, že při podání fixní dávky 1000 mg byly výsledky jen o málo horší (90,6 % vs. 81,1 % pacientů v terapeutickém rozmezí).

Přestože vankomycin i amikacin patří mezi hydrofilní antibiotika, Vd vankomycinu odpovídal lépe celkové hmotnosti, zatímco Vd amikacinu přesněji predikovaly odvozené deskriptory. Jako možné vysvětlení se nabízí rozdíly v míře hydrofility. Rozdělovací koeficient oktanol/voda vyjádřený jako logP je -7,4 u amikacinu a -3,1 u vankomycinu. Obě léčiva se tedy rozpouští více v hydrofilním rozpouštědle, ale amikacin se ve vodě koncentruje přibližně 10000krát více než vankomycin.

Specifickou problematikou byla analýza faktorů ovlivňujících farmakokinetiku fenobarbitalu u asfyktických novorozenců (příloha 4). V této demografické kohortě byl Vd fenobarbitalu sledován ve vztahu k reálné hmotnosti, délce a BSA. Další odvozené faktory (IBW, ABW, LBW) byly vyvinuty pouze pro dospělou populaci a jejich použití u novorozenců nemá fyziologické opodstatnění. Naopak jsme ale prověřili případný vliv jiných, pro tuto populaci charakteristických faktorů jako jsou gestační stáří (coby ukazatel maturace), skóre podle Apgarové, pH pupečníkové krve a přebytku bazí (coby ukazatele míry asfyxie). Vd fenobarbitalu byl v naší studii asociován s hmotností, BSA a v o něco menší míře také s délkou těla. Vzhledem k praktičnosti použití v klinické praxi jsme navrhnuli nasycovací dávku normalizovanou na hmotnost, tj. 15 mg/kg, což je v souladu s předešlými doporučeními (Gilman et al., 1989). Závislost Vd na gestačním stáří se v naší studii neprojevila, což mohlo být dáno relativně úzkým rozpětím gestačního stáří ve sledované populaci (zralí novorozenci, 37. – 41. gestační týden). Stejně tak vliv asfyxie na Vd se neprokázal. To mohl ovlivnit fakt, že do studie však byli zařazeni pouze pacienti se střední až těžkou asfyxií a chyběla kontrolní, neasfyktická skupina.

Ve druhém tematickém okruhu, který je zpracován v publikacích v přílohách 2, 3, 4 a 6, jsem se zabýval možnostmi odhadu clearance a následně dávkování léčiv pomocí ukazatelů funkčního stavu ledvin.

Většina studií zabývajících se problematikou dávkování léčiv podle funkčního stavu ledvin používá pro odhad GF rovnici Cockcroft-Gault. Současná doporučení však tuto rovnice považují za obsolentní a doporučují GF odhadovat pomocí rovnice CKD-EPI.

Ve studii v příloze 2 jsme se snažili porovnat schopnost čtyř známých rovnic pro odhad GF (CKD-EPI, MDRD, Cockcroft-Gault a Jelliffe) predikovat CL vankomycinu. CKD-EPI rovnice odpovídala CL vankomycinu nejlépe, nicméně vzorec Cockcroft-Gault vykazoval prakticky stejnou predikční schopnost. Odhady pomocí MDRD a Jelliffe metody vycházely hůře, což může být dáno tím, že byly vyvinuty především pro pacienty s chronickou renální insuficiencí, respektive průměrnou velikostí těla, zatímco naše studijní populace byla heterogenní jak funkčním stavem renálních funkcí, tak demografií. Výsledky regresní analýzy se odrazily i v rozboru MD odvozených z jednotlivých rovnic, kdy podíl pacientů s Css vankomycinu v terapeutickém pásmu klesal v pořadí CKD-EPI > Cockcroft-Gault >MDRD = Jelliffe. Na základě regresního modelu byla jako optimální stanovena denní udržovací dávka 842 × CKD-EPI CL-CR (mL/s) + 414 mg. Vzhledem k omezené využitelnosti takovéto rovnice v klinické praxi jsme vypracovali nomogram pro odečtení optimální MD kontinuálně podávaného vankomycinu podle CKD-EPI.

Podobně jako u vankomycinu, je i u amikacinu velmi málo zkušeností s úpravou dávkování pomocí novějších rovnic pro odhad GF. Výsledky naší analýzy opět ukázaly, že nejpřesnější odhad poskytuje rovnice CKD-EPI. MDRD a Cockcroft-Gault poskytovaly mírně horší výsledky, což může být opět vysvětleno heterogenitou sledované populace. Optimální dávkovací interval amikacinu podle hodnot CKD-EPI byl stanoven na základě regresního modelu a byl následující: $228{,}7 \times e^{-3{,}08 \times \text{CKD-EPI CL-CR (mL/s)}} + 15{,}84$ hod. Pro možnost jednoduchého využití byl z tohoto vzorce opět odvozen nomogram pro odečtení optimálního dávkovacího intervalu amikacinu podle CKD-EPI.

Podobně jako je uvedeno v diskuzi prvního tematického okruhu, i zde platí, že analýzu kovariát CL fenobarbitalu u asfyktických novorozenců je třeba přizpůsobit charakteristice této populace. CL zde byla sledována ve vztahu k hmotnosti, gestačnímu stáří (deskriptory maturace), CL kreatininu, hladinám bilirubinu, ALT, AST, INR (laboratorní markery funkčního stavu ledvin a jater), skóre Apgarové, pH pupečníkové krve a přebytku bazí (ukazatele míry asfyxie). Regresní modely neodhalily vztah CL fenobarbitalu s žádnou z výše uvedených proměnných. Pro nenalezení vztahu s gestačním stářím a s ukazateli míry asfyxie se nabízí stejné vysvětlení, jaké bylo uvedeno v diskuzi kovariát distribučního objemu. Eliminace fenobarbitalu je velmi komplexní. Snížená funkce jedné eliminační dráhy tak může být kompenzována jinou cestou eliminace. To je

pravděpodobné vysvětlení pro absenci vztahu mezi CL fenobarbitalu a markery funkčního stavu ledvin a jater. Relativně menší rozpětí v hmotnosti pacientů ve srovnání s jinými studiemi může být jen stěží vysvětlením, proč se neprojevila závislost CL na hmotnosti. Kromě toho v případě Vd se při stejném rozpětí hmotnosti závislost projevila. V literatuře často popisovanou závislost CL fenobarbitalu na hmotnosti přisuzujeme vývojovým změnám, kdy eliminační funkce organismu roste současně, ale nezávisle s tělesnou hmotností. Hmotnost je tak vlastně jen zástupný parametr pro maturační změny. Vzhledem k úzkému rozpětí gestačního stáří a tedy i stavu maturace se proto závislost CL na hmotnosti v naší studii neprojevila. Na základě naší analýzy se jako optimální jeví fixní udržovací dávka 9 mg/den, což odpovídá normalizované udržovací dávce 3 mg/kg/den.

Studie uvedená v příloze 6 se zabývá možnostmi odhadu CL perindoprilátu pomocí odhadu funkčního stavu z důvodu posouzení compliance pacientů k antihypertenzní medikaci. Porovnává predikční schopnost dvou markerů GF – kreatininu a cystatinu C. Mnoho předešlých studií popisuje, že cystatin C lépe koreluje s CL/plazmatickou koncentrací léčiv ve srovnání s kreatininem (Brou et al., 2015, Halacova et al., 2008). Naše studie se se svými zjištěními tomuto tvrzení nevymykala. Rozdíly mezi predikční schopností jednotlivých rovnic využívajících cystatin C (CKD-EPI pro cystatin C, kombinovaná CKD-EPI, Hoekova rovnice) byly minimální, což naznačuje možnost využití jednoduché Hoekovy rovnice jako alternativy sofistikované CKD-EPI. Je ale třeba upozornit, že naše pozorování bylo provedeno jen na malém souboru pacientů.

Obecně lze výsledky tohoto tematického okruhu shrnout tak, že rovnice CKD-EPI, která je v současnosti považovaná za nejpřesnější pro odhad GF se ukázala být nejvhodnější také pro odhad CL a následně udržovacích dávek léčiv. Rozdíl oproti jiným rovnicím se projevuje s rostoucí heterogenitou populace, především ve smyslu tělesné hmotnosti a funkčního stavu ledvin. Dále se potvrdilo, že cystatin C umožňuje přesnější odhad CL léčiv než kreatinin.

Ve třetím tematickém okruhu, zpracovaném v publikaci v příloze 5, jsem sledoval vliv lékových interakcí na distribuci a eliminaci fenobarbitalu. Do analýzy byla zahrnuta pouze léčiva, která se často používají na neonatologických JIP.

Kromě na dávce nezávislého rozdílu v CL fenobarbitalu mezi skupinou pacientů s a bez dopaminu jsme nezaznamenali žádný vliv vazoaktivní medikace (noradrenalin, dopamin, dobutamin) na FK parametry. Při kritickém zhodnocení nalezené interakce jsme došli k závěru, že se s největší pravděpodobností jedná o artefakt. Jednak u dopaminu

nebyl potvrzen na dávce závislý vliv na FK fenobarbitalu, a dále žádná jiná vazoaktivní látka, ani jejich souhrnný účinek (definovaný pomocí vasoaktivního-inotropního skóre) tento efekt nevykazovaly. I když literatura uvádí, že furosemid významně snižuje množství celkové, extracelulární a intersticiální tekutiny (O'Donovan and Bell, 1989), nepozorovali jsme žádný vliv furosemidu na Vd (a ani na CL) fenobarbitalu. Žádný na dávce závislý ani nezávislý vliv na FK fenobarbitalu jsme nepozorovali ani u léčiv, která by potenciálně mohla ovlivnit aktivitu enzymů cytochromu P450 (fenytoin, sufentanil, midazolam, tramadol). Fenytoin by mohl s fenobarbitalem interagovat jak ve smyslu inhibice, tak indukce (Encinas et al., 1992). U ostatních sledovaných léčiv je interakce s fenobarbitalem málo pravděpodobná, vzhledem k faktu, že se metabolizují jinou cestou (CYP3A4, CYP2D6) než fenobarbital (CYP2C9, CYP2C19, CYP2E1), a nepatří mezi silné enzymové induktory ani inhibitory (Tateishi et al., 1996, Gorski et al., 1994, Subrahmanyam et al., 2001). Nicméně, v naší studii jsme nepozorovali žádnou interakci ani na úrovni metabolizmu. Jako možné vysvětlení lze uvést relativně krátkou dobu současného podávání léčiv na neonatologických JIP. Dalším důvodem může být již zmiňovaná komplexnost eliminace fenobarbitalu (renální exkrece parentní látky, metabolizace cestou CYP2C9, CYP2C19, CYP2E1 a N-glukosidací), kdy alterace jedné eliminační cesty může být kompenzována jinou.

6. Závěr

Předmětem předložené disertační práce bylo studium faktorů ovlivňujících distribuci a eliminaci léčiv a možností individualizace dávkování léčiv pomocí těchto faktorů.

Výsledky lze shrnout následovně:

- Distribuční objem a následně optimální nasycovací dávku vankomycinu lze nejpřesněji predikovat pomocí reálné tělesné hmotnosti. Jako optimální se u dospělých pacientů na JIP léčených kontinuální infuzí vankomycinu ukázala být nasycovací dávka 10,7 mg/kg. Při podání této dávky došlo ke zkrácení mediánu času do navození účinných hladin ze 17 na 1 hodinu.
- Clearance a následně optimální udržovací dávku vankomycinu lze nejpřesněji predikovat pomocí CKD-EPI rovnice pro odhad glomerulární filtrace. Byl vyvinut nomogram pro odhad optimální udržovací dávky pomocí CKD-EPI rovnice u dospělých pacientů na JIP léčených kontinuální infuzí vankomycinu.
- Distribuční objem a následně optimální jednotlivé dávky amikacinu lze nejpřesněji predikovat pomocí BSA, popř. pomocí ABW, která vykazovala prakticky stejnou predikční schopnost. Jako optimální se u dospělých pacientů na JIP ukázala být dávka 517 mg/m^2, respektive 14 mg/kg ABW.
- Clearance a následně optimální interval mezi dávkami amikacinu lze nejpřesněji predikovat pomocí CKD-EPI rovnice pro odhad glomerulární filtrace. Byl vyvinut nomogram pro odhad optimálního intervalu mezi dávkami amikacinu pomocí CKD-EPI rovnice u dospělých pacientů na JIP.
- Distribuční objem a následně optimální nasycovací dávku fenobarbitalu u donošených asfyktických novorozenců lze nejpřesněji predikovat pomocí reálné tělesné hmotnosti (případně povrchu těla, což je ale méně intuitivní). Jako optimální se ukázala být nasycovací dávka 15 mg/kg.
- Clearance fenobarbitalu u donošených asfyktických novorozenců v naší studii nekorelovala s žádnou ze sledovaných charakteristik (hmotnost, clearance kreatininu, atd.). Proto se jako optimální jevila fixní udržovací dávka 9 mg/den, což odpovídá normalizované dávce 3 mg/kg/den.

- Clearance perindoprilátu lze lépe predikovat pomocí cystatinu C než s využitím kreatinnu. Byl popsán inovativní přístup v hodnocení compliance pacientů k antihypertenzní medikaci, kdy změřené sérové koncentrace léku byly pomocí principů TDM zasazeny do kontextu užívaných dávek a demografické/klinické charakteristiky konkrétního pacienta.
- Nebyl pozorován žádný vliv běžně užívané komedikace (vazoaktivní látky, furosemid, fenytoin, midazolam, sufentanyl, tramadol) na farmakokinetické parametry (Vd, CL) fenobarbitalu u donošených asfyktických novorozenců na neonatologické JIP.

7. Použitá literatura

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Příloha 1

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ORIGINAL ARTICLE

A simulation of loading doses for vancomycin continuous infusion regimens in intensive care

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ABSTRACT

Background: Delayed achievement of target vancomycin serum concentrations may adversely affect clinical outcomes. The objective of this retrospective study was to compare the prediction accuracy of different body weight descriptors for volume of distribution and to propose an optimal loading dose (LD) for continuous infusion regimens in adults.

Methods: Pharmacokinetic variables were computed using one-compartmental analysis. Simulated LDs of vancomycin were evaluated for each patient.

Results: Volume of distribution, clearance, and half-life median values (interquartile range) for vancomycin in the study population ($n = 30$) were 0.45 (0.39–0.61) $L.kg^{-1}$, 0.026 (0.015–0.040) $L.h^{-1}.kg^{-1}$, and 10.3 (7.7–21.3) h, respectively. The observed volume of distribution was better predicted by total body weight (TBW) than by the ideal body weight or the adjusted body weight.

Conclusions: An LD of 10.7 mg per kg TBW was optimal in our study population. Using this LD, 17.9% of simulated vancomycin serum levels were just below the therapeutic range, only 10.7% concentrations exceeded the target range and no concentration was toxic. The use of a LD would lead to reduced median time to reach target concentrations from 17 to 1 h.

KEYWORDS
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Introduction

Vancomycin, a glycopeptide antibiotic, is one of the first choices for treating nosocomial infections caused by Gram-positive bacteria [1]. Vancomycin exhibits concentration-independent bactericidal activity against sensitive bacteria, while the ratio of the 24-hour area under the concentration–time curve (AUC_{24}) to the minimal inhibitory concentration (MIC) predicts the clinical and bacteriological outcomes of vancomycin treatment [2]. Based on *in vitro* and limited *in vivo* data, an AUC_{24}/MIC ratio of $\geq$400 was the pharmacokinetic (PK)/pharmacodynamic target value for vancomycin in therapeutic guidelines [3,4]. Previously various therapeutic ranges of vancomycin serum concentrations were proposed for continuous infusion of vancomycin [5–8]. Considering recent data that indicate that the optimal vancomycin AUC_{24}/MIC ratio for efficacy is approximately 400 (for MIC 1 $mg.L^{-1}$) [2,9] and a safety threshold of 700 (corresponding to risk of nephrotoxicity) [10], the target therapeutic concentration range between 15 and 30 $mg.L^{-1}$ seems to be appropriate. Although there is no direct comparison of clinical outcomes for various concentration ranges of vancomycin, continuous infusion steady-state levels ranging 15–30 $mg.L^{-1}$ should be considered satisfactory.

There are two administration strategies in clinical settings based on intermittent or continuous infusions. Sufficient data exist to support the use of continuous as an alternative to intermittent infusion in adult patients [11], however, continuous infusion did not consistently give clinical benefits with respect to efficacy or safety compared to intermittent dosing in published clinical studies [12].

In critically ill patients, antibiotics should be administered as soon as possible once infection is identified [13,14] and an early attainment of effective vancomycin concentrations is crucial for treatment success. When vancomycin treatment is initiated by continuous infusion without a loading dose (LD), serum concentrations gradually increase until equilibrium is established between administration and elimination. Therapeutic concentrations are achieved with a delay that may have deleterious effects on clinical outcomes [15]. In order to achieve therapeutic serum concentrations as early as possible a LD should be considered [16–18]. An LD of 15–20 $mg.kg^{-1}$ was used in previous studies [7,19,20]. Nevertheless, LD administration is not common in clinical practice, likely due to the fact that the currently valid summary of product characteristics does not recommend a LD.

LD can be calculated based on volume of distribution (Vd) [21]. Due to potential differences in Vd in the highly heterogeneous patients in intensive care units (ICU), LD calculated from population PK values may not be accurate [22]. Vd is a PK parameter related to structural aspects of the body, therefore most LD calculations are based on body weight [23]. Mohammedi et al. suggested that a total body weight (TBW)-based LD of 15 $mg.kg^{-1}$ was a better option than a fixed dose of 500 mg [17]. Besides TBW, alternative weight descriptors are sometimes used to define drug doses, namely ideal body weight (IBW) and adjusted body weight (ABW) [24]. IBW was derived from insurance data collected by the Metropolitan Life Insurance Company of New York [25]. Since it relates size to mortality and is unrelated to TBW, extrapolation of IBW to a dosing schedule does not seem biologically very plausible, since it would lead to the unlikely assumption that patients of the same height should receive the same dose. ABW was the first weight descriptor specifically developed for dosing calculations of hydrophilic compounds adjusting IBW for body weight excess. It was first used during PK studies on aminoglycosides [25,26]. Since vancomycin is a hydrophilic drug, ABW could be an appropriate weight descriptor for dosing calculations on continuous regimens.

The aim of our study was to compare the prediction accuracy of different body weight descriptors for the Vd of vancomycin and to simulate the effect of LD based on TBW, IBW and ABW on the time to reach target concentrations. Based on these PK simulations we aimed to propose an optimal LD for use in adult patients at the ICU.

Materials and methods

Study design

A retrospective observational PK study was performed in adult patients treated with continuous infusion of vancomycin at the General University Hospital in Prague between January and June 2016. Patients meeting the following criteria were included: age $\geq$18 years, not receiving dialysis, received vancomycin for at least three days, did not receive a LD, and vancomycin serum levels were measured during the first three days of therapy. Since the study only involved retrospective analysis of routine clinical data, study-specific patients' informed consent and Ethics Committee approval were not obtained. Moreover, at admission to the hospital patients sign an approved general informed consent

wherein they state, inter alia, that anonymous data can be used for research.

Pharmacokinetic analysis

Vancomycin serum concentrations were measured by a turbidimetric inhibition immunoassay (Beckman Coulter, Inc., Brea, CA).

Individual PK parameters, Vd, clearance (CL) and half-life (T1/2) were calculated in a one-compartmental PK model based on individual demographic and clinical data and observed vancomycin serum levels using MWPharm^{++} software (MediWare, Prague, Czech Republic). The population PK one-compartmental model was individualized to maximize fitting of the simulated PK profile curve to the observed concentrations in each patient.

The times required to achieve vancomycin serum concentration of 20 mg.L^{-1} from the start of treatment were computed using individualized PK simulations.

Loading dose analysis

Optimal simulated LD were calculated for each patient based on individual Vd values using the formula

$$\text{LD } (\text{mg.kg}^{-1}) = \text{Vd } (\text{L.kg}^{-1}) \times \text{Cvan } (\text{mg.L}^{-1}),$$

where vancomycin serum concentration (Cvan) of 22.5 mg.L^{-1} was set as a midpoint of the target therapeutic range (20–25 mg.L^{-1}). Subsequently, simulated Cvan after median simulated LD were calculated in each patient using the formula

$$\text{Cvan } (\text{mg.L}^{-1}) = \text{median LD } (\text{mg.kg}^{-1}) \times \text{TBW } (\text{kg}) \div \text{Vd } (\text{L})$$

Dosage per kg of IBW and ABW was also examined, where IBW and ABW were calculated as

IBW (kg) = 50 kg +2.3 kg for each inch over 5 feet (males) or 45.5 kg +2.3 kg for each inch over 5 feet (females)

$$\text{ABW} = \text{IBW} + 0.4 \times (\text{BW–IBW})[24]$$

Statistical analysis

Medians and interquartile ranges (IQR) were calculated using MS Excel 2010 (Microsoft Corporation, Redmond, WA). The 95% confidence intervals (CI) for medians were calculated by the Bonett & Price method [27].

Linear regression models were used to evaluate the relationships of total Vd of with TBW, IBW and ABW using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, CA).

Results

Thirty patients were enrolled into the study (21 males, nine females). Their demographic and clinical characteristics are summarized in Table 1. Initial vancomycin dose ranged between 7 and 40 mg.kg^{-1}.day^{-1}.

Totally 88 vancomycin serum levels for PK analysis were obtained (1–7 concentration points per patient). Vancomycin PK parameters in the whole study group are summarized in Table 2.

Two patients with morbid obesity (BMI >40 kg.m^{-2}) were excluded from the LD analysis, since their extremely low normalized Vd could distort the analysis. Median optimal simulated vancomycin LD was 10.7 (IQR: 8.8–14.2) mg.kg^{-1}. For ease of calculations in real clinical settings we set the LD at 10 mg.kg^{-1}.

The rates of achievement of therapeutic concentrations in serum following the simulated LD of 10 mg per kg based on TBW, IBW, and ABW are summarized in Table 3. LD normalized per kg TBW lead to achievement of the target therapeutic range in more patients compared to calculations based on IBW or ABW. Nearly three quarters of patients would reach serum levels in the range of 15–30 mg.L^{-1}, if they received LD calculated based on TBW. Approximately 29% of concentrations were in the range of 20–25 mg.L^{-1}, following LD based on TBW in comparison with 7% and 14% after LD based on IBW and ABW, respectively. Median serum levels after simulated LD in the group not reaching the lower limit of target concentrations (<15 mg.L^{-1}) were 13 (IQR: 13–14), 13 (IQR: 11–13) and 13 (IQR: 12–14) mg.L^{-1} when LD was based on TBW, IBW and ABW, respectively.

Table 2. Vancomycin pharmacokinetic parameters.

$N = 30$	Vd (L)	Vd (L.kg^{-1})	CL (L.h^{-1})	CL (L.h^{-1}.kg^{-1})	T1/2 (h)
Median	34.28	0.45	2.180	0.026	10.3
IQR	27.47–48.26	0.39–0.61	1.238–2.735	0.015–0.040	7.7–21.3
Min	15.48	0.10	0.600	0.007	3.9
Max	75.92	0.80	5.540	0.083	49.4

Table 1. Demographic and clinical data.

$N = 30$	Age (years)	Weight (kg)	Height (cm)	BMI (kg.m^{-2})	Serum creatinine (μmol.L^{-1})
Median	63	74	175	25.5	117
IQR	49–73	68–88	171–180	22.9–29.4	76–175
Min	20	50	146	16.0	33
Max	91	280	198	86.4	408

Table 3. Proportion of patients achieving simulated peak serum levels of 15–30 mg.L^{-1},<15 mg.L^{-1}, or >30 mg.L^{-1} and median simulated peak serum levels after loading dose of 10 mg.kg^{-1} calculated using total body weight (TBW), ideal body weight (IBW), and adjusted body weight (ABW).

	n (%); *N* = 28			
Dose size	15–30 mg.L^{-1}	<15 mg.L^{-1}	>30 mg.L^{-1}	Median (95% CI) (mg.L^{-1})
10 mg per kg of TBW	20 (71.4)	5 (17.9)	3 (10.7)	21.1 (17.1–25.1)
10 mg per kg of IBW	16 (57.1)	10 (35.7)	2 (7.1)	19.5 (14.0–25.0)
10 mg per kg of ABW	17 (60.7)	8 (28.6)	3 (10.7)	20.1 (14.6–25.6)

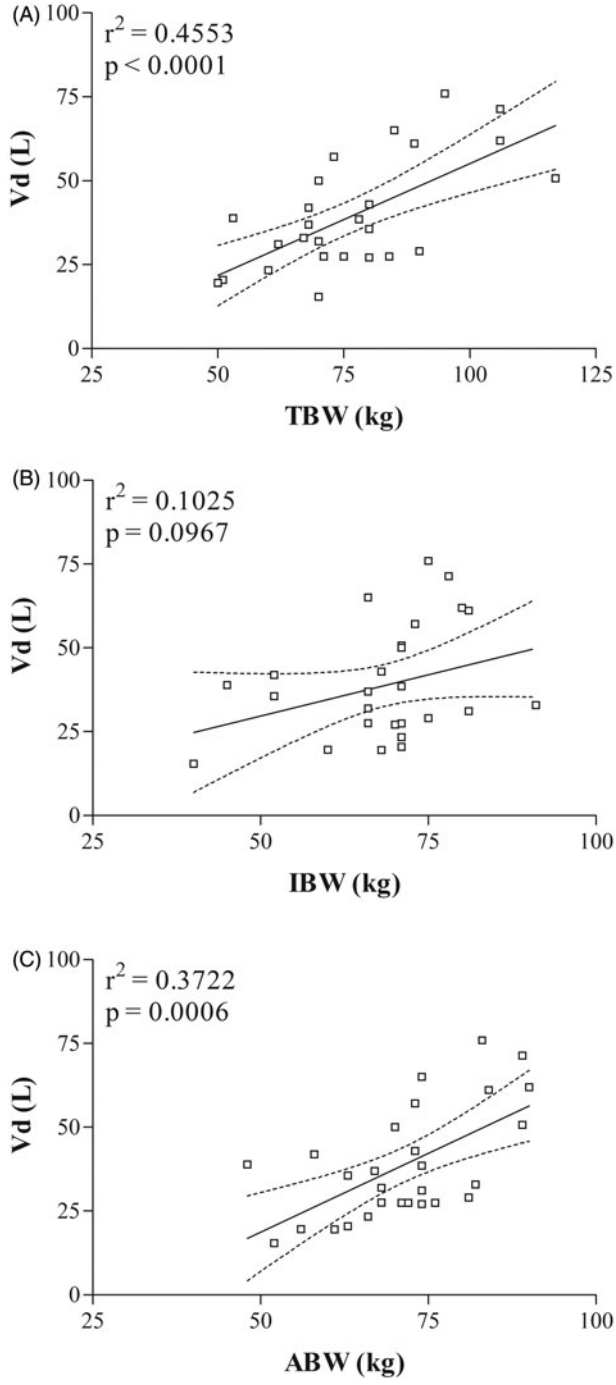

Figure 1. Regression analysis of vancomycin volume of distribution (Vd) and (A) total body weight (TBW), (B) ideal body weight (IBW), and (C) adjusted body weight (ABW).

The median concentrations in the group exceeding the target therapeutic range (>30 mg.L^{-1}) was 31 (IQR: 31–38), 35 (IQR: 35–35) and 31 (IQR: 31–33) mg.L^{-1} when LD was based on TBW, IBW and ABW, respectively.

The total Vd was better predicted using TBW than using IBW and ABW based on a linear regression model (Figure 1).

Median time to achieve a serum concentration of 20 mg.L^{-1} without LD was 17 (IQR: 11–24) h from start of treatment. After a simulated LD (10 mg per kg of TBW) median time to reach this target concentration was 1 (IQR: 1–4) h. In patients who would not achieve vancomycin serum levels ≥15 mg.L^{-1} after a simulated LD (10 mg per kg of TBW), the time to reach a serum concentration of 20 mg.L^{-1} would be reduced from 23 (IQR: 18–31) h to 8 (IQR: 1–9) h from start of treatment.

Discussion

Accurate antibiotic dosing normalized for weight and body size still represents a challenge, especially in obese patients. Different methods have been proposed for antimicrobial dosing with respect to body size descriptors [28]. For lipophilic drugs, which are extensively distributed into tissues, including adipose tissue, the most relevant size descriptor for Vd appears to be TBW, while ABW or IBW are suggested for hydrophilic agents as these have limited distribution to adipose tissues [28]. Although the water content in adipose tissue varies from 4.4 to 36.1% [29] the relative water content in fat is approximately 30% of that in other tissues. Thus, the extent of distribution in fat for hydrophilic drugs may be a only third of that in other tissues [30]. The true Vd of vancomycin therefore might not linearly correlate with TBW and the use of TBW for vancomycin dosing may in theory result in a significant overdose in obese patients. However, due to the variability of water content in fat, the age-dependent decrease of water content in tissues and to other factors, TBW is used as an optimal

descriptor for dose calculations also for some hydrophilic compounds [28].

In our study, linear regression analysis showed that the observed Vd of vancomycin was better predicted by TBW compared with IBW or ABW. It is, however, important to mention that subjects with morbid obesity (BMI $>40\,kg.m^{-2}$) were excluded from the analysis. For populations with normal weight or for overweight patients the amount of excessive fat tissue could represent a rather small additional volume available for the distribution of vancomycin. The number of obese patients (BMI $>30\,kg.m^{-2}$) in our study was relatively small and the majority of the study patients was of normal weight or overweight (76.6%).

This relationship between Vd and body weight descriptors was reflected by the result that the highest chance of reaching the target therapeutic range, was with a LD computed per kg of TBW.

Therapeutic guidelines recommend an LD of $25–30\,mg.kg^{-1}$ for intermittent vancomycin administration [1], while no consensual therapeutic guidelines are available for continuous administration. Since the target serum levels differ for the two administration regimens, the LD preceding continuous and intermittent administration are not equal. While the LD for intermittent regimens should induce vancomycin serum concentrations similar to the peak concentrations at steady state, LD for continuous therapy should generate serum concentrations equal to the plateau level at steady state [11]. Indeed, most studies on vancomycin LD before continuous infusion used an LD of 15–20 mg per kg of TBW [11]. A study by Cristallini et al. used considerably higher LD for continuous therapy ($35\,mg.kg^{-1}$ TBW) but concentrations reached with this LD were unnecessarily high for continuous regimens with a median concentration of $44\,mg.L^{-1}$ [8].

Based on our simulations, the optimal vancomycin LD in our study ($10\,mg.kg^{-1}$) was lower than usually reported, which is, however, consistent with the lower values observed for Vd in our study. The median $0.45\,L.kg^{-1}$ corresponds to the lower values for Vd reported in the literature [1]. A possible reason for the lower Vd may be heterogeneity of renal function and clinical characteristics in our patient population. Higher Vd values would be expected especially in critically ill septic patients [31]. Although no significant relationship between vancomycin Vd and creatinine clearance was observed in a previous report [32], Vd might in theory increase in patients with renal failure due to fluid retention. Further, we used a one-compartmental model in the PK analysis, which is likely to give lower Vd values than a multi-compartmental model. A two-compartmental model may provide a more accurate PK simulation [33]. However, a larger number of concentration values would be needed to reliably individualize estimates for all PK parameters, but were not available for our study.

Although our study was relatively small, we believe, it can be used as a practical tool to predict optimal LD estimates in adult ICU patients treated with continuous infusion of vancomycin. Our study was based on PK data derived from the hospital medical records system. Therefore, the retrospective nature of our work should not impact on the validity of the results. However, the results of our exploratory study should be confirmed in a prospectively conducted trial.

Conclusions

In conclusion, the results of our study suggest that an optimal LD in adult patients treated with continuous infusion of vancomycin in the ICU is 10 mg per kg of TBW. Using this LD, 17.9% of vancomycin serum levels were just below the therapeutic range (minimum post-loading concentration was $13\,mg.L^{-1}$), only 10.7% of concentrations exceeded the therapeutic range and no concentration was toxic ($>50\,mg.L^{-1}$). This LD would lead to a significant reduction of the time required to reach target serum levels from 17 (IQR: 11–24) to 1 (IQR: 1–4) h. An individual approach is needed in extremely obese patients with BMI $>40\,kg.m^{-2}$. Since our findings were based on a PK simulation using one-compartmental model, these results need to be evaluated via a prospective clinical trial to confirm that 10 mg per kg of TBW is the optimal LD. Nevertheless, this analysis shows the importance of a LD before continuous infusion of vancomycin.

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Disclosure statement

The authors report no conflict of interest.

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Příloha 2

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Creatinine clearance estimations for vancomycin maintenance dose adjustments

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Vancomycin maintenance dose adjustment

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Conflict of interest:

The authors declare that there is no conflict of interests regarding the publication of this paper.

Key words:

Vancomycin, CKD-EPI, continuous infusion, intensive care

Introduction:

Vancomycin is one of the first choices for treating serious infections caused by Gram-positive bacteria [1]. In order to manage its efficacy and toxicity, therapeutic drug monitoring is recommended and routinely conducted [1, 2]. However, the initial maintenance dose (MD) must be determined based on the estimated clearance. Previous studies have found linear relationship between vancomycin clearance (CL-VAN) and creatinine clearance (CL-CR) estimated by Cockcroft–Gault (C-G) [3, 4] and MDRD formulas [5, 6]. There is only a very limited knowledge on the relationship between CL-VAN and up to date method for CL-CR calculation – CKD-EPI [7]. A few nomograms for continuous vancomycin initial MD based on C-G [3, 4], or MDRD [6] have been published, but no nomogram based on CKD-EPI is available.

In order to clarify the possibility to predict CL-VAN we compared the performance of four well-known equations for CL-CR estimation, i.e. CKD-EPI, MDRD, C-G, and Jelliffe, and then we propose initial MD estimate based on the best correlating equation in adult ICU patients treated with vancomycin continuous infusion.

Methods:

A retrospective observational study was conducted in adult patients treated with vancomycin continuous infusion at the mixed ICU between September 2015 and August 2016. Patients meeting the following criteria were included: age ≥ 18 years, not eligible for dialysis, vancomycin treatment for at least 3 days, and having vancomycin level measured within the first 3 days of therapy. Since nature of this study patients´ informed consent was unnecessary.

Creatinine plasma concentrations were recorded and CL-CR were estimated according to the CKD-EPI ($CL\text{-}CR_{CKD\text{-}EPI}$) [8], MDRD ($CL\text{-}CR_{MDRD}$) [9], C-G ($CL\text{-}CR_{C\text{-}G}$) [10], and Jelliffe ($CL\text{-}CR_{Jelliffe}$) [11] formulas for each patient.

Individual CL-VAN was calculated using non-compartmental pharmacokinetic (PK) model based on individual demographic, clinical data and observed vancomycin plasma levels using MWPharm^{++} software (MediWare, Prague, Czech Republic). The population PK model for vancomycin was individualized to maximize fitting of the simulated profile curve with observed drug concentration points in each patient.

Linear regression models were used to evaluate the relationships of CL-VAN and CL-CR estimated according to particular formulas using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

MD were calculated for each patient based on CL-VAN values using following formula: MD ($mg.day^{-1}$) = 24 h × CL-VAN ($L.h^{-1}$) × 22.5 $mg.L^{-1}$. The value of 22.5 $mg.L^{-1}$ was selected as the target value for vancomycin steady-state concentration.

Results:

Fifty-one patients were enrolled into the study (36 men, 15 women). Median (IQR) age, body weight and serum creatinine were 63 (53-74) years, 80 (68-90) kg and 110 (80-179) $\mu mol.L^{-1}$, respectively. Totally 170 vancomycin plasma levels for PK analysis were obtained (1-12 per patient). Vancomycin PK analysis showed CL-VAN median (IQR) value of 2.33 (1.27-3.54) $L.h^{-1}$.

The $CL\text{-}CR_{CKD\text{-}EPI}$ was the most predictive for the vancomycin CL based on linear regression models ($r^2 = 0.4878$). $CL\text{-}CR_{C\text{-}G}$ as similarly predictive ($r^2 = 0.4810$), and the other equations $CL\text{-}CR_{MDRD}$ ($r^2 = 0.4298$), and $CL\text{-}CR_{Jelliffe}$ ($r^2 = 0.4228$) were also significantly related ($p < 0.0001$).

The daily maintenance dose calculation using the following formula has resulted in optimal PK results: $842 \times \text{CL-CR}_{\text{CKD-EPI}}$ (mL.s^{-1}) + 414. However, since the practical utility of such an equation is very limited, we propose maintenance dose nomogram based on this formula that could be easily used in clinical settings (Figure 1).

Discussion and conclusion:

CKD-EPI formula has shown the most accurate prediction for vancomycin clearance and dosing, while the performance of the traditionally used C-G formula was almost identical. C-G formula is no longer recommended for clinical use because it has not been expressed using standardized creatinine values. Our results indicate that the clinical experience generated over the long time, when C-G formula was used as a basis for vancomycin dosing, can be extrapolated to CKD-EPI method with no need for any corrective adjustments. Estimations based on MDRD and Jelliffe methods have indicated slightly less optimal dose predictions. The numerically worse performance may be due to heterogeneity of our study population in renal function status and demographics, as MDRD and Jelliffe formulas are applicable primarily on chronic kidney disease subjects and average size patients, respectively. However, our study population represents the real life patient group that is currently indicated for vancomycin treatment with its inherent heterogeneity of demographic as well as medical history characteristics.

In conclusion, we demonstrated that CL-VAN best correlates with $\text{CL-CR}_{\text{CKD-EPI}}$ and that the clinical experience with C-G formula could be extrapolated to CKD-EPI method with no need for any corrective adjustments. Furthermore, vancomycin MD nomogram based on $\text{CL-CR}_{\text{CKD-EPI}}$ has been designed.

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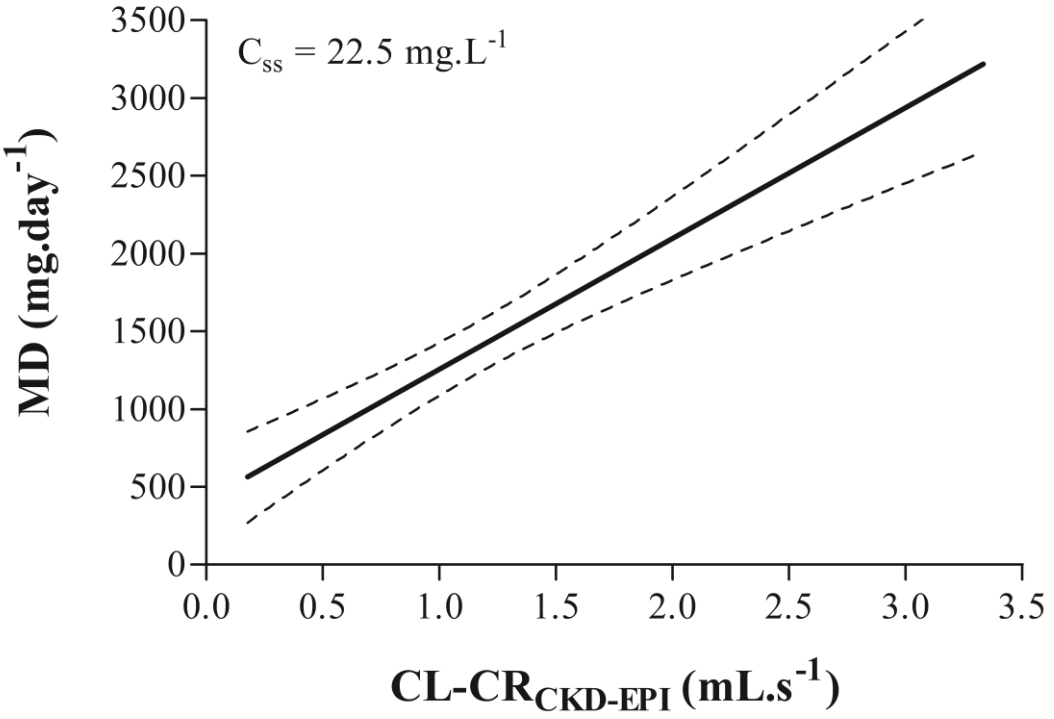
Figure 1: Nomogram for calculation of vancomycin daily maintenance doses (MD) administered by continuous infusion to target steady-state concentration (C_{ss}) of 22.5 $mg.L^{-1}$ based on CKD-EPI creatinine clearance ($CL\text{-}CR_{CKD\text{-}EPI}$)



Dashed lines represent 95% confidence interval

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I am pleased to inform you that your work has now been accepted for publication in American Journal of Therapeutics. All manuscript materials will be forwarded immediately to the production staff for placement in an upcoming issue.

Thank you for submitting your interesting and important work to the journal.

With Kind Regards,

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Příloha 3

ŠÍMA, M., HARTINGER, J., CIKÁNKOVÁ, T. & SLANAŘ, O. 2017. Estimation of once-daily amikacin dose in critically ill adults. *J Chemother*, v recenzním řízení.

Estimation of once-daily amikacin dose in critically ill adults

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Running title:
Estimation of once-daily amikacin dose

Abstract:
Purpose: This study aimed at investigating variables affecting amikacin pharmacokinetics, and then to propose optimal initial dosing based on these relationships in critically ill adult patients treated with once-daily amikacin regimen.
Methods: Amikacin pharmacokinetics was calculated based on plasma concentrations measurements using one-compartmental analysis. Relationships between amikacin pharmacokinetic parameters and demographic/clinical data were explored in linear regression models. Simulated amikacin dose and dosing intervals were derived from body size descriptors and estimated creatinine clearances for each patient.
Results: Volume of distribution and clearance median values (interquartile range) for amikacin in the whole study population (n = 53) were 0.26 (0.23-0.29) $L.kg^{-1}$and 0.024 (0.014-0.040) $L.h^{-1}.kg^{-1}$, respectively. Amikacin volume of distribution best correlated with body surface area, while amikacin clearance was best predicted by CKD-EPI creatinine clearance. Our study suggests that dose size of 517 mg per m^2 of body surface area leads to amikacin levels most approaching target peak concentration. Universal administration of 1000

mg is slightly less accurate, but simple for clinical routines. Dosing interval calculated as $228.7 \times e^{-3.08 \times \text{CKD-EPI creatinine clearance (mL.s-1)}} + 15.84$ most closely approximated optimal dosing intervals based on individual amikacin pharmacokinetics. The dosing nomogram based on CKD-EPI creatinine clearance was designed.

Conclusions: This study presents basis for once-daily amikacin initial dosing. Amikacin dose size of 517 $mg.m^{-2}$ leads to reach goal peak concentrations in 91% patients in comparison with 81% after administration of fixed dose of 1000 mg. Dosing interval estimation based on CKD-EPI creatinine clearance is accurate in 66% patients.

Key words:

Amikacin, pharmacokinetics, body size descriptors, creatinine clearance, dosing, intensive care

Conflict of interest:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Introduction:

Amikacin, an aminoglycoside broad-spectrum antibiotic, is widely used to treat primarily patients with serious Gram-negative infections at intensive care units.

Aminoglycosides exhibit concentration-dependent bactericidal activity against sensitive bacteria, and the ratio of the maximum achieved concentration (C_{max}) to the minimal inhibitory concentration (MIC) is considered to predict the clinical and bacteriological outcomes of the treatment. A C_{max}/MIC ratio of ≥ 8 is strongly associated with clinical response [1]. Moreover, this class of antibiotics shows considerable post-antibiotic effect, which is also concentration-dependent. The estimated length of post-antibiotic effect of amikacin is approximately four to six hours at clinically relevant concentrations [2].

Aminoglycosides belong among narrow therapeutic index drugs. Nephrotoxicity and ototoxicity are the most common adverse effects. Nephrotoxicity (usually transient) is caused by drug accumulation in the proximal tubule cells, while ototoxicity (which may be

irreversible) appears to be related with total drug exposure and no relationship between ototoxicity and actual plasma levels was found [3].

There are two administration strategies in clinical practice: conventional dosing scheme is administration of a weight-based dose divided two to three times daily, while once-daily strategy involves the administration of all daily weight-based dose size at once with extended dosing interval (every 24 hours for patients with normal renal functions). Over the past twenty years, there has been a general trend toward the preference of once-daily administration strategy. This approach has been advocated to improve drug efficacy while reducing its potential toxicity and to increase the cost-effectiveness of amikacin use [4].

In order to further increase the clinical efficacy of aminoglycosides and to decrease its toxicity, therapeutic drug monitoring (TDM) is recommended and routinely conducted [5, 6]. However, since TDM may be carried out only after therapy initiation, the starting doses must be computed based on the estimated volume of distribution (Vd) or clearance (CL) for dose (D) or dosing interval (DI), respectively [7, 8]. Critically ill patients are highly heterogeneous population. Pathophysiologic alterations can significantly affect pharmacokinetics (PK) of drugs [9], which may be highly clinically relevant in case of narrow therapeutic index compounds including amikacin. Due to the potential changes in drug disposition, the dosing estimated on the basis of population PK may not be accurate and possible individualization based on easily accessible patients´ characteristics, which could serve as biomarkers for dose adjustments, may be beneficial.

Amikacin is a hydrophilic compound that is distributed primarily into extracellular water as reflected in its Vd of 0.25 $L.kg^{-1}$ [10]. Vd is a parameter that is related to structural aspects of the body, therefore the most frequent is D calculations based on body weight (BW) [11]. Besides total BW, alternate weight descriptors have been developed to attenuate the overexposure of drugs that are dosed according to BW in obese patients, namely ideal body weight (IBW), adjusted body weight (ABW), and lean body weight (LBW) [12]. Another body size descriptor is body surface area (BSA), which considers both BW and height in its derivations. BSA has been widely used in clinical practice to calculate doses in chemotherapy [13].

The dosage of amikacin for once-daily administration has not been robustly determined; the widely used doses usually ranged from 11 to 30 $mg.kg^{-1}$ [14]. The originator´s summary of product characteristics (SmPC) currently recommends amikacin total daily doses of 15 $mg.kg^{-1}$ in patients with normal renal functions. The SmPC further recommends adjusting the dosage to ABW in obese patients.

Since aminoglycosides are eliminated exclusively by renal glomerular filtration as intact compounds, its dosing regimen should be altered in patient with impaired renal functions. Some studies have reported D de-escalation corresponding with reduced renal function, thereby allowing the patient to be maintained on a 24 h dosing regimen, while others have chosen a fixed dose and extended the DI in response to variations in renal function. If the principles of high-dose and less frequent aminoglycoside dosing therapy should be followed, it would seem more appropriate to maintain a fixed dose and lengthen the interval for patients with decreased renal function [14]. Most guidelines that recommend reducing the initial aminoglycoside dose in patients with impaired renal function suggest using the Cockroft-Gault (C-G) equation to estimate creatinine clearance as a surrogate for glomerular filtration [15]. Two newer equations, the Modification of Diet in Renal Disease (MDRD) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), have been introduced to improve glomerular filtration rate estimations [16, 17]. There is only a very sparse data about predictive value of the MDRD and CKD-EPI equations to estimate amikacin CL or its dosing. Some studies showed comparable or better predictive performance of C-G than MDRD [18, 19]. Pai et al. have reported that the CKD-EPI best predicts aminoglycoside clearance [20], but this study included only patients who received gentamicin or tobramycin. Only one study by Lim et al. have described CKD-EPI creatinine clearance as the best predictor of amikacin clearance [15].

The aim of this study was to identify variables affecting amikacin pharmacokinetics in critically ill adult patients treated with once-daily amikacin regimen, and subsequently to propose optimal initial dosing based on these relationships. In addition, we estimated the proportion of patients in whom this setting shall be accurate.

Materials and methods:

Study design

A retrospective observational clinical PK study was conducted in adult patients who were admitted to the ICU at the General University Hospital in Prague between September 2015 and December 2016 and who were treated with amikacin administered once-daily. Patients meeting the following criteria were included: age ≥ 18 years; not eligible for dialysis, amikacin treatment for at least 3 days, and having amikacin serum concentration measured within the first 3 days of therapy. Since the study involved only retrospective analysis of routinely obtained clinical data collection, formal approval and informed patient consent is not required. Our study follows the principles of the Declaration of Helsinki.

Data collection

Clinical records of enrolled patients were reviewed to collect information concerning gender, age, height, BW, creatinine and amikacin serum levels, as well as amikacin dosing and administration times.

Creatinine levels were measured using Jaffe photometric method without deproteinization on Modular analyzer (Roche Diagnostics, Basel, Switzerland), while amikacin serum concentrations were measured by a turbidimetric inhibition immunoassay (Beckman Coulter, Inc., Brea, USA).

For each patient, body mass index, Du Bois BSA, IBW, ABW, and LBW were estimated according to standard formulas [12]. Creatinine clearance values were computed according to the Chronic Kidney Disease Epidemiology Collaboration ($CrCL_{CKD-EPI}$) [17], Modification of Diet in Renal Disease ($CrCL_{MDRD}$) [16], and Cockroft-Gault ($CrCL_{C-G}$) [21] formulas.

Pharmacokinetic analysis

Individual PK parameters – Vd, CL, half-life (T1/2), and elimination rate constant (K_e) were calculated using one-compartmental PK model based on individual demographic, clinical data and recorded amikacin plasma levels using MWPharm^{++} software (MediWare, Prague, Czech Republic). The population PK model for amikacin was individualized to maximize fitting of the simulated PK profile curve with recorded drug concentration points in each patient.

Dose analysis

Optimal D normalized per BW, ABW, LBW, and BSA, respectively were calculated for each patient based on individual Vd values using formulas (1)-(4):

(1) D_{BW} (mg.kg^{-1}) = Vd (L.kg^{-1}) × 50 (mg.L^{-1}) ÷ BW (kg),

(2) D_{ABW} (mg.kg^{-1}) = Vd (L.kg^{-1}) × 50 (mg.L^{-1}) ÷ ABW (kg),

(3) D_{LBW} (mg.kg^{-1}) = Vd (L.kg^{-1}) × 50 (mg.L^{-1}) ÷ LBW (kg),

(4) D_{BSA} (mg.m^{-2}) = Vd (L.kg^{-1}) × 50 (mg.L^{-1}) ÷ BSA (m^2).

The value of 50 mg.L^{-1} was selected as the target value for amikacin peak concentration.

Subsequently, the maximum amikacin serum concentrations after median D normalized per BW, ABW, and BSA, respectively were simulated in each patient using formulas (5)-(8):

(5) $Cpl\ (mg.L^{-1}) = median\ D_{BW}\ (mg.kg^{-1}) \times BW\ (kg) \div Vd\ (L)$,

(6) $Cpl\ (mg.L^{-1}) = median\ D_{ABW}\ (mg.kg^{-1}) \times ABW\ (kg) \div Vd\ (L)$,

(7) $Cpl\ (mg.L^{-1}) = median\ D_{LBW}\ (mg.kg^{-1}) \times LBW\ (kg) \div Vd\ (L)$

(8) $Cpl\ (mg.L^{-1}) = median\ D_{BSA}\ (mg.m^{-2}) \times BSA\ (m^2) \div Vd\ (L)$.

Amikacin serum concentrations after fixed dose of 1000 mg were also simulated in each patient using formula (9):

(9) $Cpl\ (mg.L^{-1}) = 1000\ (mg) \div Vd\ (L)$.

Dosing interval analysis

Optimal DI were calculated for each patient based on individual amikacin K_e values using formula (10):

(10) $DI\ (h) = (\ln C_{max1000} - \ln 2.5) \div K_e\ (h^{-1})$,

where $C_{max1000}$ is the maximum achieved amikacin concentration after administration of fixed dose of 1000 mg calculated for each patient according formula 9); the value of 2.5 $mg.L^{-1}$ was selected as the midpoint of target trough concentration range (0-5 $mg.L^{-1}$).

Subsequently, patients were stratified into four groups according to their DI: DI = 0-30 h in group 1 (amikacin administration every 24 h), DI = 31-42 h in group 2 (amikacin administration every 36 h), DI = 43-54 h in group 3 (amikacin administration every 48 h), and DI > 54 h in group 4 (once-daily amikacin not recommended).

Statistical analysis

Descriptive parameters medians and interquartile range (IQR) were calculated using MS Excel 2010 (Microsoft Corporation, Redmond, USA). The 95% confidence intervals (CI) for medians were calculated by Bonett & Price method [22].

Linear regression models were used to evaluate the relationships between amikacin Vd and body size descriptors (BW, IBW, ABW, LBW, and BSA) or the relationship between amikacin CL and creatinine clearance values calculated according to particular formulas (CKD-EPI, MDRD, C-G).

One phase exponential decay nonlinear regression model was used to describe relationship between optimal DI and CKD-EPI creatinine clearance.

All regression models were performed using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

Results:

Fifty-three patients were enrolled to the study (27 males, 26 females). Demographic and clinical characteristics of the patients are summarized in Table 1. Initial amikacin once-daily dose ranged between 500 and 1500 mg (7-20 $mg.kg^{-1}$). Dosing interval ranged between 24 and 87 hours.

Totally 134 amikacin plasma levels for PK analysis were obtained (1-7 concentration points per patient). PK analysis results are summarized in Table 2.

Linear regression models showed the best prediction of amikacin Vd by BSA (Figure 1), but BW, ABW and LBW were also significantly related. IBW was not a significant covariate of amikacin Vd ($r^2 = 0.0649$, $P = 0.0657$).

Median of optimal amikacin dose was 1027 (IQR: 882-1127) mg. Medians of optimal amikacin dose normalized per BW, ABW, LBW, and BSA were 13 $mg.kg^{-1}$, 14 $mg.kg^{-1}$, 19 $mg.kg^{-1}$, and 517 $mg.m^{-2}$, respectively.

The estimated rates of achievement of the target range for the simulated amikacin peak plasma concentrations, when the patients received 13 mg per kg of BW, 14 mg per kg of ABW, 19 mg per kg of LBW, 517 mg per m^2 of BSA, and fixed dose of 1000 mg are summarized in Table 3. D based on BSA, ABW, and LBW led to simulated amikacin peak plasma concentrations achieving the target range of 35-65 $mg.L^{-1}$ in more than 90% of subjects, which was numerically slightly better than when using other D estimations

The $CrCL_{CKD-EPI}$ was the most predictive for the amikacin CL based on linear regression models (Figure 2), but the other estimations $CrCL_{MDRD}$ and $CrCL_{C-G}$ were also significantly related to amikacin CL.

Calculated DI after the fixed D of 1000 mg ranged from 7 to 403 h and exponentially correlated with $CrCL_{CKD-EPI}$ (Figure 3). Regression exponential curve was formulated as shown in formula (11):

(11) $$DI\ (h) = 228.7 \times e^{-3.08 \times \text{CKD-EPI creatinine clearance (mL.s-1)}} + 15.84.$$

When we stratified DI estimated from CKD-EPI creatinine clearance into four groups as described in DI calculated from individual pharmacokinetics, calculated and estimated DI

consensus occurred in 66% of subjects. In 21% of patients, the estimated DI was longer than the calculated, while it was shorter in 13% of cases.

Discussion:

This study was conducted to describe clinically usable tools that could allow prediction of the best possible initial amikacin doses for each individual patient.

We focused on two theoretically expected determinants of amikacin PK dispositions: body size descriptors for amikacin Vd and creatinine clearance estimations for amikacin CL.

Many methods for measuring weight and body size have been proposed for accurate antimicrobial dosing, especially in obese patients [23]. In our study population, 21% of patients were obese (body mass index ≥ 30 $kg.m^{-2}$). For lipophilic drugs, which are extensively distributed into tissues including body fat, the most relevant size descriptor for Vd appears to be total BW, while ABW and LBW are suggested for hydrophilic agents as these have limited distribution to adipose tissues [23]. IBW was derived from insurance data collected by the Metropolitan Life Insurance Company of New York [13]. Since it relates body size to mortality and its value is unrelated to real BW, extrapolation of its use to estimate drug dosing is of questionable merit. It does not seem biologically plausible, that all patients of the same height should receive the same dose. LBW is equal to BW without adipose tissue. It was derived from fractional fat mass, which was initially computed to describe the increasing prevalence of obesity in the UK [13]. Although the original purpose was to relate patient size to epidemiological trends in morbidity and mortality, LBW is a potentially useful predictor of the PK behaviour of hydrophilic drugs. ABW was the first weight descriptor specifically developed for the use in PK experiments as a part of aminoglycosides dosing analysis, where some proportion of excess real weight above IBW was added to IBW [13, 24]. Du Bois formula was derived based on the assumption that both BW and height were related to BSA. Combinations of these known variables were then regressed against real BSA, which was identified from series of anatomical measurements. Additional constants in the computation were then determined by graphical interpolation [13]. Since it considers both BW and height in its derivation, BSA might be better predictor of Vd than only BW descriptors.

Our analysis indicates that these theoretical assumptions may translate into the clinical praxis, since BSA was shown as the most accurate predictor of amikacin Vd, although the performance of ABW, which was specifically developed for dosing of aminoglycosides, was irrelevantly lower. BW and LBW were also significantly predictive for amikacin Vd. Similar

proportions of patients achieving the target C_{max} when D were normalized per BSA, ABW and LBW. Fixed dose of 1000 mg led to numerically slightly lower rate of achievement target C_{max}, but the difference was not statistically significant and the absolute difference in success rates was less than 10%. Therefore fixed amikacin dose of 1000 mg seems to be optimal for the easiness of use in clinical settings.

Dosage adjustment in patients with renal impairment is important for renally excreted antimicrobials such as amikacin. Few formulas are available for renal function assessment, such as the CKD-EPI, MDRD, and C-G equations. The C-G equation was the most frequently used method for dosing adjustments of many drugs. Most guidelines recommend this formula also for estimating aminoglycoside dosing, but the C-G formula is no longer recommended for clinical use because it has not been expressed using standardized creatinine values. The experience with other creatinine clearance estimations is very limited with regards to amikacin dosing. MDRD equation was developed on the basis of a large study evaluated the effect of dietary protein intake on the rate of renal disease progression [16]. However, this equation had limitation that includes only patients with chronic kidney disease. Therefore, the same authors attempted to create a new equation that would be applicable for healthy population. The result was a CKD-EPI equation which is currently considered as the best method for glomerular filtration estimation [17].

In our analysis, the CKD-EPI formula has shown the most accurate prediction for amikacin CL and dosing. Estimations based on MDRD and C-G methods have indicated numerically less optimal dose predictions, although the differences have not been significant. The slightly worse performance may be due to heterogeneity of our study population in renal function status and BW, as MDRD method is applicable primarily on chronic kidney disease subjects and C-G formula includes BW, which can lead to distortion of resulting creatinine clearance values in obese patients.

There were 5 patients, whose demographic characteristics are probably significantly affecting the creatinine clearance calculations. Three of these points represent malnourished patients with decreased creatinine levels because of decreased muscle mass, while two patients represent morbidly obese patients in which the total estimated creatinine clearance is increased due to high body surface area. When we excluded these five patients (corresponding respective $CrCL_{CKD-EPI}$, CL pairs 1.48, 0.39; 1.53, 0.53; 1.78, 0.43; 2.14, 0.70; and 1.94, 0.65 in linear regression model with $CrCL_{CKD-EPI}$ – Fig. 2A) we observed strong linear relationship (r^2 = 0.8008, 0.7700, and 0.8167 for $CrCL_{CKD-EPI}$, $CrCL_{MDRD}$, and $CrCL_{C-G}$, respectively). As expected, exclusion of these outlying patients leads to decreased differences

in prediction performance of particular formulas and C-G formula then compares with CKD-EPI. It confirms the MDRD and C-G susceptibility to distortion due to patients´ characteristics heterogeneity. However, our study population represents the real life patient group that is currently indicated for amikacin treatment with its inherent heterogeneity of demographic as well as medical history characteristics. Therefore, we consider CKD-EPI as the best method for amikacin DI prediction in general adult population.

The DI calculation using the following formula has resulted in optimal PK results: DI (h) = $228.7 \times e^{-3.08 \times \text{CKD-EPI creatinine clearance (mL.s-1)}} + 15.84$. However, since the practical utility of such an equation is very limited, we propose DI nomogram based on this formula that could be easily used in clinical settings (Figure 3). It should be noted that patients with severe renal insufficiency (dosing interval more than 48 h) are not appropriate candidates for once-daily dosing, since this dosing regimen has not been well studied in this population [25].

Although our study was relatively small, we believe, that our exploratory data can be used as a basis for practical tool to predict optimal initial dosing in ICU patients treated with once-daily amikacin. Our study was based on objective PK data derived from the hospital medical records system. Therefore the retrospective nature of our work shall not impact on the validity of the results. However, the results of our exploratory study should be confirmed in a prospectively conducted trial.

In conclusion, we have shown that amikacin Vd is well described by BSA, while amikacin CL is predicted by $CrCL_{CKD-EPI}$. It is estimated that 91% of patients achieve the target amikacin peak concentrations after administration of 517 $mg.m^{-2}$ dose, while the estimated achievement rate following 1000 mg fixed dose was 81%. Dosing interval estimation based on $CrCL_{CKD-EPI}$ was accurate in 66% simulations. With respect to high variability of measured amikacin PK parameters, TDM shall follow the treatment initiation with the estimated dosing.

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Table 1: Demographic and clinical data

	Median	IQR	Min	Max
Age (years)	70	60-76	38	92
Weight (kg)	74	68-89	33	140
Height (cm)	174	167-175	150	187
BMI ($kg.m^{-2}$)	25.5	22.9-29.4	13.6	54.7
BSA (m^2)	1.87	1.77-2.09	1.24	2.49
IBW (kg)	66	60-71	43	81
ABW (kg)	69	66-80	43	99
LBW (kg)	53	47-61	26	80
SCr ($\mu mol.L^{-1}$)	137	84-176	28	621
$CrCL_{CKD-EPI}$ ($mL.s^{-1}$)	0.79	0.52-1.32	0.12	2.45
$CrCL_{MDRD}$ ($mL.s^{-1}$)	0.77	0.54-1.29	0.12	3.23
$CrCL_{C-G}$ ($mL.s^{-1}$)	0.72	0.47-1.17	0.10	3.65

Legend:

BMI is body mass index

BSA is body surface area

IBW is ideal body weight

ABW is adjusted body weight

LBW is lean body weight

SCr is creatinine serum concentration

$CrCL_{CKD-EPI}$ is CKD-EPI creatinine clearance

$CrCL_{MDRD}$ is MDRD creatinine clearance

$CrCL_{C-G}$ is Cockroft-Gault creatinine clearance

IQR is interquartile range

Table 2: Amikacin pharmacokinetic data

	Median	IQR	Min	Max
Vd (L)	20.53	17.63-22.53	12.47	50.79
Vd ($L.kg^{-1}$)	0.26	0.23-0.29	0.15	0.51
CL ($L.h^{-1}$)	1.730	1.1800-2.940	0.192	9.360
CL ($L.h^{-1}.kg^{-1}$)	0.024	0.014-0.040	0.002	0.121
T1/2 (h)	8.5	4.5-12.0	1.6	107.5
K_e (h^{-1})	0.082	0.058-0.154	0.006	0.447

Vd is volume of distribution

CL is total clearance

T1/2 is elimination half-life

K_e is elimination rate constant

IQR is interquartile range

Table 3: Proportion of patients achieving simulated peak plasma levels of 35-65 mg.L^{-1}, < 35 mg.L^{-1}, or > 65 mg.L^{-1} and median simulated peak plasma levels after doses calculated using real body weight (BW), adjusted body weight (ABW), lean body weight (LBW), body surface area (BSA) or fixed dose of 1000 mg

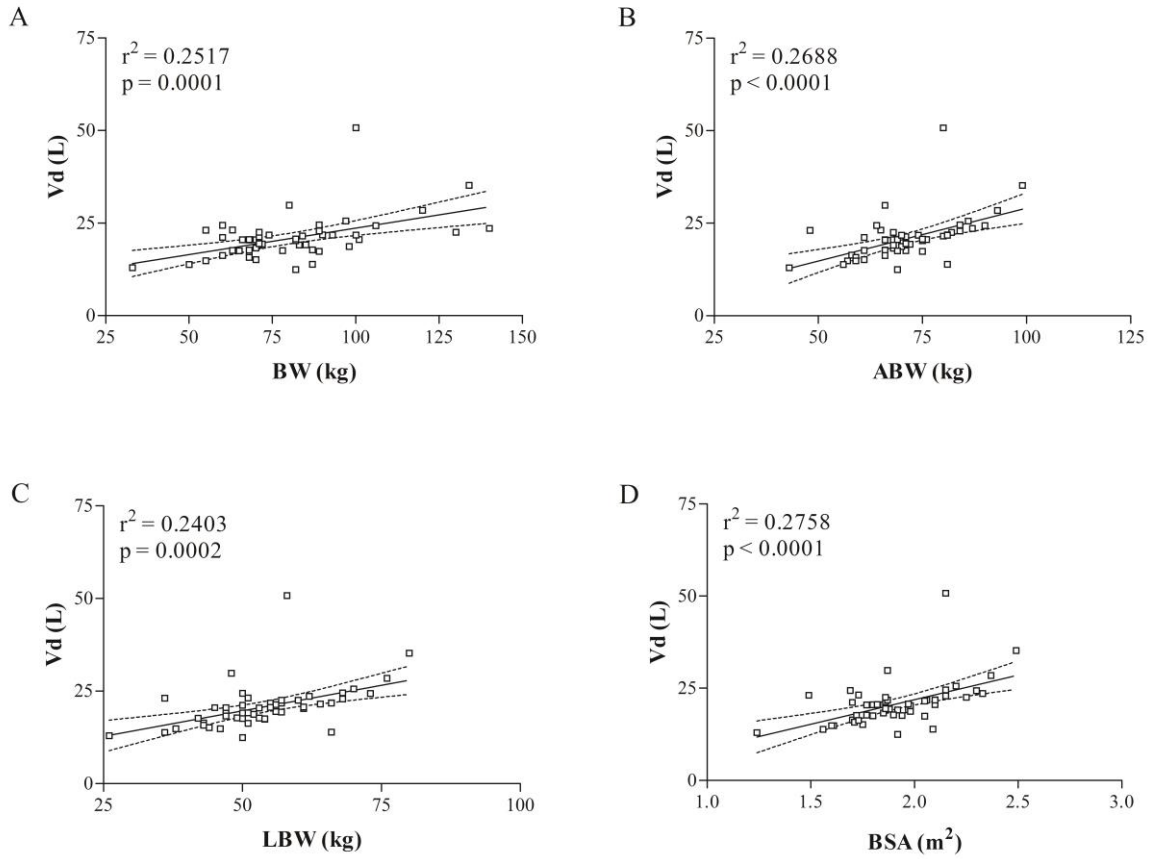
Dose	n (%); N = 53			Median (95% CI) (mg.L^{-1})
	35-65 mg.L^{-1}	< 35 mg.L^{-1}	> 65 mg.L^{-1}	
13 mg per kg of BW	44 (83.0)	4 (7.5)	5 (9.4)	50 (47-53)
14 mg per kg of ABW	48 (90.6)	3 (5.7)	2 (3.8)	52 (50-53)
19 mg per kg of LBW	48 (90.6)	3 (5.7)	2 (3.8)	51 (49-52)
517 mg per m^2 of BSA	48 (90.6)	3 (5.7)	2 (3.8)	50 (49-51)
1000 mg	43 (81.1)	3 (5.7)	7 (13.2)	49 (46-52)

n is number of simulated amikacin peak plasma levels in each interval

N is total number of simulated amikacin peak plasma levels

CI is confidence interval for median

Figure 1: Amikacin volume of distribution – body size descriptors relationships



A: Relationship between amikacin volume of distribution (Vd) and real body weight (BW)

B: Relationship between amikacin volume of distribution (Vd) and adjusted body weight (ABW)

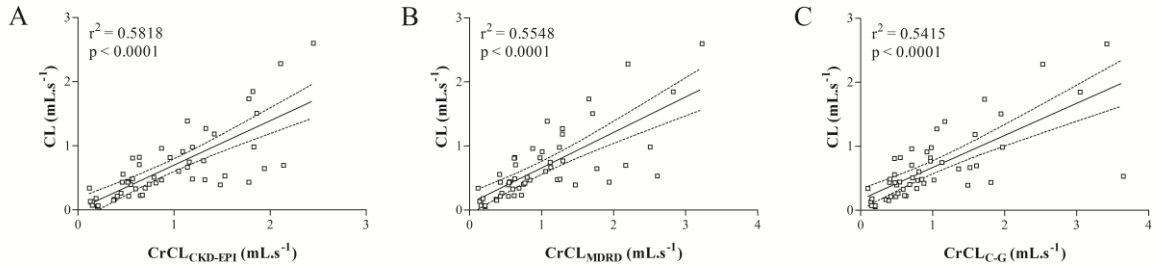
C: Relationship between amikacin volume of distribution (Vd) and lean body weight (LBW)

D: Relationship between amikacin volume of distribution (Vd) and body surface area (BSA)

r^2 is coefficient of determination

p is p-value

Figure 2: Amicacin clearance - creatinine clearances relationships



A: Relationship between amikacin clearance (CL) and CKD-EPI creatinine clearance ($CrCL_{CKD-EPI}$)

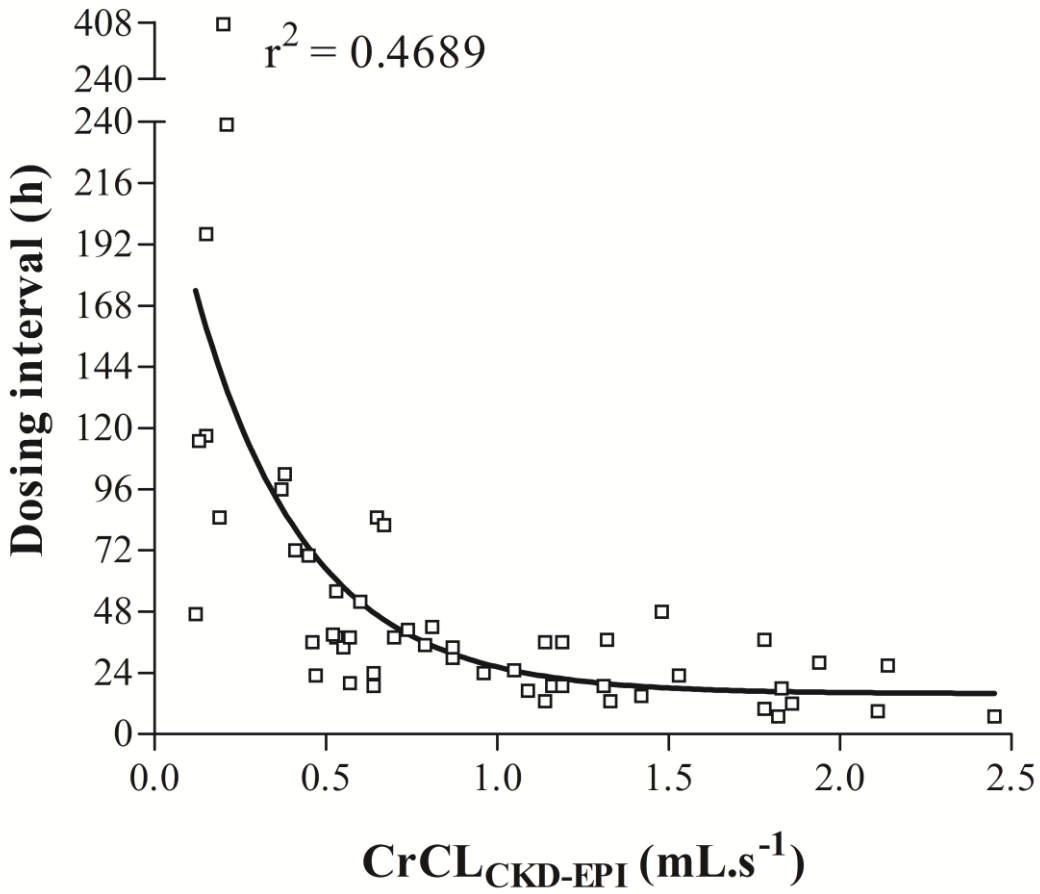
B: Relationship between amikacin clearance (CL) and MDRD creatinine clearance ($CrCL_{MDRD}$)

C: Relationship between amikacin clearance (CL) and Cockcroft-Gault creatinine clearance ($CrCL_{C-G}$)

r^2 is coefficient of determination

p is p-value

Figure 3: Nomogram for calculation of dosing interval after amikacin administration of 1000 mg to reach trough concentration 0-5 mg.L^{-1} based on CKD-EPI creatinine clearance ($CrCL_{CKD-EPI}$)



r^2 is coefficient of determination

Příloha 4

ŠÍMA, M., POKORNÁ, P., HARTINGER, J. & SLANAŘ, O. 2017. Estimation of initial phenobarbital dosing in full-term asphyxiated neonates. *J Clin Pharm Ther*, v recenzním řízení.

Estimation of initial phenobarbital dosing in full-term asphyxiated neonates with hypoxic ischemic encephalopathy

Short title:

Estimation of phenobarbital dosing

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Conflicts of interest:

No conflict of interests have been declared.

Summary:

What is known and objective: Phenobarbital is the first-line treatment of seizures in asphyxiated neonates, however, due to the high pharmacokinetic variability in this population there is no consensus on the optimal dosage regimen. This study was conducted to identify variables that affect phenobarbital fate during routine clinical care, and then to evaluate the dosage schedule that could be applied in full-term asphyxiated neonates with respect to achieving the target therapeutic range.

Methods: Phenobarbital pharmacokinetics was calculated based on serum concentrations measurements using one-compartmental model. Body weight, body surface area, gestational age, creatinine clearance, total bilirubin, alanine aminotransferase, aspartate aminotransferase, international normalized ratio, Apgar scores, umbilical cord arterial pH and base excess were explored as covariates in linear regression models. Based on this analysis, phenobarbital loading and maintenance dose regimen were projected.

Results and discussion: In the whole study population (n = 36), phenobarbital volume of distribution, clearance, and half-life median (interquartile range) values were 1.50 (1.19-2.05) L, 0.0142 (0.0121-0.0163) L/h, and 75.1 (60.2-103.3) h, respectively. The drug volume of distribution was associated with body weight, length and body surface area, while clearance was not in relationship with any explored features. Weight-normalized loading dose of 15

mg/kg and fixed daily maintenance dose of 9 mg proved to be optimal in our study population to reach phenobarbital therapeutic range.

What is new and conclusions: This study presents basis for phenobarbital initial dosing in full-term asphyxiated neonates during first week of life. Phenobarbital weight-normalized loading dose of 15 mg/kg lead to simulated target peak concentrations in 72% of neonates, weight-normalized maintenance dose of 3 mg/kg lead to steady state within therapeutic window in the same proportion of patients.

Key words:

Asphyxia, dosing regimen, neonates, pharmacokinetics, phenobarbital

What is known and objective:

Phenobarbital remains the most common anticonvulsive drug for control and treatment of seizures in asphyxiated neonates with hypoxic-ischemic encephalopathy.[1]

There is no clear consensus recommendation for target therapeutic levels. Jalling states the approximate range of phenobarbital concentration when convulsions ceased 12-30 mg/L.[2] Some studies targeted at range of 10-30 mg/L,[3, 4] others 15-40 mg/L.[5-8] Based on these data phenobarbital levels between 10 and 40 mg/L can be considered likely to be effective. Routine therapeutic drug monitoring (TDM) is recommended during phenobarbital treatment in order to maximize efficacy and safety.[9]

TDM-based dose adjustment is feasible just after pharmacotherapy introduction but initial dosage is necessary to be estimated using the other tools. Loading (LD) and maintenance dose (MD) can be calculated from the volume of distribution (Vd) and total drug clearance (CL), respectively.[10] Postnatal changes in body composition and maturation can significantly alter pharmacokinetics of druds.[11] Due to the potential changes in drug disposition, the dosing estimated on the basis of population pharmacokinetics may not be accurate. Individualization based on easily accessible patients´ characteristics, which could serve as biomarkers for dose adjustments, may be beneficial.

Most frequently considered covariates for phenobarbital pharmacokinetics are body weight (BW) and gestational age (GA) or postnatal age in preterm and term neonates.[3, 12, 13] In addition, Touw et al. have also described association of height and body surface area (BSA) with Vd and CL, respectively.[3] However, other studies indicated inconsistent data, making any conclusions on valid covariates for the drug dosing impossible. Pitlick et al. observed no correlation between Vd and GA, while CL increased during the first month after birth.[14] Grasela et al. have shown that neither Vd nor CL was affected by GA.[15] Gilman et al. have found no correlation between half-life (t1/2) and either gestational or postnatal age.[16] The

impact of asphyxia has also been covered. Gal et al. have reported CL reduction in asphyxiated neonates,[17, 18] while Grasela et al. have noticed no effect on CL, but increase in Vd in the presence of asphyxia.[15]

Phenobarbital dosing based on BW is usually used in clinical practice: the initial LD of 15-20 mg/kg is given intravenously (sequential bolus doses of 5-10 mg/kg up to serum levels of 40 mg/L may be administered if seizures persist);[19] the initial MD of 3-4 mg/kg per day is recommended.[20] Subsequently, dosage should be adjusted according to the achieved phenobarbital serum levels and clinical response.

The aim of this study was to describe relationships between individual phenobarbital pharmacokinetic parameters and patients´ demographic or clinical data in order to suggest optimal initial phenobarbital dosing regimen prior to TDM in full-term asphyxiated neonates treated with intravenous phenobarbital. Subsequently, we tried to estimate the proportion of patients in whom the proposed dosing would be accurate.

Methods:

Study design

A retrospective observational pharmacokinetic study was conducted among full-term neonates with moderate to severe asphyxia who were admitted to the Neonatal Intensive Care Unit of the General University Hospital in Prague and treated for perinatal asphyxia and hypoxic ischemic encephalopathy (HIE) with intravenous phenobarbital from the first day of life between August 2007 and March 2013. Patients meeting the following criteria were included: 1) GA $\geq$ 37 weeks; 2) not receiving dialysis; 3) having at least two phenobarbital levels measured in the course of pharmacotherapy. Approval of the study was issued by the Ethics Committee of the General Faculty Hospital, in Prague.

Perinatal asphyxia was evaluated using AAP criteria 1996,[21] i.e. presence of profound metabolic or mixed acidemia in umbilical cord blood, persistence of low Apgar scores, amplitude-integrated electroencephalography (aEEG) criteria by Hellstrom-Westas,[22] and biochemistry examinations. The criteria of severe asphyxia were cord or an arterial pH < 7.1 or base deficit of 12 or more within 60 minutes of birth and Apgar score ≤5 at 10 minutes.

Hypoxic ischemic encephalopathy was defined based on Thompson score[23] ≥7 within 6 hours after birth or hypoxic insult and the severity of HIE was assessed using Sarnat stage[24] 1 (mild), stage 2 (moderate), and stage 3 (severe). LD of Phenobarbital (Luminal 200 mg/mL inj sol 5×1mL, Desitin Arzneimittel GmbH, Germany) was administered over 5 minutes in neonates diagnosed with moderate and severe HIE at 6 hours after hypoxemic insult were administered to achieve clinical and/or aEEG response. The patients received MD divided in two daily doses based on international guidelines.[25] Additional anticonvulsive co-medication could be used based on clinical or aEEG seizures (additionally phenytoin, midazolam or clonazepam).

Data collection

Clinical records of the patients were reviewed to collect the following data: gender, GA, length, BW, serum creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), Apgar scores at 1, 5, and 10 minutes, umbilical cord arterial blood pH (pH), and base excess (BE). In addition, serial phenobarbital serum levels (sampling times included), phenobarbital dosing and administration times were recorded. Samples were collected in the range of 2-5 days (median 3.5 days) for each patient. Serum creatinine levels were measured at the time of the first phenobarbital concentration.

For each patient, BSA according to Meban formula (BSA_{Meban}) and creatinine clearance value according to Schwartz formula ($CrCL_{Schwartz}$) were estimated.[26, 27]

Pharmacokinetic analysis

Phenobarbital serum concentrations were measured using a fluorescence polarization immunoassay on AxSYM analyser (Abbott Laboratories, Abbott Park, USA).

Individual pharmacokinetic parameters – Vd, CL and t1/2 were calculated in a one-compartmental pharmacokinetic model based on individual demographic, clinical data and recorded phenobarbital serum levels using MWPharm^{++} software (MediWare, Prague, Czech Republic). The phenobarbital population pharmacokinetic one-compartmental model was individualized to maximize fitting of the simulated pharmacokinetic profile curve with recorded concentration points in each patient. The fitting was performed using Marquardt nonlinear least square method.

Loading dose analysis

Optimal fixed and weight-normalized loading doses were calculated for each patient based on individual values of Vd using following formulae: fixed LD (mg) = Vd (L) × C_{peak} (mg/L) and weight-normalized LD (mg/kg) = fixed LD (mg) ÷ BW (kg), where C_{peak} is 30 mg/L as an optimal phenobarbital peak concentration. Subsequently, phenobarbital peak concentrations after median fixed and weight-normalized LD were simulated for each patient using following formulae: C_{peak} (mg/L) = median fixed LD (mg) ÷ Vd (L) and C_{peak} (mg/L) = [median weight-normalized LD (mg/kg) × BW (kg)] ÷ Vd (L).

Maintenance dose analysis

Optimal fixed and weight-normalized daily maintenance doses were calculated for each patient based on individual values of CL using following formulae: fixed MD (mg) = CL (L/h) × C_{ss} (mg/L) × 24 (h) and weight-normalized MD (mg/kg) = fixed MD (mg) ÷ BW (kg), where C_{ss} is 25 mg/L as a midpoint of target therapeutic range (10-40 mg/L). Subsequently, phenobarbital steady-state serum concentration after median fixed and weight-normalized MD were simulated for each patient using following formulae: C_{ss} (mg/L) = median fixed MD (mg) ÷ [CL (L/h) × 24 (h)] and C_{ss} (mg/L) = [median weight-normalized MD (mg/kg) × BW (kg)] ÷ [CL (L/h) × 24 (h)].

Statistical analysis

Medians and interquartile ranges (IQR) were calculated using MS Excel 2010 (Microsoft Corporation, Redmond, USA). The 95% confidence intervals (CI) for medians were calculated by Bonett & Price method.[28]

Linear regression models were used to evaluate the relationships of phenobarbital primary pharmacokinetic parameters (Vd, CL) and patients´ demographic/clinical features (BW, length, GA, BSA_{Meban}, serum creatinine, $CrCL_{Schwartz}$, total bilirubin, ALT, AST, INR, Apgar scores, pH, BE) using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

Results:

Thirty-six neonates were enrolled to the study (21 males, 15 females). Demographic and clinical characteristics of the patients are summarized in Table 1. Phenobarbital loading dose ranged from 10 to 120 mg (5-34 mg/kg) and the daily maintenance dose ranged between 8 and 20 mg (2-8 mg/kg) based on clinical and aEEG response.

Pharmacokinetic parameters were calculated over a period of 2-8 days (median was 5 days). Totally 108 phenobarbital serum levels for pharmacokinetics analysis were obtained

(2-5 concentration points per patient). Phenobarbital Vd, CL, and t1/2 median (IQR) values in our study population were 0.49 (0.38-0.59) L/kg, 0.0045 (0.0034-0.0055) L/h/kg, and 75.1 (60.2-103.3) h, respectively.

Linear regression models showed significant relationships between Vd (L) and BW, length, and BSA_{Meban} (r^2 = 0.3097, 0.1593, and 0.3112, respectively), while CL (L/h) was not related with either demographic or clinical features.

Median phenobarbital LD simulated from pharmacokinetic data was 44.9 (95% CI: 38.1-51.6) mg corresponding to the weight-normalized value of 14.7 (95% CI: 13.7-15.7) mg/kg. The rates of achievement the target peak serum concentrations following the simulated LD of 45 mg and weight-normalized LD of 15 mg/kg are summarized in Table 2. Weight-normalized LD was only insignificantly more accurate than the fixed dose. Median (IQR) serum levels after simulated LD in the group not reaching the lower limit of target concentrations (< 20 mg/L) were similar after fixed or weight-normalized doses reaching 17 (16-17) or 17 (16-19) mg/L, respectively. The respective values in the group exceeding the target therapeutic range (> 40 mg/L) were again very similar reaching 46 (43-50) or 46 (42-54) mg/L. In both dosing simulations only one phenobarbital serum level reached toxic zone > 60 mg/L, however numerical value of this concentration was considerably lower when dosing was weight-normalized (63 mg/L vs. 83 mg/L).

Median phenobarbital daily MD simulated from pharmacokinetic data was 8.5 (95% CI: 7.9-9.1) mg corresponding to the weight-normalized value of 2.7 (95% CI: 2.5-3.0) mg/kg, respectively. The rates of achievement the target steady-state serum concentrations following the simulated fixed MD of 9 mg and weight-normalized MD of 3 mg/kg are summarized in Table 2. Fixed MD was only insignificantly more accurate than the weight-normalized dose. In both dosage simulations no phenobarbital concentration was below the therapeutic window (< 15 $mg.L^{-1}$). The median (IQR) concentrations in the group exceeding

the target therapeutic range (> 35 mg/L) were again similar after the fixed or weight-normalized MD reaching 42 (39-51) or 43 (40-51) mg/L, respectively.

Discussion:

Phenobarbital is the first-line treatment of seizures in asphyxiated neonates, however, due to the high pharmacokinetic and pharmacodynamic variability in this population there is no consensus on the initial dosage regimen.

Theoretically plausible determinants of phenobarbital Vd and CL included in our study evaluations were BW, length, and BSA (as body size descriptors) or gestational age (representing maturation status), while creatinine clearance, total bilirubin, ALT, AST and INR (as laboratory indicators of renal and hepatic functional status) might relate with CL. In addition, we investigated association of phenobarbital pharmacokinetic parameters with Apgar scores, pH, and BE (as indicative parameters of asphyxia severity). Since the patients were all within the first week of life we did not include postnatal age in the analysis.

Phenobarbital dosing is commonly based on body weight in routine clinical use. However, we observed significant relationship only between Vd and BW, while CL did not relate with BW (Figure 1). BSA was associated with Vd similarly as BW (r^2 are 0.3112 and 0.3097, respectively) and with respect to ease of use we consider BW as optimal predictor of phenobarbital Vd. The patients´ BW ranged from 1.46 to 4.29 kg in our study group. In comparison, some studies that described relationship between BW and phenobarbital CL included patients with larger BW range (0.59-4.07 and 0.67-4.65 kg, respectively).[3, 12] This might be a possible explanation of unobserved BW-CL relationship in our study. On the other hand, a study of Shellhaas describes BW-CL linear relationship although this study population was similar to ours.[13] Moreover, we observed significant association between phenobarbital Vd and BW despite the same range of BW values. Therefore, we assume that phenobarbital

CL was likely truly BW-independent in our study. The frequently reported increase of CL with increasing BW can be attributed to developmental changes of the rapidly growing subjects occurring in parallel in the elimination functions and thus it can be assumed that BW serves as a marker for maturation in this patient population. Due to the small GA span in our study population (see below) GA-CL and hence BW-CL relationship did not reach statistical significance.

Various studies produced inconsistent results with regard to relation between phenobarbital pharmacokinetic parameters and maturation status. We observed no relation between Vd or CL and GA similarly to few other reports.[15, 16] This finding in our study is likely due to the small GA span in our study population (37-41 weeks) that makes the analysis of maturational changes in our study population unfeasible. Indeed, studies that showed significant relationship between GA and pharmacokinetic parameters enrolled study population of much higher GA span, while preterm neonates were identified as a subgroup largely affecting these analyses.[3, 12]

We observed no relationships between creatinine clearance, total bilirubin, ALT, AST or INR values and phenobarbital CL. This can be explained by multiple pathways involved in phenobarbital metabolism in the liver and simultaneous renal excretion of unchanged compound,[29] which minimizes possible impact of decreased elimination capacity of a single pathway/organ.

Phenobarbital pharmacokinetics has been previously reported to be affected by asphyxia.[15, 17, 18] Our study was conducted only in patients with moderate to severe asphyxia. The severity of asphyxia was not a significant covariate for phenobarbital pharmacokinetics in our study, but it was not sufficiently powered for this analysis. Our study also lacked a control (non-asphyxiated) group.

The phenobarbital therapeutic range was considered between 10 and 40 mg/L. When loading, we targeted to peak concentration of 30 ± 10 mg/L. The upper limit (40 mg/L) corresponds to the level with increased risk of adverse effects, while the lower limit (20 mg/L) was based on the consideration that in case of minimal phenobarbital t1/2 of 24 h, concentration at the end of dosing interval (maximum 24 h) shall be higher than 10 mg/L. During the maintenance dosing, we targeted to reach steady-state concentration of 25 ± 10 mg/L as a midpoint of therapeutic range.

Weight-normalized loading dose of 15 mg/kg and fixed daily maintenance dose of 9 mg were optimal in our study population. This finding is quite consistent with conclusions of the other studies except lack of MD normalization on BW.[19, 20, 30] Taking into account average birthweight of approximately 3 kg, fixed MD of 9 mg was roughly equivalent to weight-normalized MD of 3 mg/kg. Considering that superiority of fixed maintenance dose in our study could only be an artefact caused by relative homogeneity of our study population, we suggest to prefer weight-normalized maintenance dosing.

Our study enrolled relatively low number of patients, although it compares well with other previously published phenobarbital pharmacokinetic studies in asphyxiated neonates. Retrospective design should not impact the conclusions of the study, since it is based on objective pharmacokinetic, demographic and clinical data recorded in the Hospital Information System. However, the results of our exploratory study should be confirmed in a prospectively conducted trial. The proposed dosage is based only on the pharmacokinetic principles with the focus to achieving therapeutic levels. It should be noted that phenobarbital dosing must be also guided using pharmacodynamic principle, i.e. with respect to clinical and aEEG response.

What is new and conclusion:

We demonstrated that phenobarbital volume of distribution was associated with body weight, length, and body surface area, while clearance was not in relationship with any of the explored parameters in asphyxiated full-term neonates with HIE. We suggest weight-normalized loading dose of 15 mg/kg and weight-normalized initial maintenance dose of 3 mg/kg in asphyxiated full-term neonates. High variability of pharmacokinetic parameters points to necessity of subsequent dose adjusting and guiding using TDM.

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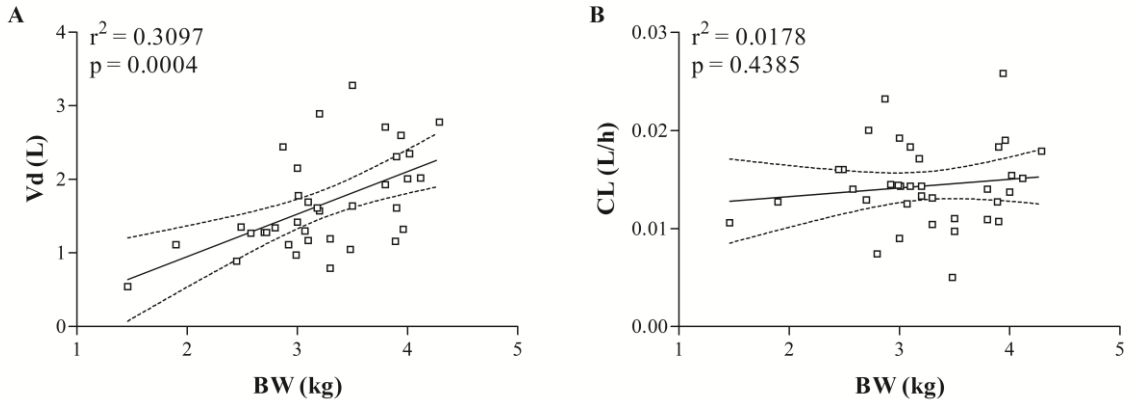
Table 1: Demographic and clinical data

	Median (IQR)
Gestational age (weeks)	40 (39-40)
Body weight (kg)	3.19 (2.91-3.82)
Length (cm)	50 (49-52)
Body surface area according Meban formula (cm^2)	2119 (1989-2365)
Serum creatinine (μmol/L)	67 (56-75)
Creatinine clearance according Schwartz formula (L/h)	0.2042 (0.1522-0.2635)
Total bilirubin (μmol/L)	37.6 (28.6-59.9)
Alanine aminotransferase (IU/L)	19.41 (15.88-30.00)
Aspartate aminotransferase (IU/L)	82.35 (65.29-150.00)
International normalized ratio	1.63 (1.35-2.07)
Apgar score at 1 min	2 (1-3)
Apgar score at 5 min	5 (3-7)
Apgar score at 10 min	7 (5-8)
Umbilical cord arterial blood pH	7.05 (6.80-7.18)
Base excess (mmol/L)	-6.9 (-13.9--3.0)

Table 2: Proportion of patients achieving simulated peak serum levels of 20-40 mg/L, < 20 mg/L, or > 40 mg/L and median simulated peak serum levels after fixed loading dose (LD) of 45 mg and after weight-normalized LD of 15 mg/kg, and proportion of patients achieving simulated steady-state serum levels of 15-35 mg/L, < 15 mg/L, or > 35 mg/L and median simulated steady-state serum levels after fixed maintenance dose (MD) of 9 mg and after weight-normalized MD of 3 mg/kg.

	n (%); N = 36			
P = 0.3222	20-40 mg/L	< 20 mg/L	> 40 mg/L	Median (IQR) (mg/L)
LD = 45 mg	21 (58)	8 (22)	7 (19)	30 (22-38)
LD = 15 mg/kg	26 (72)	3 (8)	7 (19)	31 (26-40)
P = 0.2454	15-35 mg/L	< 15 mg/L	> 35 mg/L	Median (IQR) (mg/L)
MD = 9 mg	31 (86)	0 (0)	5 (14)	27 (23-31)
MD = 3 mg/kg	26 (72)	0 (0)	10 (28)	28 (23-37)

Figure 1: Regression analysis between (A) phenobarbital volume of distribution (Vd), (B) phenobarbital clearance (CL) and body weight (BW)



Příloha 5

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Effect of Co-Medication on the Pharmacokinetic Parameters of Phenobarbital in Asphyxiated Newborns

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Summary

Phenobarbital is an anticonvulsive drug widely used in newborns with hypoxic-ischemic encephalopathy. The objective of our study was to describe possible effect of frequently co-administered medications (dopamine, dobutamine, norepinephrine, furosemide, phenytoin, and analgesics) on the phenobarbital pharmacokinetics in full term newborns with hypoxic-ischemic encephalopathy. Phenobarbital pharmacokinetic parameters (standardized intravenous loading dose was 10-20 mg/kg, maintenance dose 2-6 mg/kg/day) were computed using non-compartmental analysis. Co-medication was evaluated throughout the whole treatment period up to 5 days. Volume of distribution, clearance, and half-life median values (95 % CI) for phenobarbital in the whole study population (n=37) were 0.48 (0.41-0.56) l/kg, 0.0034 (0.0028-0.0040) l/h/kg, and 93.7 (88.1-99.2) h, respectively. Phenobarbital pharmacokinetic parameters were not significantly affected by vasoactive drugs (dopamine, dobutamine, and norepinephrine), furosemide, phenytoin, or analgesics. Furthermore, no dose-dependent alteration of phenobarbital pharmacokinetic parameters was noted for vasoactive medication at doses equivalent to cumulative vasoactive-inotropic score (area under the curve in a plot of vasoactive-inotropic score against time) 143.2-8473.6, furosemide at cumulative doses of 0.2-42.9 mg/kg, or phenytoin at cumulative doses of 10.3-46.2 mg/kg. Phenobarbital pharmacokinetics was not affected by investigated co-administered drugs used in newborns with hypoxic-ischemic encephalopathy in real clinical settings.

Key words

Phenobarbital • Pharmacokinetics • Drug interactions • Newborn • Asphyxia

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Introduction

Phenobarbital (PB) is an anticonvulsive drug used as a first line treatment option for control and treatment of seizures in asphyxiated newborns in case of hypoxic-ischemic encephalopathy (HIE) either under therapeutic whole-body hypothermia or without hypothermia (Hall *et al.* 1998). PB shows highly variable pharmacokinetics, especially distribution and elimination show high inter-individual variability. About 25 % of a PB dose is excreted unchanged, while the major part is metabolized by oxidation *via* 2C9 enzyme of cytochrome P450 (CYP). Additionally, CYP2C19, CYP2E1, and N-glucosidation contribute to the drug metabolism to a lesser extent (Kwan and Brodie 2004). PB pharmacokinetics in newborns is different as compared with the adult population; postnatal changes in body composition and maturation have been suggested to alter pharmacokinetics (Alcorn and McNamara 2003). Touw *et al.* (2000) described the main pharmacokinetic (PK)

parameters of PB in neonates as follows: volume of distribution normalized per kg of body weight (Vd) 0.71 (0.21) l/kg, clearance normalized per kg of body weight (CL) 0.0043 (0.0011) l/kg/h and half-life (T1/2) 107.0 (64.0) h. In theory, the drug disposition could also be affected by body temperature (Zanelli *et al.* 2011), although no clinically relevant effect of moderate therapeutic hypothermia on PB pharmacokinetics has been identified recently (Filippi *et al.* 2011, van den Broek *et al.* 2012, Shellhaas *et al.* 2013).

Since metabolism is the dominant elimination pathway, there is a risk of PK interactions with concomitantly administered drugs (Patsalos *et al.* 2008). Although there is a considerably wide armamentarium of drugs that are occasionally used at the pediatric/neonatal intensive care unit (PICU/NICU) departments of which co-administration with PB could result in a PK interaction affecting the PB concentrations, only few drugs/drug classes are often used. Among the frequently used co-medications there is a theoretical risk of PK interaction between PB and vasoactive drugs (dopamine, dobutamine, and norepinephrine) that could alter the PB clearance by possible changes in renal perfusion (Schetz 2002). Furosemide could alter the volume of distribution for PB by altered body water content in various compartments (O'Donovan and Bell 1989) and co-medication with inducers/inhibitors/competitive inhibitors (phenytoin, sufentanil, midazolam, and tramadol) of cytochrome P450 could alter the metabolic fate of PB in the organism.

This study builds upon our previous work, in which we analyzed the pharmacokinetics of PB in critically ill asphyxiated newborns with the aim to evaluate the role of covariates (age, disease, and therapeutic hypothermia) on the PB pharmacokinetics. The PK parameters in our study were not substantially different from those published previously in similar patient population (Touw *et al.* 2000), Vd 0.4941 (0.2439) l/kg, CL 0.0040 (0.0023) l/h/kg and T1/2 106.55 (59.07) h. However, therapeutic hypothermia did not significantly affect the PB pharmacokinetics in critically ill asphyxiated newborns.

The objective of this study was to describe possible effect of frequently co-administered medications (dopamine, dobutamine, norepinephrine, furosemide, phenytoin, midazolam, sufentanil, and tramadol) on the PB pharmacokinetics in full-term newborns with HIE.

Methods

Study design

This was a prospective open-label clinical study that included full term asphyxiated newborns (gestational age ≥ 37 weeks) with HIE treated with PB. The study was conducted at PICU/NICU of the Department of Pediatrics, General University Hospital and First Faculty of Medicine Charles University in Prague from January 2006 to December 2013. Approval of the study was provided by the Ethics Committee of the General Faculty Hospital, in Prague. Parents of newborns included in the study signed the written informed consent prior to enrollment into the study. Exclusion criteria were neonatal abstinence syndrome, intracranial hemorrhage, severe congenital abnormalities and encephalopathy due to other causes.

Standardized per protocol PB (Luminal inj., Desitin Arzneimitttel GmbH, Hamburg, Germany) dosing consisted from a loading dose of PB 10-20 mg/kg/dose intravenously (iv) administered in 15 min infusion followed by repeated loading doses of PB to a maximal daily loading dose of 40 mg/kg/day (Gal *et al.* 1982). Newborns without clinical or amplitude-integrated electroencephalography (aEEG) response (clinical or subclinical seizures) to the administration of a maximum loading dose of PB received either phenytoin (Epanutin inj., Hameln Pharmaceuticals GmbH, Hameln, Germany) loading dose of 15-20 mg/kg iv, followed by maintenance dosing of 2.5-4 mg/kg iv twice a day or midazolam (Midazolam Torrex inj., Chiesi Pharmaceuticals GmbH, Vienna, Austria) dose of 0.05-0.3 mg/kg iv as continuous infusion until the end of clinical or aEEG/subclinical seizures. The PB maintenance dose was 1-3 mg/kg iv administered in 15 min infusion twice a day (Fischer *et al*. 1981). Blood samples for PB levels monitoring were to be collected from an arterial line at 2-3, 24, 48, 72, and 96 h after PB loading dose.

Pharmacokinetic analysis

Plasma concentrations of phenobarbital (cPB) were measured using a fluorescence polarization immunoassay (FPIA, AxSYM Phenobarbital, Abbott laboratories, Abbott Park, USA) or by quantitative enzyme immunoassay (CEDIA® Phenobarbital II, Microgenics Corporation, Fremont, USA).

Individual PK parameters – Vd and elimination rate constant (Kel) were calculated in a non-compartmental PK model based on individual

demographic, clinical data and observed cPB using MWPharm 3.01 software (MediWare, Prague, Czech Republic). The PB population PK non-compartment model was individualized to maximize fitting of the simulated PK profile curve with observed concentration points in each patient. Other individual PK parameters – CL and T1/2 – were calculated using following formulae: CL = Kel*Vd and T1/2 = ln 2/Kel.

Evaluation of co-medication effect on the PB pharmacokinetics

Any used of co-medication, the time of drug administration, posology and dosing were recorded throughout the study. The primary evaluated co-medication were dopamine, dobutamine, norepinephrine, phenytoin, sufentanil, midazolam, tramadol and furosemide, while the other drugs were recorded for exploratory analyses only. To evaluate the cumulative effect of vasoactive compounds (dopamine, dobutamine, and norepinephrine) on the PB pharmacokinetics a standardized vasoactive-inotropic score (VIS) was used VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100*norepinephrine dose (μg/kg/min) (Kumar *et al*. 2014).

Both possible dose-dependent and dose-independent interactions between PB and the co-medication were evaluated. To detect the dose-dependent interactions, cumulative doses of co-medication within acute phase of treatment normalized per kg of body weight were used, while for dose-independent interactions any dosing of co-administered compound was considered.

Statistical analysis

Descriptive parameters means, standard deviations (SD) and medians of PB PK parameters were calculated using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA). The 95 % confidence intervals (CI) for medians were calculated by method of Bonett and Price (2002).

Linear regression models and Mann-Whitney U test were used to evaluate the impact of co-medication on PB PK parameters using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

Table 1. Proportion of patients using specific co-medication.

	Any co-medication	**Any vasopressor**	**Dopamine**	**Dobutamine**	**Norepinephrine**
n/N	37/37	32/37	31/37	30/37	4/37
(%)	(100.00)	(86.49)	(83.78)	(81.08)	(10.81)
	Phenytoin	**Sufentanil**	**Midazolam**	**Tramadol**	**Furosemide**
n/N	11/37	27/37	26/37	14/37	26/37
(%)	(29.73)	(72.97)	(70.27)	(37.84)	(70.27)

Results

Thirty seven full term newborns were enrolled to the study (22 males, 15 females); 24 patients were treated under full body hypothermia, while normothermic conditions were applied in 13 patients. Mean (SD) gestational age in the study population was 39.32 (1.36) weeks, body weight 3.24 (0.65) kg. PB loading dose ranged from 5.04 to 34.29 mg/kg body weight and the maintenance dose ranged between 1.07 and 20.31 mg/kg/day.

Totally 110 cPB points for pharmacokinetics analysis were obtained (2-5 cPB points per patient). Mean (SD) Vd, CL, and T1/2 values for PB were 0.4941 (0.2439) l/kg, 0.0040 (0.0023) l/h/kg, and 106.55 (59.07) h, respectively. There was high inter-individual variability of all PK parameters in our study population indicated by coefficient of variation of 49.35 %, 58.00 %, and 55.44 % for Vd, CL, and T1/2, respectively.

Distribution of the use of co-administered compounds in the study population is summarized in the Table 1 and comparison of PB PK parameters in subgroups with and without co-medication is shown in the Table 2.

There were no significant dose-dependent drug-drug interactions affecting PB pharmacokinetics between the studied drugs and PB as indicated by linear regression between PB PK parameters and cumulative doses of

co-medication normalized per kg of body weight. Similarly, linear regression between PB PK parameters and VIS showed no significant relationship (Fig. 1). We did not observe significant dose-independent interactions between co-administered drugs and PB (Table 2). There was significantly decreased CL among patients treated with dopamine as compared with the patient subgroup without dopamine treatment (P=0.0246).

Table 2. Medians (95 % CI) of phenobarbital pharmacokinetic parameters in subgroups with (Y) and without (N) co-medication.

		Vd (l/kg)	CL (l/h/kg)	T1/2 (h)
All patients		0.4837 (0.4065-0.5609)	0.0034 (0.0028-0.0040)	93.65 (88.08-99.21)
Any vasoactive (inotropic) drug	Y	0.4703 (0.3670-0.5736)	0.0034 (0.0028-0.0040)	93.02 (73.88-112.17)
	N	0.4884 (0.3423-0.6345)	0.0043 (0.0032-0.0055)	93.65 (66.58-120.72)
Dopamine	Y	0.4468 (0.3447-0.5489)	0.0033* (0.0026-0.0040)	93.65 (70.83-116.47)
	N	0.5389 (0.4138-0.6639)	0.0044 (0.0035-0.0052)	93.02 (78.96-107.09)
Dobutamine	Y	0.4703 (0.2660-0.5746)	0.0034 (0.0026-0.0042)	93.02 (73.38-112.67)
	N	0.4884 (0.3759-0.6009)	0.0043 (0.0035-0.0052)	93.65 (72.79-114.50)
Norepinephrine	Y	0.4428 (0.1355-0.7501)	0.0052 (0.0028-0.0075)	62.78 (-94.89-220.45)
	N	0.4837 (0.4109-0.5565)	0.0034 (0.0029-0.0039)	93.65 (79.82-107.48)
Phenytoin	Y	0.4569 (0.2779-0.6359)	0.0034 (0.0020-0.0047)	128.33 (97.04-159.63)
	N	0.4841 (0.3614-0.6067)	0.0035 (0.0026-0.0044)	92.40 (82.15-102.65)
Sufentanil	Y	0.4844 (0.3802-0.5886)	0.0034 (0.0024-0.0043)	93.65 (74.32-112.97)
	N	0.4703 (0.2984-0.6422)	0.0039 (0.0031-0.0048)	93.02 (65.18-120.87)
Midazolam	Y	0.4841 (0.3716-0.5965)	0.0034 (0.0025-0.0043)	93.02 (87.96-98.09)
	N	0.4569 (0.2663-0.6475)	0.0037 (0.0026-0.0048)	99.00 (64.55-133.45)
Tramadol	Y	0.4841 (0.3314-0.6367)	0.0034 (0.0024-0.0043)	99.00 (50.13-147.87)
	N	0.4569 (0.3567-0.5571)	0.0037 (0.0026-0.0048)	92.40 (85.88-98.92)
Furosemide	Y	0.4844 (0.3547-0.6141)	0.0034 (0.0024-0.0044)	92.40 (60.67-124.13)
	N	0.4519 (0.3137-0.5900)	0.0035 (0.0024-0.0046)	93.65 (86.86-100.44)

* $p<0.05$ vs. group without co-administered drug.

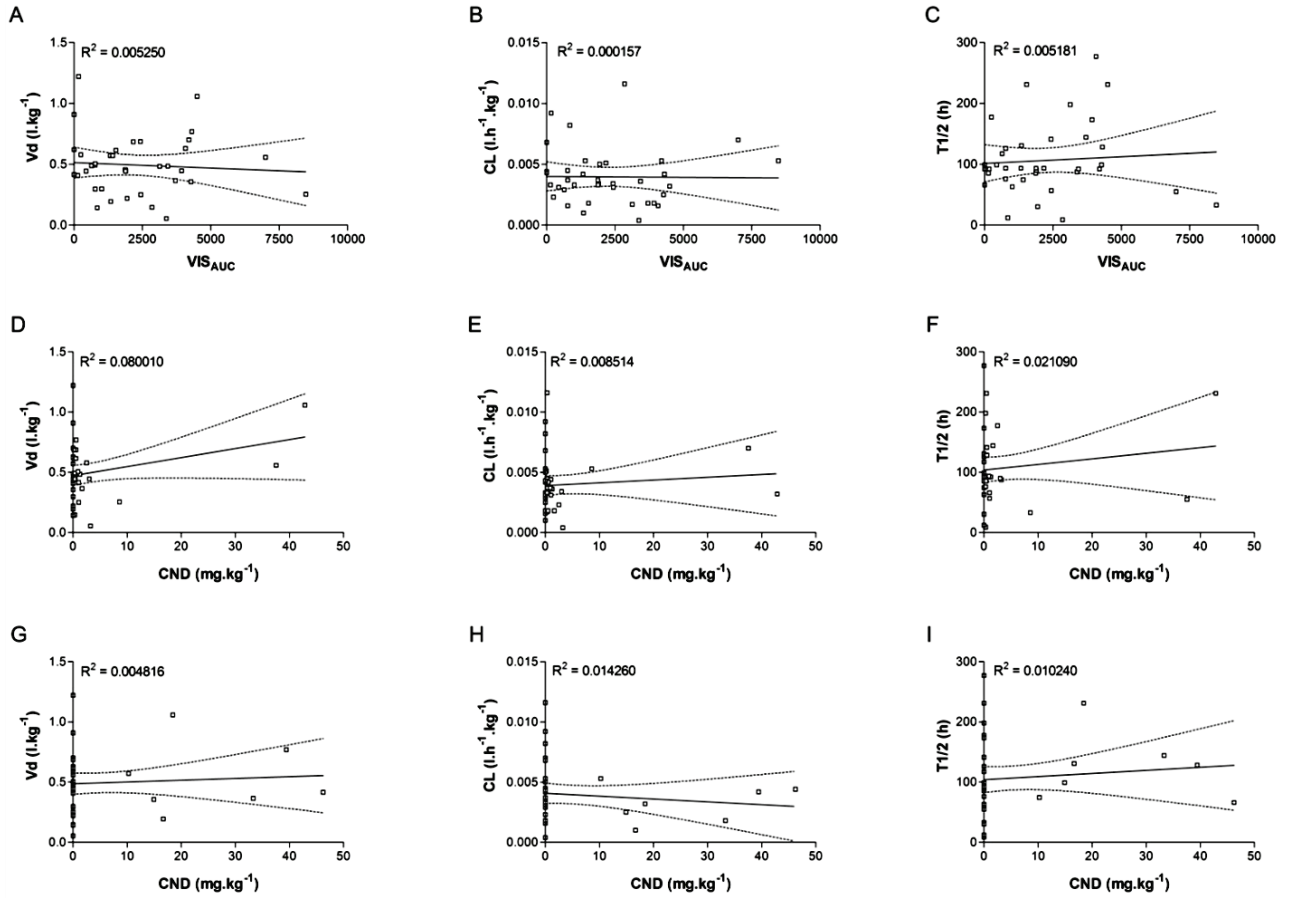

Fig. 1. A. Relationship between phenobarbital volume of distribution and vasoactive-inotropic score; **B**. Relationship between phenobarbital clearance and vasoactive-inotropic score; **C**. Relationship between phenobarbital half-life and vasoactive-inotropic score; **D**. Relationship between phenobarbital volume of distribution and furosemide cumulative dose; **E**. Relationship between phenobarbital clearance and furosemide cumulative dose; **F**. Relationship between phenobarbital half-life and furosemide cumulative dose; **G**. Relationship between phenobarbital volume of distribution and phenytoin cumulative dose; **H**. Relationship between phenobarbital clearance and phenytoin cumulative dose; **I**. Relationship between phenobarbital half-life and phenytoin cumulative dose. CND is cumulative dose of co-medication normalized per kg of body weight. VIS_{AUC} is the area under the curve in a plot of vasoactive-inotropic score against time. R^2 is coefficient of determination.

Discussion

This study was conducted to evaluate, if there are any clinically relevant drug-drug interactions affecting PB pharmacokinetics caused due to frequently co-administered compounds in critically ill newborns with HIE.

We focused on three theoretically possible mechanistic pathways for these PK interactions, i.e. alteration of renal blood flow after vasoactive medications, changes in body water content in numerous compartments induced by diuretics, and also alterations in elimination due to alterations of liver drug metabolism.

Since norepinephrine may induce decreased renal blood flow, while low-dose dopamine counteract this effect (Richer *et al.* 1996), there is a theoretical concern that the vasoactive medication may alter PB clearance due to the changes in renal blood flow. Therefore we examined the effect of vasoactive drugs (dopamine, dobutamine, and norepinephrine) that are frequently used in this patient population. However, there was no apparent interaction between vasoactive medication and PB, although statistical analysis has indicated dose-independent difference in CL of PB between the subgroups with and without dopamine. When we critically analyzed this finding and we also took into account the limitations of our study, we came to a conclusion that this is most likely an artifact. Firstly, there was no clear trend in dose-dependency of the possible dopamine-PB interaction. Secondly, neither the other vasoactive compounds nor VIS affected PB clearance. Further, the patient population is very specific and difficult for conducting any clinical study in it, but the sample size is rather limited as also indicated that there were only 6 patients in the non-dopamine group.

While it was previously shown that furosemide

significantly decreases total body water, extracellular water, and interstitial water (O'Donovan and Bell 1989) no possibly expected effect on PB volume of distribution was seen in this study.

We also explored the possible effect of co-medication with possible effects on PB metabolic elimination *via* cytochrome P450 (phenytoin, sufentanil, midazolam, and tramadol). Phenytoin could interact with PB either as an inducer or an inhibitor of metabolism, depending on the length of treatment with the combination of both drugs as suggested previously (Encinas *et al.* 1992). An increase in PB plasma levels during the initial phase of concomitant treatment with phenytoin due to competition on same metabolic pathways (CYP2C9, CYP2C19) could be expected (Patsalos *et al.* 2008). On the contrary, longer treatment could result in subsequently decreased PB plasma levels after phenytoin-induced synthesis of CYP enzymes *via* activation of nuclear receptors (pregnane X receptor, constitutive androstane receptor) (Brodie *et al.* 2013). However, these interactions have not been observed in our study, similarly as with the other co-administered compounds, although the drug interactions with sufentanil, midazolam, and tramadol were less likely, because these drugs are dominantly metabolized by other enzymes than PB (CYP3A4, CYP2D6) and do not represent strong enzyme inducers/inhibitors (Gorski *et al.* 1994, Tateishi *et al.* 1996, Subrahmanyam *et al.* 2001). Overall, the lack of observed metabolic interactions may be due to the short time of concomitant treatment in real clinical settings and/or due to the fact that there are multiple elimination pathways involved in PB metabolism and elimination (namely renal excretion of parent substance, metabolism *via* CYP2C9, CYP2C19, CYP2E1 and N-glucosidation), where alteration of one elimination pathway may be compensated by another one.

During an exploratory analysis, no interaction between PB and other rather erratically co-administered drugs was seen, similarly as there was no apparent effect of therapeutic whole body hypothermia, although the study population size is too small for proper analysis of these possible confounding factors. Most patients (94.59 %) were treated by two or more co-administered drugs simultaneously. Except the VIS no synergistic effect of two or more co-administered drugs was analyzed due to low patient number in each subgroup.

Observed high variability of PB PK parameters suggests a suitability of routine therapeutic drug monitoring of PB in newborns with HIE.

We acknowledge that there is a slight limitation of our study resulting from the fact that it was carried out in naturalistic clinical settings and thus there were number of protocol deviations mainly with respect to PB dosing and the blood sample collection times for cPB analyses. However, we did not exclude the patients with these deviations from PK analyses, since the protocol differences were compensated by individualized analysis of PB PK parameters that took the deviations from per protocol doses or sample times into account.

In conclusion, this study did not show clinically relevant effects of frequently used co-medication on PB pharmacokinetics in newborns with HIE.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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Příloha 6

ŠÍMA, M., VODIČKA, M., MAREŠOVÁ, V., ŠÁLEK, T., ČABALA, R. & SLANAŘ, O. 2017. Adherence with perindopril therapy – a pilot study using TDM of perindoprilat plus evaluation of perindoprilat clearance estimation. *Int J Clin Pharm*, přijato do tisku.

Title:

Adherence with perindopril therapy – a pilot study using TDM of perindoprilat plus evaluation of perindoprilat clearance estimation

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Running title:

Adherence with perindopril therapy

Abstract:

Background: Although measurement of drug serum levels is an objective direct method for testing compliance, it can be distorted by "white-coat compliance" or by variations in drug elimination.

Objective: The aim of this prospective study was to evaluate the prevalence of non-compliance with perindopril therapy in adult out-patients using pharmacokinetic simulations. The additional aim was to compare the predictive performance of two glomerular filtration rate markers – creatinine and cystatin C.

Setting: Department of Cardiology, Tomas Bata Regional Hospital in Zlín, Czech Republic.

Method: Perindoprilat pharmacokinetic models individualized according to patient characteristics were compared with measured perindoprilat serum concentrations to document compliance. Linear regression was used to evaluate the relations between perindoprilat clearance and glomerular filtration rate estimated using creatinine and cystatin C.

Main outcome measure: Assessment of non-compliance with medication using drug concentration measurements reinforced with therapeutic drug monitoring.

Results: Non-detectable perindoprilat levels were observed in 26.1% of patients. Another 21.7% were classified as non-compliant based on therapeutic drug monitoring pharmacokinetic simulations. Volume of distribution, clearance and half-life median value (interquartile range) for perindoprilat were 408.3 (360.4-456.8) L, 10.1 (4.9-17.0) $L.h^{-1}$ and 24.7 (19.4-62.7) h, respectively. Linear regression models showed tight relationship between cystatin C and perindoprilat clearance.

Conclusions: Assessment of adherence with medication reinforced with therapeutic drug monitoring and pharmacokinetic simulations is proposed as an optimal method reducing disadvantages of simple drug concentration measurements. Cystatin C proves to be better surrogate marker for perindoprilat elimination than creatinine.

Impact of findings on practice statements

- Assessment of adherence with medication reinforced with TDM procedures is an optimal method reducing disadvantages of simple drug concentration measurements.
- Cystatin C proves to be better surrogate marker for perindoprilat elimination than creatinine.

Key words:

Perindopril, ACE inhibitors, compliance, creatinine, cystatin C, therapeutic drug monitoring

Introduction:

Hypertension remains one of the most significant causes of morbidity and mortality worldwide. It is a major risk factor for heart failure, coronary artery disease, stroke and renal insufficiency. Current hypertension management guidelines recommend angiotensin-converting enzyme inhibitors as one of the first-line pharmacological treatments for reduction of absolute cardiovascular risk in patients with hypertension [1].

Comprehensive meta-analysis documented a high proportion of patients (45.2%), who do not adhere with antihypertensive treatment [2]. A possible explanation for the high frequency of non-compliance may be because hypertension is asymptomatic until complications appear or may be due to adverse effects of the drugs. In addition, there is an inverse relationship between the complexity of a drug regimen and the adherence rate [3].

Assessment of non-compliance of individual patients in real practice may be complicated. No method for testing compliance is considered the gold standard [4]. Patient diaries, self-reports and questionnaires, pill counting, ascertaining rates of prescription refills, assessment of the patient´s clinical response, measurement of physiologic markers or electronic medication monitoring are indirect methods susceptible to distortion as they may be easily manipulated by the patient or affected by other factors (e.g. lack of response). In comparison, measurement of the serum drug concentrations represents an objective direct method. However, variations in drug elimination and “white-coat compliance” can result in a false impression of adherence. As therapeutic drug monitoring (TDM) is much more accurate for

individualization of a drug dose regimen [5], the pharmacokinetic (PK) interpretation of antihypertensive drug serum concentrations may reduce the limitations of simple serum drug concentration measurements.

Aim of the study:

This study aimed firstly to evaluate the prevalence of non-compliance with perindopril therapy in adult out-patients, and secondly to compare the predictive performance of two glomerular filtration rate (GFR) markers – creatinine and cystatin C – for perindoprilat clearance estimation.

Ethics approval:

The study has been approved by the Ethics Committee of the Tomas Bata Regional Hospital in Zlín. The patients gave written informed consent. Our study follows the principles of the Declaration of Helsinki.

Method:

Study design:

This was a prospective clinical study that enrolled adult outpatients (age ≥ 18 years) treated with perindopril continuously for at least 7 days, who were admitted to the Department of Cardiology, Tomas Bata Regional Hospital in Zlín, Czech Republic from 1.11.2015 to 30.11.2015.

Data collection:

Gender, age, height, body weight, blood pressure, creatinine and cystatin C serum concentrations, perindopril dose and administration times, and drug anamnesis were recorded for each patient. Patients´ GFRs were estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulae based on creatinine, cystatin C, and both creatinine and cystatin C [6]. In addition, formula by Hoek (based on cystatin C) was also used [7]. Blood samples for perindoprilat concentrations monitoring were collected from the

brachial vein in the morning prior to perindopril administration. Measurement of serum perindoprilat concentrations were performed at the Laboratory of Toxicology, Institute of Forensic Medicine and Toxicology, First Faculty of Medicine, Charles University and General University Hospital in Prague using a validated LC-MS/MS method. The chromatographic separation was performed on a 1200 series LC (Agilent, Waldbronn, Germany), consisting of a degrasser, binary pump, autosampler and thermostated column compartment. The mass spectrometry analysis was performed using a 3200 Q-trap triple quadrupole/linear ion trap mass spectrometer with TurboIonSpray source (MDS Sciex, Ontario, Canada). Detection limit of the analytical method was 0.25 $ng.mL^{-1}$, while its quantification limit was 1 $ng.mL^{-1}$.

Medical histories were obtained during personal interview by trained pharmacists or pharmacy students that were held in parallel with regular physicians´ medical anamnesis. Patients completed a questionnaire on their medication adherence prior to hospitalization. Questionnaire results were compared with measured perindoprilat levels. Patients were classified into three categories according to their perindoprilat level. Patients who had undetectable perindoprilat serum concentrations were deemed completely non-compliant. Patients whose measured perindoprilat concentrations reached < 25% of simulated population PK model were classified as partially non-compliant, while patients with measured concentrations ≥ 25% of simulated population PK model were considered compliant.

Pharmacokinetics analysis:

PK analysis was performed at the Department of Pharmacology, First Faculty of Medicine, Charles University and General University Hospital in Prague. Individual perindoprilat PK parameters –clearance (CL) and half-life (T1/2) were calculated using one-compartmental PK model with first-order elimination kinetics based on individual demographic, clinical data and observed perindoprilat serum levels using $MWPharm^{++}$ software (MediWare, Prague, Czech Republic). The population PK model used “a priory” was designed as Vd = 6.88 L per kg of lean body weight, and renal CL = CKD-EPI creatinine clearance. The perindoprilat CL was “a posteriori” individualized to maximize fitting of the simulated PK profile curve with recorded drug concentration point in each patient.

Statistical analysis

Descriptive parameters medians and interquartile range (IQR) were calculated using MS Excel 2010 (Microsoft Corporation, Redmond, USA).

Mann-Whitney U test was used to compare patients´ blood pressures between patient groups using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

Fisher´s exact test and odds ratio were used to determine gender differences in compliance using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

Linear regression models were used to evaluate the relationships between perindoprilat CL and GFRs calculated according to particular formulas, and to evaluate the relationships between perindoprilat CL and creatinine/cystatin C serum levels using GraphPad Prism 3.02 (GraphPad Software, Inc., La Jolla, USA).

Results:

Twenty-three patients (18 males, 5 females) met the enrollment criteria of this study. Demographics and clinical characteristics of patients are summarized in Table 1. Two patients were taking 2.5 mg of perindopril per day, 15 patients were taking 5 mg per day, and 6 patients were taking 10 mg per day. One perindoprilat serum concentration was measured in each patient. Median number (range) of used antihypertensive drugs was 3 (1-5) in the whole study population. Monotherapy was used in 17.4% of patients, additional agents were diuretic(s) (69.6%), beta-blockers (34.8%), calcium channel blockers (26.1%) and rilmenidine (4.3%).

Only three patients acknowledged failures in the use of perindopril in their questionnaires. One of them was completely non-compliant, while two were classified as compliant based on measured perindoprilat levels.

Six patients (26.1%) were completely non-compliant, five subjects (21.7%) were partially non-compliant and twelve patients (52.2%) were compliant with perindopril therapy based on this study. Females were significantly more compliant than males (Table 2) (P=0.0373).

Median seated single measurements of systolic/diastolic blood pressure did not significantly differ among compliant, partially non-compliant, and completely non-compliant groups. The respective median values were 135/80, 140/80, and 145/80 mm Hg.

PK analysis was performed only in the group of compliant patients and its results are summarized in Table 3.

Linear regression models showed that both creatinine and cystatin C-based GFR estimations (eGFR) are significantly related with perindoprilat CL, but estimations based on cystatin C have much better predictive performance (Figure 1).

Discussion:

In currently conducted adherence-focused studies, patients with any detectable drug serum levels are usually considered as compliant [8, 9], but this approach may cause falsely high adherence rate due to patients taking drug irregularly or intentionally taking single dose prior to scheduled follow up visits. Therefore this problem may be eliminated by comparison of the measured perindoprilat concentrations with expected value obtained from PK simulation based on population PK characteristics, individual patient demographics, clinical status and recommended dosage regimen. This procedure is still based on a single blood sample, so the burden for the patient does not increase and the PK simulations are available at any clinical pharmacology units.

The patients were classified as partially non-compliant if the measured perindoprilat value was below 25% of the simulated population PK model. This cutoff value was chosen for two reasons. Firstly, the measured level lower than 25% of the population PK model cannot be explained by the common range of the PK variability. Secondly, this value approximately corresponds to the concentration after one dose intake based on the population model, in the case of white coat drug users. All patients in partially non-compliant group declared drug intake at fasted state. Therefore, the food effect resulting in a reduced bioavailability is unlikely to explain the low perindoprilat levels in these patients.

The lower rate of completely non-compliant patients in our study (26.1%), as opposed to the previously reported ones [2], could be explained by a higher proportion of patients with complicated hypertension, in whom better adherence can be expected.

Although there were non-significant differences in median blood pressures between groups, we observed increase in systolic pressure in the order of compliant < partially non-compliant

< completely non-compliant patients. However, this exploratory study has not been powered for blood pressure comparisons.

Since perindoprilat is mainly excreted into the urine and its serum levels are in strong inverse relationship with the degree of renal function [10], proper eGFR is expected to be of crucial importance for proper prediction of perindoprilat CL. Creatinine and cystatin C are markers frequently used as clinical surrogates for eGFR. The combined creatinine-cystatin C CKD-EPI equation is currently considered as the best method for eGFR [6, 11]. Serum creatinine has become the most commonly used marker to assess kidney function in routine clinical practice. However, cystatin C as an earlier marker of mild renal damage may be more sensitive, since it is also independent of muscle mass, age, or sex, or active renal secretion/resorption [12]. Most studies demonstrated that cystatin C better correlated with drug CL/concentration compared with creatinine [13].

Accordingly, cystatin C showed the superior predictive accuracy for perindoprilat CL estimation (Figure 1) in our study. It should be noted, that differences in predictive performance of combined CKD-EPI, cystatin C CKD-EPI and Hoek equations were negligible. This finding indicates that simple Hoek formula could be used as adequate alternative of sophisticated CKD-EPI. However, it must be acknowledged that relatively low patient type variability and small sample size deserves awareness when extrapolating the results into general population.

Conclusion:

Innovative approach to medical adherence assessment based on TDM and PK simulations is proposed as an optimal method reducing disadvantages of simple drug concentration measurements. Further, cystatin C proves to be a better surrogate marker for perindoprilat elimination than creatinine.

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Conflicts of interest:

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Table 1 Demographic and clinical data

(n=23)	Median	IQR	Min	Max
Age (years)	69	65-75	54	92
Weight (kg)	88	80-97	51	130
Height (cm)	169	162-172	153	187
Serum creatinine ($\mu mol.L^{-1}$)	98	86-114	67	205
Serum cystatin C ($mg.L^{-1}$)	1.21	1.11-1.68	0.91	2.88
eGFR CKD-EPI_{creat} ($mL.s^{-1}$)	1.2	0.9-1.5	0.5	1.9
eGFR CKD-$EPI_{creat+cystC}$ ($mL.s^{-1}$)	0.8	0.5-1.4	0.4	1.6
eGFR CKD-EPI_{cystC} ($mL.s^{-1}$)	0.7	0.5-1.2	0.3	1.6
eGFR $Hoek_{cystC}$ ($mL.s^{-1}$)	1.1	0.7-1.4	0.4	1.6

Legend: eGFR is glomerular filtration rate estimation

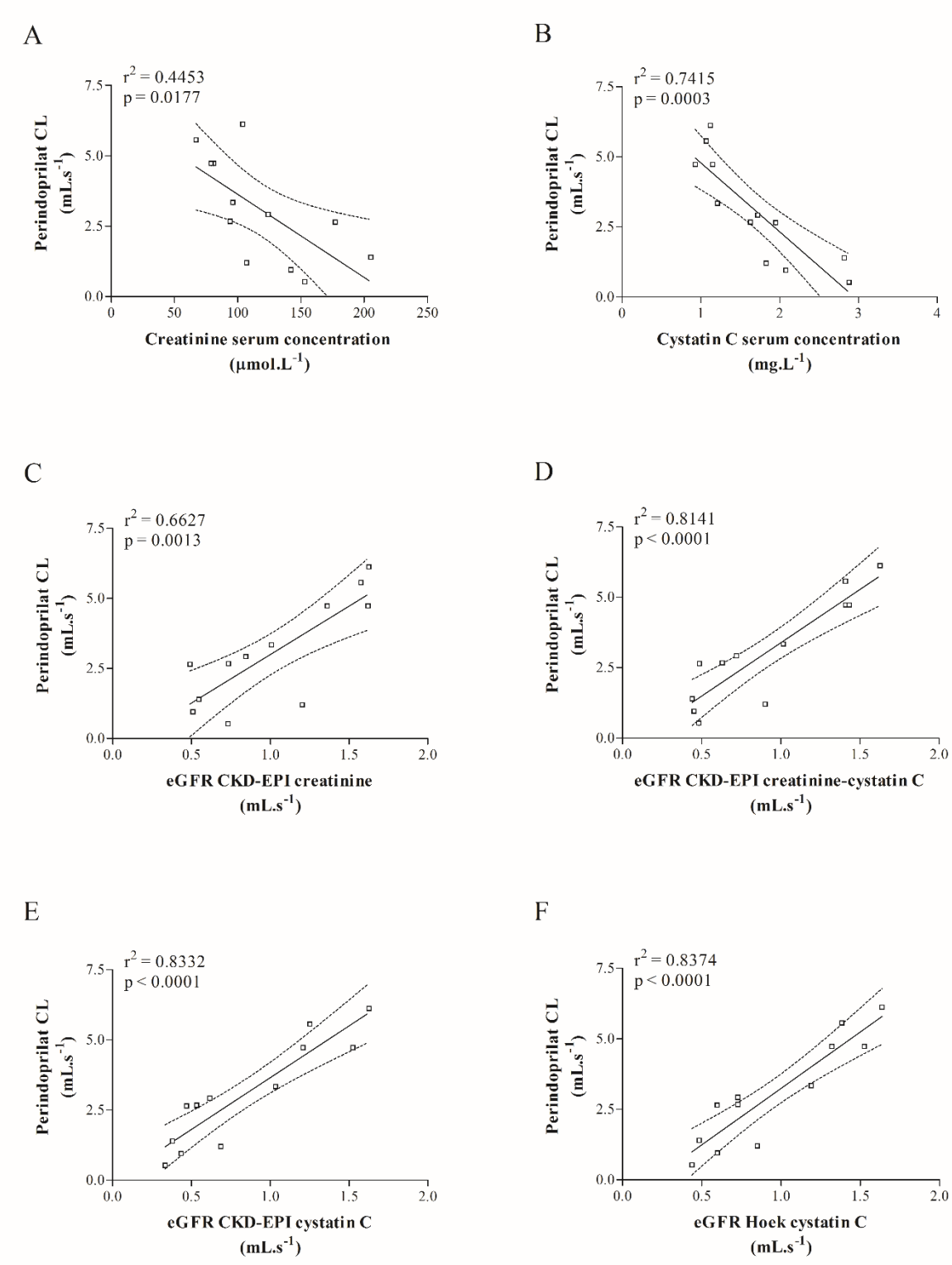
Table 2 Medical compliance stratified by gender

	Compliant	Non-compliant	Total
Males	7	11	18
Females	5	0	5
Total	12	11	23
Two-sided P-value	0.0373		
Odds ratio (95% CI)	0.0593 (0.0028-1.2380)		

Table 3 Perindoprilat individualized pharmacokinetic data

(n=12)	Median	IQR	Min	Max
CL ($L.h^{-1}$)	10.1	4.9-17.0	1.9	22.0
T1/2 (h)	24.7	19.4-62.7	14.7	170.0

Fig 1 Relationships of perindoprilat clearance (CL) with creatinine/cystatin C serum concentrations (A-B) and with glomerular filtration rate estimations (eGFR) based on creatinine/cystatin C (C-F)



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Dear Dr. Šíma,

We are pleased to inform you that your manuscript, "Adherence with perindopril therapy - a pilot study using TDM of perindoprilat plus evaluation of perindoprilat clearance estimation", has been accepted for publication in International Journal of Clinical Pharmacy .

Please remember to quote the manuscript number, IJCP-D-17-00230R1, whenever inquiring about your manuscript.

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Reviewer #1: The authors have adequately addressed each of the concerns raised in the review, and have made appropriate changes to express the findings in a careful and limited way, acknowledging the limitations of the small sample.

Reviewer #2: The editing changes made to the manuscript make the study much clearer to understand, as do the changes made clarifying the scientific validity.

While the study does have a small sample size, even for a pilot study, the authors have presented a novel method for assessing compliance/concordance/adherence, using published PK data which is readily accessible, though a understanding of population PK modeling is required to perform this. While it is unlikely that this methodology would be used by prescribers in everyday practice, it is a tool that could be used in clinical studies to provide a much greater degree of information on adherence. From this future tools could be developed that would be more 'prescriber-friendly'.

The information on perindopril clearance, and how this is better correlated with cystatin C than creatinine, is an excellent reminder that while creatinine is easy to obtain and use it has many deficiencies as a marker of GFR for predicting drug clearances. But it does highlight that the different equations used give only a slight variation.

Note - the term is 'a priori' rather than 'a priory' and in line 114 'correlated' is probably more appropriate than 'related'.