SUMMARY

Gentamicin (Ge) belongs to the group of aminoglycoside antibiotics frequently used in the treatment of neonates with sepsis in combination with betalactams. The first part of the disertation investigates a kinetically guided therapy with gentamicin (Ge) and the impact of covariates on pharmacokinetics/pharmacodynamics (PK/PD) while the second part describes the tolerability of treatment.

This open-label, prospective study included preterm and term neonates (n=108) who experienced critically illness during the first week of life and were treated with Ge and admitted to the neonatal intensive care unit. The primary goal of the study was to perform a pharmacokinetic study after the first dose of Ge. The influence of covariates on PK was analyzed (body weight, gestational age-GA, fluid retention, persistent ductus arteriosus-PDA, postnatal age, therapeutic hypothermia-HT) as well as the success rate in the achivement of target therapeutic concentrations in the first week of pharmacotherapy. Fitting of the parameters of two-compartment model to the four plasma concentrations of Ge (C_{plGe}) concentations after the first dose was used to estimate individual PK of Ge: distribution volume (Vd_1) and clearance (CL_1). Neonates were stratified into four groups according to GA and the presence of a PDA ($S_{1\text{-}PDA}$=18, $S_{1\text{-}nonPDA}$=14, S_{2PDA}=4 a $S_{2\text{-}nonPDA}$=18). In very preterm nonates, a larger Vd_1, (p = 0.032) was foun which corresponded to a lower value of $C_{peak,1.}$ The CL_1 was significantly reduced in very preterm eonates as compared to moderately preterm neonates (p=0.016). The initial standard dose was individualized in 46/54 (85%) of preterm neonates. The impact of PDA was documented in very preterm treated for PDA with ibuprofen. The CL_1 was significantly reduced in very preterm neonates with PDA in omparison to those without PDA (p< 0.0001). In term neonates, a reduced Vd_1 was found in comparison with a premature groups S_1 and S2 (p= 0.005) and, CL_1 was significantly higher in S_3 compared to S_1 and S_2 groups (p < 0.05). The impact of PA and HT was shown in the group S_3 where boh the CL_1 (p = 0.009) and Vd_1 (p<0,05) were significantly reduced.

The proportion of neonates with glomerular dysfunction was higher in the group S1 than S2 (16/32 vs. 4/22; p<0.05). Serum concentrations of creatinine and urea and fractional sodium excretion in urine raised with decreasing GA (P<0.001), whereas PDA exerted no influence. In all four groups, pharmacotherapy with Ge resulted in the elevation of the ratio of calcium to creatinine urinary concentrations and of the fractional urinary excretion of magnesium (2- to7-fold, P<0.01). The correlation between the biochemical parameters under the study and Ge concentrations were weak. Nephrocalcinosis was detected in two out of 46 children undergoing sonography and cochlear toxicity was absent.

Acute renal dysfunction is relatively modest and transient in most of premature neonates treated in the intensive care unit. Pharmacotherapy with Ge results, among other effects, in the increase of calcium excretion in urine. This hypercalciuric adverse effect contributes to other risk factors for nephrocalcinosis. Long-term follow-up of kidney function seems warranted because chronic renal dysfunction can develop in a minority of children.