

The aim of the present Thesis was to investigate the possibility of the improvement of analgesic efficacy of novel non-opioid analgesics selectively or preferentially inhibiting COX-2, coxibs and meloxicam, by combinations with other substances. These analgesics have favourable profile of gastrointestinal tolerability. For this purpose, a few different approaches were used.

Based on the published data, two members of the cyclooxygenase-2 inhibitors group were selected, etoricoxib and celecoxib, and their interactions with the weak opioid codeine were assayed. Analgesic efficacy of the individual drugs and their combinations was evaluated using the preclinical model of acute visceral pain (the writhing test), in mice, and the statistical method of isobolographic analysis was used to investigate the manner of interactions. Subsequently, the interactions of paracetamol and ibuprofen with codeine were also assayed using the same methods. The interaction between celecoxib and codeine was found to be additive, while that between etoricoxib and codeine was sub-additive. On the other hand, the interactions of paracetamol and ibuprofen with codeine were synergistic.

In the second part of the Thesis, the potential improvement of the pharmacological properties of meloxicam was evaluated after its complexation with beta-cyclodextrin. Compared with non-modified meloxicam, beta-cyclodextrin-meloxicam demonstrated higher analgesic efficacy in two preclinical algometric pain models, acute thermal hyperalgesia in rats and also acute visceral pain in mice. Moreover, the higher serum concentrations of meloxicam were observed after peroral administration, when administered in complex form, compared with non-modified form.

The present results suggest that probably it is not possible to expect higher analgesic efficacy in combinations of selective cyclooxygenase-2 inhibitors with codeine in contrast to combinations of paracetamol and ibuprofen with codeine. On the other hand, the present results of stronger analgesic efficacy and of higher meloxicam serum levels after oral administration of meloxicam in complex with beta-cyclodextrin are promising.