Abstract

**Background:** A drug must reach the central nervous system (CNS) in order to directly cause CNS adverse effects (AEs).

**Objective:** Our current study addressed the pharmacokinetic (PK) background of the assumption that CNS concentrations of drugs may directly cause CNS AEs such as headache, drowsiness and sleep disturbance.

**Materials and Methods:** In neurological patients, paired serum and CSF samples were withdrawn simultaneously. Some of them were treated with pantoprazole (n=23, daily chronic doses 20-80 mg), bisoprolol (n=9, 2.5-10 mg), metoprolol (n=10, 47.5-200 mg), hydrochlorothiazide (HCT, n=15, 7.5-25 mg) or ramipril (n=9, 2.5-10mg). Total concentrations of aforementioned drugs were quantified in these samples. To this end, sensitive liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods were developed.

**Results:** CSF reached 2.0% (interquartile ranges 1.0-4.5%) of total serum concentrations for pantoprazole, 55% (47-64%) for bisoprolol, 43% (27-81%) for metoprolol, 4.1% (2.5-5%) for HCT and 2.3% (1.7-5.7%) for ramiprilate, corresponding to about 100% (pantoprazole), 78% (bisoprolol), 48% (metoprolol) 11.3% (HCT) and 5.5% (ramiprilate) of respective unbound serum concentrations.

**Conclusion:** The PK/Pharmacodynamic characteristics of the quantified drugs in the CNS is unknown. However, since the CSF levels of the unbound pantoprazole was equal and of the betablockers nearly as high as in serum, it is likely that the observed CNS AEs are mediated primarily via direct effects in the brain. Since the CSF levels of HCT and ramiprilate were much lower than the corresponding concentrations in serum, it is unlikely that the observed CNS AEs are mediated primarily via direct effects in the brain.