

## Gender-differences in pharmacokinetics and pharmacodynamics

Petra Thuermann<sup>1</sup>

<sup>1</sup> HELIOS Klinikum Wuppertal, University Witten/Herdecke, Wuppertal, Germany

Sex-based differences in pharmacokinetics (pk) and pharmacodynamics (pd) are well known since many years. However, due to the tragedies with thalidomide and diethylstilbestrol, in the 1970ies women were largely excluded from clinical trials especially in phase I, where pk and pd of new drugs are studied. Recent data show that women are included to about 25 % in phase I trials (Evelyn B et al, [www.fda.gov/cder/reports/womens\\_health/women\\_clin\\_trials.htm](http://www.fda.gov/cder/reports/womens_health/women_clin_trials.htm)), but may be still underrepresented in large outcome trials (Harris DJ et al. *N Engl J Med* 2000;343:475-480). Even today, no systematic approach does exist for the studies of sex-differences in pk and pd. Cytochrome P4503A4 is expressed in female livers to a significant higher extent than in male livers, correlating well with faster metabolism of CYP 3A4 substrates such as verapamil, nifedipine and methylprednisolone. On the other hand, women appeared to be slower metaboliser for CYP2D6 substrates, e. g. metoprolol (Meibohm B et al. *Clin Pharmacokinet* 2002;41: 329-342). With respect to pd, women seem to respond to opioids and other analgesics and sedatives different from men. In addition, women suffer more frequently from adverse drug reactions (ADRs) than men, e.g. metoprolol-induced bradycardia, morphine-associated nausea and mefloquine-induced psychosis. Especially QT-prolongation occurs more frequently in women than in men (Ebert S et al. *J Women's Health* 1998;7: 547-557). As already demanded by the FDA, new drugs should be studied with regard to sex-differences, but also outcome studies sponsored by public funding should implement sex-specific aspects.