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DISSERTATION TITLE: *Studies of hepatic, intestinal and renal pharmacokinetic processes contributing to variability in drug disposition and response*

Farmakokinetisk variabilitet er en viktig årsak til ulik legemiddelrespons mellom pasienter, og kan gi opphav til bivirkninger eller terapisvikt. I dette arbeidet studerte vi farmakokinetiske prosesser i lever, tarm og nyre fra ulike pasientgrupper. Resultatene kan bidra til økt forståelse av interindividuell variasjon i disposisjon og respons av legemidler, som på sikt kan bidra til å optimalisere legemiddelbehandlingen til den enkelte pasient.

Differences in pharmacokinetics between patients can give rise to therapy failure or drug toxicity. In these studies, we have investigated possible sources of variability in drug disposition and response in two patient populations. In patients with morbid obesity, we determined activities of important drug metabolizing enzymes in liver and small intestine samples. These enzymes are involved in restricting the fraction of a drug dose reaching the blood after oral administration as well as in elimination of drug from the body. The data can be applied for modelling and prediction of pharmacokinetic properties in patients with obesity. Drug metabolism in the liver was also investigated in non-obese patients in order to study whether activities of the drug metabolizing enzymes were associated with body size. We found that the activity of CYP3A4, which metabolizes approximately half of all drugs in use, decreased with increasing body size. This could implicate a need for dose adjustments of some drugs in patients with morbid obesity. Furthermore, a method was developed for determining concentration of tacrolimus in small kidney biopsies. Tacrolimus is an immunosuppressive drug used after kidney transplantation and long-term use is associated with kidney damage. This method can be applied for investigating whether accumulation of tacrolimus in the kidney is a risk factor for developing toxicity.