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Nanodose study of the CYP3A paradigm substrate midazolam to evaluate pharmacokinetic linearity of parent drug before and during CYP3A inhibition

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New ultrasensitive techniques such as LC/MS/MS, AMS, and PET make it possible to investigate pharmacokinetic data in humans already after administration of subtherapeutic nano- and microgram doses. These microdosing studies enable to predict the pharmacokinetics of therapeutic drug doses without achieving any pharmacological effect or adverse event. To date, ~ 35 compounds have been tested with regard to whether their microgram doses can accurately predict pharmacokinetics of therapeutic doses. The majority showed linear relationships.

In this study the objective was to show linearity between therapeutic and microgram doses of midazolam and to establish the lowest measurable dose of midazolam that reliably predicts midazolam pharmacokinetics of a therapeutic dose. A further aim was to establish an in vivo method for assessing CYP3A activity by nanogram doses of the probe drug midazolam to evaluate drug interactions. Therefore four escalating doses of oral midazolam (0.0001-3 mg) to twelve healthy volunteers were administered, stratified according to their CYP3A5 carrier status, to assess pharmacokinetic linearity. I then evaluated the pharmacokinetics of the drug interaction of midazolam with the CYP3A inhibitor ketoconazole (400 mg q.d) after nanogram and therapeutic doses of midazolam. The assessment of midazolam pharmacokinetics such as AUC and C_{max} by an ultrasensitive LC/MS/MS method revealed linearity over a 30,000-fold dose range. During the inhibition phase, ketoconazole reduced the mean oral clearance of midazolam by 92.8% and increased the mean AUC and C_{max} by 1,540 and 363%, respectively, the extent of reduction being similar in both dose ranges studied. The CYP3A5 polymorphism showed no influence on midazolam pharmacokinetics irrespective of the presence of ketoconazole. Thus, inactive nano- and microgram doses of midazolam reliably and safely predicted the pharmacokinetics of therapeutic midazolam doses, without

causing adverse events. Because this holds also true in the presence of potent inhibitors, microdosing with midazolam can also reliably predict changes of CYP3A activity induced by therapeutic doses of CYP3A inhibitors and therefore supports drug interaction studies. Whether it can and will replace evaluation with standard doses of probe drugs in the future will depend on further validation studies. These should include also less potent inhibitors than ketoconazole and also inducers.

Currently the microdosing concept is used by the pharmaceutical industry in the transition phase from preclinical to clinical evaluation of IMPs to support in vitro, in silico, and in vivo animal approaches e.g. by optimizing lead compound identification. Moreover, if validated as now done for midazolam, microdosing studies may favourably impact the evaluation of pharmacokinetic drug interactions and thus make these studies safer. This may ultimately also allow the assessment of drug interactions in the target population for whom such information is generally lacking and, instead, extrapolation of interaction data from healthy volunteers is common. Indeed, it is still not well known whether data from healthy volunteers reliably predict the nature and extent of interactions in the target population. Using this validated practice such studies may be facilitated and thus promote the evaluation of interactions in relevant patient populations.

Another task for microdosing is to investigate the influence of genetic variants of enzymes and transporters on drug metabolism or to use microdosing strategies in the assessment of pharmacokinetics in defined subpopulations such as children, pregnant women, patients with impaired liver or kidney function, as well as for defined substance classes like oncological drugs, biologicals, or immune modulators. To apply microdosing to all these fields, more compounds need to be investigated to understand all mechanisms for nonlinearity in the metabolic pathways.