

# Transmucosal nasal drug delivery: systemic bioavailability of nasally applied midazolam

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Transmucosal nasal drug delivery is a drug delivery option for challenging clinical situations where common drug administrations (e.g., intravenous, intramuscular, or oral) are inapplicable. For drugs with constricted oral bioavailability, due to degradation in the intestinal tract or hepatic first-pass metabolism, transmucosal nasal delivery is a convenient alternative to intravenous and intramuscular drug administration. The considerable blood flow, actually responsible for breath conditioning, benefits efficient systemic drug uptake and provides direct access to the systemic circulation for transmucosal absorbed drugs. Often, in nasal drug delivery the limited nasal capacity is disregarded and the instilled volumes exceed the limited capacity of the nose. Consequently, the administered preparations are partially swallowed and resulting pharmacokinetic characteristics refer to a combination of transmucosal nasal and gastrointestinal drug absorption. Due to low midazolam concentration, the commercially available preparations for intravenous administration (e.g. Dormicum®, Roche) is inappropriate for transmucosal nasal midazolam delivery. For the optimization of transmucosal nasal midazolam delivery minimized administration volumes are essential to prevent swallowing of nasally administered preparations. Therefore, nasal preparations with enhanced midazolam concentrations need to be provided. In Project I different preparations for transmucosal nasal midazolam delivery were developed. The impact of vehicle and application modality on the pharmacokinetics of nasally applied midazolam was studied by administration of the developed preparations to healthy volunteers (Project II). The benefit of two nasal midazolam preparations for procedural anxiolysis in anxious patients undergoing MRI examinations was compared (Project III). Project I: Midazolam solubilization with RM $\beta$ CD (randomized methylated- $\beta$ -cyclodextrin, a cyclodextrin derivative) facilitated compounding of midazolam preparations adjusted to the limited volumetric capacity of the nose. RM $\beta$ CD (added in equimolar or higher concentration to solubilize midazolam) reduced midazolam release in drug release studies with semi-permeable cellophane membranes (in vitro). Stability data affirmed shelf life of at least months for RM $\beta$ CD containing nasal midazolam preparations. Addition of chitosan hydrochloride (penetration enhancer) affected midazolam stability; therefore shelf life of the chitosan containing nasal midazolam preparation was reduced. The developed preparations for transmucosal nasal midazolam delivery were the basis to study the influence of the vehicle and the application modality on pharmacokinetics and systemic bioavailability of nasally applied midazolam (Project II). Project II: Pharmacokinetic characteristics following nasal application of 1 mg midazolam (Preparation 1, 2, and 3) and 3 mg midazolam (Preparation 4 and 5) were compared with pharmacokinetic characteristics of 1 mg i.v. administered midazolam (Dormicum®, Roche). The impact of RM $\beta$ CD (solubilizer), chitosan hydrochloride (penetration enhancer) and the application modality (one- versus two-sided nasal administration) was investigated in this open-label study with healthy volunteers. Volunteers were asked to describe nasal midazolam administration and to classify local irritation after nasal midazolam administration. Pharmacologic effects were assessed by computer-controlled self-adjusting reaction time test (CRTT, recording reaction time and interstimulus interval) and visual analog scale (VAS). Blood samples were serially obtained until 6 hours after midazolam administration. Serum concentrations of midazolam and two metabolites (a-hydroxymidazolam and 4-hydroxymidazolam) were quantified by liquid

chromatography-mass spectrometry (LC-MS). Non-compartment and two-compartment pharmacokinetic modeling was performed to estimate pharmacokinetic parameters. Bioequivalence testing was performed according to the requirements of EMEA (European Agency for the Evaluation of Medicinal Products). Systemic bioavailability of nasally applied midazolam ranged from 78% (Preparation 5) to 93% (Preparation 2), differences of bioavailability were not significant. After nasal administration of 1 mg midazolam by Preparation 1, 2, and 3 mean C<sub>max</sub> was, 28.1 ± 9.1 mg/l, 30.1 ± 6.6 mg/l and 28.9 ± 5.4 mg/l, respectively. After nasal administration of 3 mg midazolam by Preparation 4 and 5 C<sub>max</sub> was, 72.6 ± 18.2 mg/l, and 82.2 ± 15.8 mg/l, respectively. Following nasal midazolam administration t<sub>max</sub> was between 7.1 ± 0.6 minutes (Preparation 5) and 11.7 ± 2.4 minutes (Preparation 4). All tested nasal administration modalities to deliver 1 mg midazolam proved bioequivalence. For Preparation 4 and Preparation 5 bioequivalence was not confirmed. The serum concentration time profiles of the midazolam metabolites (α-hydroxymidazolam and 4-hydroxymidazolam) demonstrated exclusive transmucosal absorption of nasally applied midazolam. Swallowing of nasally delivered preparations was prevented and hepatic first-pass effect successfully circumvented. Consequently, the assessed pharmacokinetic parameters characterized pure transmucosal nasal midazolam delivery. Neither RMbCD (equimolar to midazolam) nor application modality (one- or two-sided) changed absorption kinetics of nasally administered midazolam, whereas chitosan hydrochloride promoted absorption of nasally applied midazolam. Significant higher midazolam serum concentrations were achieved faster. The outcome of the pharmacokinetic study emphasizes the decisive role of minimized nasal application volume to prevent swallowing of nasally applied preparations and to provide for exclusive transmucosal midazolam absorption. Project III: In this randomized multicenter trial with 110 anxious and/or claustrophobic patients undergoing MRI examinations, two nasal preparations for low-dose midazolam delivery, Midazolam MD Nasal Spray 5 mg/ml (MD) and Midazolam UD Nasal Spray 1 mg (UD), were compared. Nasal administration of 1 mg or 2 mg midazolam was provided before MRI examination. Within both groups anxiety reduction was significant, but there was no difference in anxiety reduction between the MD and UD group. Local irritation following administration of UD nasal spray was slightly more intense than local irritation after administration of MD nasal spray. Nasal delivery of low-dose midazolam is a safe therapy to provide procedural anxiolysis in patients undergoing MRI examinations. The two compared low-dose midazolam preparations for transmucosal nasal delivery of midazolam proved therapeutic equivalence. Hence, anxious and/or claustrophobic patients equally benefit from procedural anxiolysis during MRI examinations following administration of low-dose midazolam by MD nasal spray or UD nasal spray. Concerning convenient handling, administration to laying patients, and hygienic aspects the new midazolam nasal spray (UD) is superior to the commonly used midazolam multidose nasal spray (MD). Overall, the presented nasal preparations facilitated characterization of exclusive transmucosal nasal absorbed midazolam. In vivo neither RMbCD (equimolar to midazolam) nor administration modality changed the pharmacokinetic profile of nasally applied midazolam. Chitosan hydrochloride promoted nasal midazolam absorption but clinical relevance (e.g., for the treatment of status epilepticus) is to be verified in further clinical investigations. High systemic bioavailability of nasally applied midazolam demonstrated the veritable potential of transmucosal nasal drug delivery as alternative to invasive drug administration.