

## **Intranasal midazolam: a comparison of two delivery devices in human volunteers.**

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Bidirectional nasal drug delivery is a new administration principle with improved deposition pattern that may increase nasal drug uptake. Twelve healthy subjects were included in this open, nonrandomized 3-way crossover study: midazolam (3.4 mg) intravenously (1 mg mL<sup>-1</sup>), or nasally by bidirectional or traditional spray (2 x100 microL of a 17 mg mL<sup>-1</sup> nasal midazolam formulation). The primary outcome was bioavailability. Blood samples were drawn for 6 h for determination (gaschromatography-mass-spectrometry) of midazolam and 1-OH-midazolam. Pharmacokinetic calculations were based on non-compartmental modelling, sedation assessed by a subjective 0-10 NRS-scale, and nasal dimensions by non-invasive acoustic rhinometry. Mean bioavailabilities were 0.68-0.71, and T<sub>max</sub> 15 min for the sprays, which also were bioequivalent (ratio geometric means (90%) CI: 97.6% (90% CI 83.5; 113.9)). Sedation after bidirectional spray followed intravenous sedation closely, while sedation after the traditional spray was less pronounced. A negative correlation between C<sub>max</sub> and smallest cross-sectional area was seen. Adverse effects such as local irritation did not differ significantly between the sprays. Apparently bidirectional delivery did not increase systemic bioavailability of midazolam. We cannot disregard that only the traditional spray caused less sedation than intravenous administration. This finding needs to be confirmed in trials designed for this purpose.

### **Subject Headings**

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