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DRUG DISPOSITION V

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TITLE: PHARMACOKINETICS AND CLINICAL EFFECTS OF INTRANASAL MIDAZOLAM: INFLUENCE OF CIMETIDINE.

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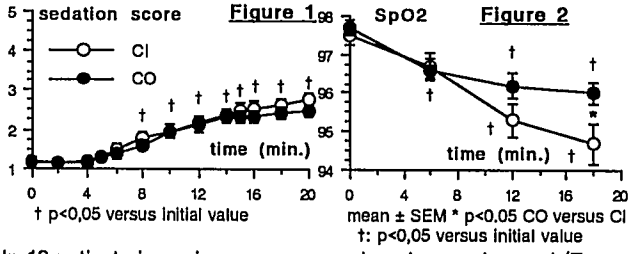
Intranasal (IN) midazolam (MDZ) is effective for sedation in children [1]. The formulation available (Versed®) contains 1 mg/ml. Therefore, in adults, the volume required to ensure sedation might lead to swallowing and digestive absorption. Cimetidine (Cl) reduces midazolam clearance [2], and might therefore decrease MDZ first pass effect. This study was designed to investigate pharmacokinetics and clinical effects of IN MDZ in adults, and to observe the influence of Cl on the biodisponibility of IN MDZ.

Methods: 59 ASA 1 male patients presented for elective surgery were randomly allocated into 2 groups after giving informed consent to receive IN MDZ 0.15 mg/kg. Group Cl patients (n=29, age 32.6 ± 9.3 yrs (mean ± SD), weight 73.4 ± 10.5 kg) received 800mg effervescent Cl 1 hour prior to IN MDZ. Group CO (control, n=30, age 32.0 ± 9.3 yrs, weight 71.9 ± 11.5) did not. After IN MDZ administration, pulse oximetry (SpO_2) and sedation (Ramsay's scale) were measured at regular intervals of time during 20 min prior to the induction of anesthesia. Venous blood samples were drawn at 5, 10, 15, 30, 60, 90, 120,240,360,and 480 min. after IN MDZ to measure MDZ plasma concentrations and allow non compartimental (AUC; Cl/F; Vss/F, T_1max; C_1max) and compartimental (T1/2 abs.; T1/2 E) (SIPHAR program) pharmacokinetic analysis. Urines were collected at 480min to measure total urinary α OH MDZ (HPLC after deconjugation). Biodisponibility (F) was estimated by the ratio $[(AUC_{IN}/dose_{IN}) / (AUC_{IV}/dose_{IV})]$ where AUC_{IV} was the area under the concentration curve observed in 9 young male patients who had received intravenous MDZ. Statistical analysis included ANOVA, unpaired t test and Wilcoxon Rank Sum test as appropriate. P <0,05 was considered significant.

Results: IN MDZ was well accepted by the patients. The score of sedation is represented in figure 1 and the evolution of SpO_2 in figure 2.



In 13 patients in each group, a second peak was observed (T_2max; C_2max). Cl enhances IN MDZ biodisponibility by reducing MDZ clearance.

	T_1max min	C_1max µg/l	T_2max min	C_2max µg/l	$T_{1/2}$ abs min	$T_{1/2}$ E min	F
Cl n=17	17.4 ±7.5	119 ±35	89 ±22	76 ±28	9.3 ±6.1	278 ±120	0.68 ± 0.23
CO n=18	14.2 ±8.1	87 ** ±31	105 * ±15	42 *** ±17	6.6 ±3.6	261 ±173	0.44 ** ±0.16

	AUC min*µg/l	Cl/F ml/min	Vss/F l/kg	αOH MDZ mg
Cl n=17	24399 ±9077	539 ±226	2.1 ±0.69	3.5 ±1.3
CO n=18	13814 *** ±6577	863 ** ±325	3.3 * ±1.8	2.6 ±1.7

mean ± SD
*p < 0.05
**p < 0.01
***p < 0.001

Discussion: IN MDZ provides rapid sedation. Nevertheless part of IN MDZ is swallowed as proven by the second peak occuring towards 90 min. after administration and by the effects of Cl (diminution of first pass effect). This easy way to administrate MDZ for sedation might be improved by a specific formulation reducing oral passage.

References:
1. Anesthesiology 69, 972 - 975, 1988.
2. Clin. Pharm. Ther. 38, 652 - 657, 1985.

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TITLE: PHARMACOKINETICS OF GLYCOPYRROLATE IN CHILDREN

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There exists no data concerning the pharmacokinetics of glycopyrrolate in children. It has been shown previously that the kinetics of atropine is dependent on age.[1] We studied the pharmacokinetics of glycopyrrolate in 21 children after a single i.v. dose administered just before the induction of anesthesia.

Methods: Following institutional approval from the Ethics Committee of Turku University Hospital and written informed consent of the parents 21 children were included in the study (table). Glycopyrrolate (5 µg/kg) was injected into the forearm vein 5 min before the induction of a combination anesthesia. A second venous cannula was inserted into the contralateral forearm for serial blood samples. A sensitive radioreceptor assay was used to determine the plasma levels of glycopyrrolate. The sensitivity of the assay was 60 ng/l, the intra-assay precision and the interassay variation were less than 15 % within the limits of detection (60 ng/l) and less than 8 % at the highest level of precision (600 ng/l).

Results: There were no statistically significant differences between the two groups of children with regard to the distribution and elimination phase half-lives ($t_{1/2\alpha}$, $t_{1/2\beta}$), respective distribution volumes ($V_{d\alpha}$, $V_{d\beta}$), plasma clearances (Cl) and areas under the curves (AUC), nor was there any correlation between age and these pharmacokinetic parameters (table).

Discussion: The kinetics of glycopyrrolate in children differs clearly from that of atropine, which has a prolonged $t_{1/2\beta}$ in patients under 2 years of age due to increased $V_{d\beta}$.[1] When the results of the present study are compared with the kinetic data glycopyrrolate in the elderly, it appears that the $t_{1/2\beta}$ is 2.5 times shorter in children due to higher Cl.[2] These results suggest that from the pharmacokinetic point of view glycopyrrolate can be safely used also in children.

References:
[1] Acta Anaesthesiol Scand 26:297-300, 1982.
[2] Acta Anaesthesiol Scand 33:513-517, 1989.

Table: Main results, mean (SD).

	Age<2 yrs	Age>2 yrs
No of patients	7	14
Age (yrs)	1.1 (0.4)	5.7 (3.0)
Weight (kg)	10.2 (1.7)	23.1 (10.1)
$t_{1/2\beta}$ (h)	0.36 (0.18)	0.32 (0.17)
$V_{d\beta}$ ($Lxkg^{-1}$)	0.61 (0.22)	0.56 (0.21)
Cl ($Lxkg^{-1}xh^{-1}$)	1.33 (0.54)	1.31 (0.40)
AUC_{0-8h} ($\mu gxL^{-1}xh$)	4.23 (1.38)	4.13 (1.14)