Plasma levels of intranasal midazolam at 0.4 mg/kg and 0.2 mg/kg doses

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Midazolam has gained recent popularity in anesthesiology, pediatrics, and dentistry because of its wide margin of safety, rapid onset, anterograde amnesia, and adequate anxiolysis.[1] Midazolam can be given intranasally, which is less invasive than intravenous administration and gives high plasma levels.[2] Most previous reports on midazolam recommended a therapeutic dose of 0.1–0.3 mg/kg for intranasal administration to obtain adequate sedation.[3] The objective of this study was to compare the plasma levels of midazolam obtained from 0.2 mg/kg and 0.4 mg/kg doses given intranasally in Rhesus monkeys over a 60-min time period. The results of this study would provide the clinician with a better understanding of the plasma levels of this drug given by the intranasal route, particularly at the higher dosage.

Materials and methods

Five young adult Rhesus monkeys were included in this study. The weight of the animals ranged from 3.4 to 4.0 kg, with a mean of 3.6 kg. Each animal was restrained and anesthetized with ketamine HCl at 25 mg/kg IM. An intravenous fluid of 5% dextrose and water with 1/4 normal saline was initiated and profused at a maintenance rate. Each monkey received intranasal midazolam (Versed™, Roche Pharma Inc, Monoti, PR) at 0.2 mg and 0.4 mg/kg of body weight, using a 1 cc syringe without a needle, at randomly assigned separate treatment sessions with a minimum of 3-day intervals separating the experimental administrations. Approximately 2 cc of blood were obtained from an accessible vein at baseline, 5-, 10-, 20-, 30-, 45-, and 60-min intervals following the administration of the midazolam dosage. Each sample was coded and stored at -80°C for a maximum of 2 weeks, then submitted for mass spectrometric analysis. The laboratory technician was blinded to the dose levels of the sample being tested.

The experimental protocol of this study was approved by the Children's Hospital Animal Protection Committee. All statistical analyses were calculated using the Statview™ statistical package (Abacus Concepts, Berkley, CA).

Results

A rapid uptake was noted for both doses of midazolam. The mean plasma peak levels occurred at the 10-min interval for both doses used (Table). A significant difference between the 0.2 and the 0.4 mg/kg dosage was found at every time interval studied (P = 0.0002–0.05) with the exception of the 60-min measurement (P = 0.09). The difference between the two peak values was highly significant (P = 0.0002). All the monkeys recovered well without assistance.

TABLE. MEAN PLASMA LEVELS OF MIDAZOLAM (NG/ML)

Dosage	0.2 mg/kg		0.4 mg/kg		
Time (Min)	Mean	SD	Mean	SD	P-Value
5	56.92	± 20.77	129.82	± 42.64	0.05
10	81.70	± 25.27	185.80	± 19.86	0.0002
20	72.50	± 17.53	158.40	± 35.75	0.002
30	63.26	± 22.63	134.66	± 37.30	0.03
45	48.20	± 17.97	108.44	± 41.85	0.05
60	39.90-	± 14.42	81.58	± 35.30	0.09

Discussion

In a study of the pharmacokinetics of intranasal administration of midazolam in children prior to general anesthesia, Walbergh, et al. reported peak serum levels within 10 min.[4] This study supports these findings with both doses used. The results of this investigation also showed unequivocally the high efficiency and consistency of the nasal route, even when higher doses of midazolam were used.

Dosage increase from 0.2 to 0.4 mg/kg results in a comparable rise in plasma levels of the drug, a phenomenon not usually encountered except with intravenous modes of administration.[5] The similarity of this administration route to the submucosal route is evident from this investigation and others.[6] Both bypass the portal circulation on the first progression through the circulatory system and peak serum levels appear within 10 min.[2]

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