TITLE: SERUM CONCENTRATIONS OF MIDAZOLAM AND THE ANESTHETIC EFFICACY

AUTHORS: Y.INAGAKI,M.D.,K.SUMIKAWA,M.D.
K.FUKUMITSU,M.D.,K.YOSHIKAWA,M.D.
I.YOSHIYA,M.D.

AFFILIATION: Anes.Dept., Osaka University Medical School, Fukushima, Osaka 553, Japan
Anes.Dept., The Center for Adult Diseases, Nakamichi, Osaka 537, Japan

Although midazolam(MZ), a water soluble potent benzodiazepine, is widely used for preanesthetic medication, induction of anesthesia and as a supplemental agent of general anesthesia, there is no detailed information on the concentration-effect relationship in humans. The present study was undertaken in humans to determine both the threshold serum concentrations of MZ for defined anesthetic events and the anesthetic efficacy of MZ in terms of its ability to reduce halothane minimum alveolar concentration (MAC).

After institutional approval, informed consent was obtained from all patients. For the study of threshold concentration, 11 patients were induced to anesthesia with continuous infusion of MZ at a rate of 17 $\mu g \cdot kg^{-1} \cdot min^{-1}$. We determined the anesthtic events according to the following signs during induction of anesthesia; sedation: spontaneous closure of eyelid, sleep: loss of response to verbal commands and/or loss of eyelid reflex, anesthesia: loss of purposeful movement for several stimuli, and collected blood samples for serum MZ concentration analysis with gas chromatography. For the study of MAC reduction, 36 female patients were randomly asingned to three groups; group A which was given no MZ, group B given MZ intravenously by a bolus of 0.1 mg/kg followed by infusion of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and group C given MZ by a bolus of 2 mg/kg followed by infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The doses of MZ were set on the basis of the preliminary study. All of three groups were administered halothane followed by endotracheal intubation without adjuvant drugs. Halothane MAC was determined using the Dixon up-and-down approach.

The correlation of anesthetic events with serum MZ concentrations was summarized in table 1. The relationship of serum MZ concentration and halothane MAC was shown in table 2.

The results clearly demonstrate the concentration-effect relationship of MZ in humans, and indicate that within the clinical dose range, MZ produced a concentration-dependent reduction of halothane MAC. A marked reduction of halothane MAC was observed even at the concentration less than the threshold concentration for sedation.

Table 1 Correlation of Anestetic Events with Serum Midazolam Concentration

| Anesthetic Event | n | Serum Midazolam Concentration ( $ng \cdot ml^{-1}$ ) |
|---|---|---|
| Sedation | 5 | 385 ± 24 |
| Sleep | 11 | 428 ± 55 |
| Anesthesia | 11 | 614 ± 67 |

Values are expressed as maen ± SD.

Table 2 Serum Midazolam Concentration and Halothane MAC

| Group | n | Serum Midazolam Concentration ( $ng \cdot ml^{-1}$ ) | Halothane MAC (%) |
|---|---|---|---|
| A | 12 | 0 | 0.76 ± 0.04 |
| B | 12 | 134 ± 26 | 0.48 ± 0.02 |
| C | 12 | 250 ± 24 | 0.37 ± 0.01 |

Values are expressed as mean ± SD.



TITLE: HEMODYNAMIC STABILITY AND THIOPENTAL, KETAMINE, THIOPENTAL/FENTANYL AND KETAMINE/FENTANYL ANESTHETIC INDUCTION

AUTHORS: RI Katz, M.D, G Alexander Ph.D.
AFFILIATION: Anes. Dept., SUNY at Stony Brook
Anes. and Psychology Depts.
Northport VAMC
Northport, NY 11768

Heart rate and blood pressure are often unstable during anesthetic induction, despite use of techniques designed to prevent this (1). The current study compares heart rate (HR) and mean arterial pressure (BP) during induction of anesthesia with 4 different methods.

With approval from the Human Studies Committee and informed patient consent, 36 subjects were studied. 10 patients received 10 cc saline, followed in 60 seconds by thiopental 5 mg/kg (pent). 7 patients received saline followed by ketamine 1.5 mg/kg (ket). 9 patients were given fentanyl 4-6 ug/kg followed by thiopental 3.0 mg/kg (fentpent) and 10 received fentanyl 4-6 ug/kg followed by ketamine 0.5 mg/kg (fentket). All received 1 mg/kg succinylcholine prior to tracheal intubation. HR and BP were recorded at 8 points: baseline, 60 seconds after saline or fentanyl, 30, 60, 90 and 120 seconds after thiopental or ketamine, 30 and 60 seconds following intubation.

Combination of ketamine and fentanyl provided the least variation in HR and BP (p 0.05) (ANOVA), both prior to and after intubation (Figures 1 and 2).

Thiopental causes venodilation and myocardial depression, resulting in a sometimes dangerous drop in BP; but it has no analgesic properties and often causes a significant rise in BP following intubation. Ketamine releases catecholamines, and hypertension during induction is the norm. A "pre-induction" dose of fentanyl given with thiopental can blunt the hypertensive response to intubation. The catecholamine response to ketamine is dose related, and can be partially counteracted by narcotics. Our results show that ketamine plus fentanyl provides superior stability of heart rate and blood pressure during induction of anesthesia.

Reference: 1) J. Clin Anesth. 1:194-200, 1989

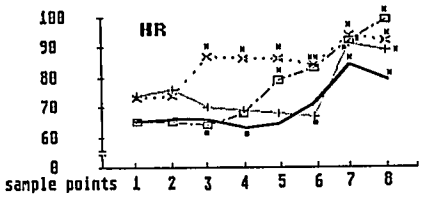


Figure 1:

* p<0.05 from baseline

# p<0.05 from pent

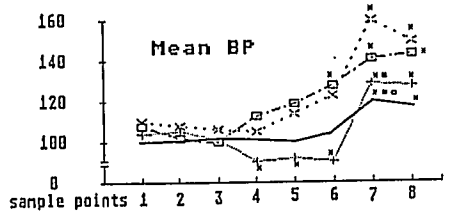


Figure 2:

* p<0.05 from baseline

# p<0.05 from pent

o p<0.05 from ket