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Title : INDUCTION OF ANESTHESIA WITH MIDAZOLAM DECREASES HALOTHANE MAC IN MAN

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Premedication with 0.2 mg/kg of diazepam decreases halothane MAC by 34%, but premedication with 0.4 mg/kg apparently has little additional effect.[1] Like diazepam, midazolam is a benzodiazepine. However, midazolam differs from diazepam in that it is water soluble, does not cause thrombophlebitis, and has a half-life of 1.7 hours, i.e., about one-tenth that of diazepam. Midazolam thus is suitable for induction of anesthesia.[2] We explored whether the larger doses that might be used for induction would cause a profound reduction in halothane MAC;[3] and whether the higher induction doses of midazolam would produce decreases in MAC proportional to the decrease achieved with lower doses (i.e., whether there is a "ceiling" to the effect of midazolam).

Twenty-nine healthy, unpremedicated patients (30-55 years of age) scheduled for elective surgery received midazolam for induction of anesthesia. Approval from the Committee on Human Research had been obtained. Midazolam was infused at 0.075 mg/kg/min in three doses (table 1). The lowest dose produced unresponsiveness to command in the majority of patients; the higher doses produced unresponsiveness in all patients. Halothane in oxygen then was administered to a level which permitted endotracheal intubation without the use of other drugs. After intubation, end-tidal halothane concentrations were monitored with infrared analysis (LB-2) and brought to a predetermined level. The level applied depended on the response to surgical incision of the previous patient (after the Dixon up-and-down approach).[4] The first patient in each group received 0.6% end-tidal halothane. The results were subjected to both the Dixon and the Waud analyses.[5]

Arterialized venous blood samples were obtained before incision and 10 min after incision (the latter only in patients who did not respond to incision) for analysis of $PaCO_2$. We looked for evidence of thrombophlebitis on the first postoperative day and between the seventh and the fourteenth days.

Midazolam decreased MAC in a dose-related fashion (table 1). MAC values obtained with the Dixon approach (table 1) were identical to those given by the Waud method. Arterial CO_2 tension increased above normal in all patients, but the increase did not correlate with the dose of midazolam (table 1). The $PaCO_2$ after incision was 5 to 9 torr less than that prior to incision. No evidence of thrombophlebitis (redness, tenderness, or induration) was found on the first postoperative day or one week later, although one patient reported feeling a burning sensation on injection.

Unmedicated patients anesthetized with halothane alone have a MAC of 0.74%. Our results show that midazolam decreases halothane MAC from 0.74% in an arithmetic fashion. No ceiling effect appears with larger doses of midazolam. However, the standard error of the MAC values appears to increase with the larger doses. This may reflect the variable nature of the effect of midazolam: variations in midazolam levels, and hence effect, would be produced by variations between time of injection and incision (not possible to standardize precisely) and pharmacokinetics (including midazolam metabolism).

The effect of an induction dose of midazolam (i.e., 0.15 mg/kg) appears to be less than the effect of a premedicating dose of diazepam.[1] Even a midazolam dose four times as great as the induction dose does not decrease MAC as much as a premedicating dose of diazepam. We speculate that this is probably due to the far shorter half-life of midazolam.[6]

The degree of respiratory depression did not increase as doses of midazolam increased. As expected, the stimulus of incision decreased $PaCO_2$ in all patients. As shown previously, thrombophlebitis is rare (if it occurs at all) with this water-soluble benzodiazepine.

Table 1. Midazolam Effect on MAC and $PaCO_2$

Midazolam (mg/kg)	Patients (n)	MAC ± 1 SE (% Halothane)	$PaCO_2$ ± 1 SE Pre-incision (torr)
0.00*	--	0.74 ± .03*	--
0.15	13	0.70 ± .03	54.6 ± 1.6
0.3	8	0.65 ± .05	51.0 ± 2.7
0.6	8	0.52 ± .08	57.6 ± 2.5

*from de Jong and Eger.[3]

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