Title : PREOPERATIVE SEDATION WITH ZOLPIDEM, MIDAZOLAM AND PLACEBO: A RANDOMIZED DOUBLE-BLIND COMPARISON

Authors : J. Pahud*, M.D., A. Forster*, M.D., Z. Gamulin*, M.D., J.-P. Sauvanet**, M.D., E. Tassonyi*, M.D.

Affiliation : *Department of Anesthesiology, University Hospital of Geneva, 1211 Genève 4, Switzerland, and **LERS Synthelabo, Paris, France

Introduction. Zolpidem is a new hypnotic agent of short elimination half-life with an imidazopyridine structure interacting with cerebral benzodiazepine (BZD) receptors type I (ω-1 receptors) (1,2). The absence of modification of sleep pattern and of memory disturbance could theorically represent an advantageous alternative to BZD, which are frequently administered to induce preoperative sedation. The purpose of the study was to compare, in a controlled and double-blind fashion, preoperative sedation induced by zolpidem, midazolam and placebo.

Patients and Methods. After institutional approval, 93 consenting patients ASA I and II undergoing elective minor surgery under spinal or epidural anesthesia were randomly allocated to 3 treatment groups: group 1, zolpidem (20mg); group 2, midazolam (15mg); and group 3, placebo. Each patient received the drug orally, in a double-blind manner, one hour before the beginning of regional anesthesia. The efficacy of the drugs was evaluated with the following variables: a) sedation, scored from 1 to 4; b) mood, according to the modified Clyde Mood State (3); c) anterograde amnesia, defined as a lack of recall of playing cards and numbers shown to and recognized by the subjects one minute after their presentation, evaluated every 15min after the administration of the drugs up to one hour, and in the immediate postoperative period; patients were also asked to recall significant events of the operative day; d) blood pressure, respiratory and cardiac frequencies; e) side effects. The variables were assessed: 1) during the preanesthetic visit; 2) on arrival in the anesthesia induction room before administration of drugs; 3) every 15min up to one hour after their administration; 4) postoperatively, when the effects of regional anesthesia had disappeared. The patients who received additional anxiolytic or analgesic medication during the surgical procedure were excluded from postoperative assessment. Statistical analysis of subjective and objective assessments were performed using the Cochran-Mantel-Haenszel test and an analysis of variance as required. $P < 0.05$ was considered significant; data are expressed as mean ± SEM.

Results. As indicated in table I, no significant difference in demographic data were noted between the 3 groups and a comparable number of patients in all 3 groups required additional anxiolytic or analgesic medication during the surgical procedure. Baseline values of all variables were similar in all three groups during the preanesthetic visit and prior to preoperative sedative drug administration on the day of surgery. As indicated in table II, zolpidem and midazolam were significantly more effective than placebo in increasing the level of sedation 45min after their administration, but no difference was noted between the 2 active drugs. Postoperatively, no difference was observed between the 3 groups. The patient's concentration and psychological tension assessed with the Clyde Mood Scale was significantly reduced 60min after the administration of zolpidem when compared to placebo (table III). A partial or total anterograde amnesia was recorded in significantly more patients after zolpidem (45%) and midazolam (46%) than placebo (7%), from 30min up to 60min after drug administration, but no statistical difference was observed between the 2 active drugs. Twenty percent of the patients after zolpidem and 30% after midazolam did not recall the administration of anesthesia, while all the patients recalled it's administration after placebo. Blood pressure, heart rate and respiratory frequency remained unchanged throughout the study. Side effects are indicated in table III and were comparable in all 3 groups.

Discussion and Conclusion. When compared to placebo, our study demonstrates a similar increase in preoperative sedation within 45 to 60min of administering zolpidem and midazolam p.o.. Nevertheless, the relief of anxiety is slightly more pronounced following zolpidem than following midazolam. Since zolpidem produced significant anterograde amnesia, our study does not confirm one of it's theoretical advantages over BZD. These 2 drugs have no or minimal cardio-respiratory effects, and the incidents of side effects are comparable to placebo.

In conclusion, zolpidem is a new hypnotic agent of rapid onset and short duration of action which may represent an alternative to midazolam for preoperative sedation.

References. 1. Deportere H., *et al.* J Pharmacol Exp Ther 237:649-658, 1986. 2. Langer S.Z., *et al.* Pharmacol Biochem Behav (in press). 3. Guy W., ECDEU, Assessment manual for psychopharmacology. NIMH, Rockville, USA, 1976.

Table I: Demographic Data (mean ± SEM)

Groups	Age (years)	Weight (kg)	Sex (M/F)	ASA I II (n)	Duration of anesth. (min)	Supplementation with analgesics or anxiolytics (n, % of patients)
Zolpidem (n=32)	42 ± 2	73 ± 2	22/10	21 11	178 ± 11	7 (22 %)
Midazolam (n=30)	46 ± 2	69 ± 3	20/10	19 11	175 ± 11	10 (33 %)
Placebo (n=31)	39 ± 3	72 ± 2	22/9	24 7	154 ± 14	13 (42 %)

Table II: Sedation Score[1] Before and After Drug Administration

Groups	Preanesth. visit	Time After Premedication (minutes) 0	15	30	45	60	Postoperative period
Zolpidem (n=32)	1.96 (1-2)	1.93 (1-2)	2.00 (1-3)	2.40* (1-4)	2.74* (1-4)	2.64* (1-4)	2.00 (1-3)
Midazolam (n=30)	1.93 (1-2)	1.93 (1-2)	2.06 (1-3)	2.76* (1-4)	2.76* (1-4)	2.73* (1-4)	2.04 (1-3)
Placebo (n=31)	1.93 (1-2)	1.93 (1-2)	2.16 (1-3)	2.27 (1-3)	2.26 (1-3)	2.26 (1-3)	1.90 (1-2)

[1]1: lack of sedation, restless patient; 2: awake, calm patient; 3: asleep, not responding to verbal stimulation; 4: asleep, not responding to physical stimulation
*$P < 0.05$ significantly different from preanesthetic visit values
Data represent mean score values of each group, with ranges in parenthesis

Table III: Concentration Scores Alertness at 60 Minutes After Drug Administration and Side Effects

Groups	Concentration Score	Alertness Score	Side Effects
Zolpidem (n=32)	12.2±0.5*	8.1±0.6*	dizziness, nausea: 1 patient confusional behaviour: 2 patients euphoria: 1 patient
Midazolam (n=30)	13.4±0.5	8.9±0.6	dysarthria: 1 patient occular irritation: 1 patient
Placebo (n=31)	13.9±0.6	9.8±0.6	bradycardia, hypotension: 1 patient cutaneous flush: 1 patient confusional behaviour: 2 patients

*$P < 0.05$ significantly different from placebo