British Journal of Anaesthesia 1990; **64**: 670–674

PREOPERATIVE SEDATION BEFORE REGIONAL ANAESTHESIA: COMPARISON BETWEEN ZOLPIDEM, MIDAZOLAM AND PLACEBO

J. PRAPLAN-PAHUD, A. FORSTER, Z. GAMULIN, E. TASSONYI AND J.-P. SAUVANET

SUMMARY

The quality of premedication induced by oral midazolam and zolpidem, a new imidazopyridine hypnotic, was assessed in a controlled, double-blind study in 93 patients undergoing elective surgery under spinal or extradural anaesthesia. The patients were allocated randomly to three groups. Each group received the same treatment twice at two different doses. The night before operation, patients received zolpidem 10 mg, midazolam 7.5 mg or placebo and, 1 h before operation, zolpidem 20 mg, midazolam 15 mg or placebo. The sleep inducing effects of the drugs were comparable. Zolpidem and midazolam were significantly more effective sedatives than placebo 45 min after administration, but no difference was noted between the drugs. There was a comparable incidence of anterograde amnesia with zolpidem and midazolam, but the onset was shorter after zolpidem. Side effects were comparable in the three groups. Zolpidem is an effective hypnotic with a rapid onset and short duration of action which may be an alternative to midazolam for premedication.

KEY WORDS

Anaesthesia: regional. Hypnotics: midazolam, zolpidem. Premedication.

Optimal premedication for regional anaesthesia requires both anxiolysis and sedation and the patient's co-operation. Benzodiazepines are administered frequently for this purpose [1] as their anticonvulsive properties may reduce local anaesthetic toxicity [2], although this action has recently been questioned [3]. Recently, zolpidem, a new imidazopyridine which acts on the central benzodiazepine receptors, has been synthesized [4, 5]. In common with the benzodiazepines, this new compound has anticonvulsant and muscle relaxant properties. It also has a short elimination half-life of 2.4 h [6]. The absence of effect on physiological sleep [4, 6, 7] or memory disturbance [8], may give zolpidem a theoretical advantage over the benzodiazepines in some clinical situations such as outpatient anaesthesia.

The present study was designed to compare the quality of premedication produced by zolpidem and midazolam in a controlled double-blind trial.

PATIENTS AND METHODS

After Ethics Committee approval, informed consent was obtained from 93 adult patients (ASA I and II), undergoing elective minor lower limb procedures ($n = 65$), varicose vein surgery ($n = 8$) or inguinal hernia repair ($n = 20$). Surgery was performed using subarachnoid (22- or 25-gauge needle) or continuous extradural anaesthesia (Tuohy 18-gauge, catheter 20-gauge). The patients were allocated randomly to treatment group 1 (zolpidem), 2 (midazolam) or 3 (placebo). The three treatments were administered double-blind. Each patient received the same drug or the placebo twice: first, on the night before the operation, zolpidem 10 mg, midazolam 7.5 mg or placebo; second, in the anaesthetic room, zolpidem 20 mg or midazolam 15 mg, 1 h before the spinal or extradural anaesthesia was performed.

J. PRAPLAN-PAHUD, M.D.; A. FORSTER, M.D.; Z. GAMULIN, M.D.; E. TASSONYI, M.D.; Department of Anaesthesiology, University Hospital of Geneva, 1211 Genève 4, Switzerland. J.-P. SAUVANET, M.D., LERS Synthelabo, Paris, France.
Accepted for Publication: January 2, 1990.
Correspondence to J. P.-P.

Efficacy of the drugs was evaluated by the same observer using the following criteria:

Quality of sleep during the night preceding the operation was assessed by asking the patients: the duration of sleep; the number of times they awoke; the manner of wakening (spontaneous or not); a subjective evaluation of the quality of sleep.

Clinical assessment of premedication. Sedation, scored: 1 = lack of sedation, patient restless; 2 = patient awake and calm; 3 = patient asleep, not responding to verbal stimulation but responding to tactile stimulation; 4 = patient asleep, not responding to verbal or to physical stimulation. *Changes in mood* were assessed by the patient, with a modified Clyde mood scale [9], which evaluates changes in mood, concentration, alertness, aggression and psychological tension [10]. *Retrograde amnesia* was assessed by asking the patient to recall, on the day of surgery after the first administration of the drugs, a number and a playing card, shown during the preanaesthetic visit. *Anterograde amnesia* was evaluated with the same method, asking the patient after the second administration of the drugs, to recall the two items 1 min after their presentation. Amnesia was considered complete if the patient did not remember either of the two items, partial if he recalled one of them and absent if he remembered both. On the evening after operation, *anterograde amnesia* was evaluated in a different manner, by asking the patient if he recalled the administration of anaesthesia, transfers to the operating room, to the recovery room and to the hospital ward. Amnesia was considered present if the patient did not remember any of these events. *Arterial pressure* was measured with automated oscillotonometry (Dinamap) and ventilatory and cardiac frequencies clinically. Side effects, additional analgesia or anxiolytic medication required during the operation were noted also.

All variables were assessed during the preanaesthetic visit on the day before surgery, on arrival in the anaesthetic room before administration of drugs, every 15 min up to 1 h after their administration and in the immediate postoperative period. In addition, subjective evaluation of the efficacy of the drugs was scored separately by the patient and the anaesthetist on the evening of surgery as follows: 1 = poor, 2 = fair, 3 = good.

Patients who received additional anxiolytic or analgesic medication during the surgical procedure were excluded from the postoperative assessments.

Statistical analysis of qualitative variables was performed with a Cochran–Mantel Haenszel test. Quantitative data were subjected to analysis of variance and the different treatments were compared with a Bonferroni's test. $P < 0.05$ was considered significant. All data are expressed as mean (SEM) or median score values.

RESULTS

There were no significant differences in demographic data, ASA class, or duration of anaesthesia and surgery between the groups (table I).

No difference was noted on the night before surgery between the hypnotic effects of zolpidem, midazolam and placebo; the onset of sleep was comparable in the three groups, as were the frequency of awakening, the patients' subjective evaluation of the quality of sleep and the manner of awakening (table II).

No statistical difference was observed in sedation scores between the three groups, on the day before surgery, during the preoperative visit and

TABLE I. *Demographic data, anaesthetic risk, duration of anaesthesia and surgery in the three groups (mean (SEM))*

Group	Sex (M/F)	Age (yr)	Weight (kg)	Height (cm)	ASA class (I/II)	Duration of anaesth. (min)	Duration of surgery (min)
Placebo ($n = 31$)	22/9	39 (3)	72 (2)	172 (1)	24/7	154 (14)	81 (10)
Midazolam ($n = 30$)	20/10	46 (2)	69 (3)	169 (2)	19/11	175 (10)	83 (7)
Zolpidem ($n = 32$)	22/10	42 (2)	73 (2)	171 (1)	21/11	177 (10)	85 (7)

TABLE II. *Clinical evaluation by patients of the quality of sleep induced by the three different premedicants administered on the evening before surgery*

	Percentage of patients in group		
	Placebo	Midazolam	Zolpidem
Onset of sleep			
< 15 min	40.0	26.7	38.7
< 30 min	26.6	53.3	22.5
< 60 min	3.3	10.0	25.8
> 60 min	30.0	10.0	12.9
Frequency of awakening			
None or once	51.7	76.7	65.6
> once	48.3	23.3	34.4
Manner of wakening in the morning			
Spontaneous	66.7	73.3	75.0
Not spontaneous	33.3	26.7	25.0
Patient's subjective evaluation			
Very good or good	71.0	90.0	75.0
Fair or bad	29.0	10.0	25.0

TABLE III. *Sedation scores before and after drug administration (median (range)). 1 = Lack of sedation, restless patient; 2 = awake calm patient; 3 = asleep, not responding to verbal stimulation; 4 = asleep, not responding to physical stimulation. * Significantly different from placebo* (P < 0.05)

		Time after premedication (min)					
Group	Preanaesth. visit	0	15	30	45	60	After op.
Placebo	2	2	2	2	2	2	2
(n = 31)	(1–2)	(1–2)	(2–3)	(2–3)	(2–3)	(2–3)	(1–2)
Midazolam	2	2	2	2	2.5*	3*	2
(n = 30)	(1–2)	(1–2)	(2–3)	(2–4)	(2–4)	(2–4)	(2–3)
Zolpidem	2	2	2	2	3*	3*	2
(n = 32)	(1–2)	(1–2)	(1–3)	(1–4)	(2–4)	(2–4)	(1–3)

before the administration of the drugs. Forty-five minutes after administration, zolpidem and midazolam were significantly more sedative than placebo, but no difference was noted between the drugs (table III). In the immediate postoperative period (140 min after drug administration) the three groups were comparable, more than 90% of the patients being considered "calm and awake" (score = 2).

No retrograde amnesia was observed in any patient. Figure 1 illustrates the results for anterograde amnesia. Fifteen minutes after administration of the drugs, the three groups were comparable. Thirty minutes after administration of zolpidem, partial or total anterograde amnesia was found in significantly more patients compared with the midazolam and placebo groups. At 45 min, partial or total anterograde amnesia was found in 50% of the zolpidem and midazolam patients, but in only 7% of the placebo group (P = 0.002). At 60 min, 40% of the patients in the zolpidem group and 38% of the patients in the midazolam group still had partial or total anterograde amnesia, compared with 6% in the placebo group (P = 0.005). The incidence of partial or total anterograde amnesia produced by the two drugs and the placebo was similar in the immediate postoperative period. On the evening after operation, 71% of the patients in the midazolam group, 80% of the patients in the zolpidem group and 100% in the placebo group recalled administration of anaesthesia.

All patients remembered being transferred to the operating room, to the recovery room and to the hospital ward.

Most of the items on the Clyde mood scale (aggression, well being and psychological tension) were not modified and were comparable in the three groups, during the whole investigation. However, 60 min after administration of zolpidem, alertness and concentration were reduced significantly compared with midazolam and pla-

cebo, but were comparable in the three groups on the day preceding operation and on the day of surgery before the drugs were administered (table IV). In the immediate postoperative period (140 min after drug administration), alertness and concentration scores returned to baseline values and were comparable in the three groups. Heart rate, mean arterial pressure and ventilatory frequency remained unchanged throughout the study period.

A similar number of patients (20 % in the active groups and 30 % in the placebo group), required additional anxiolytic or analgesic medication during the surgical procedure, and were excluded from postoperative assessment.

The incidence of the side effects was comparable in the three groups. Confusional behaviour was observed in two patients in the zolpidem group, euphoria in one patient and conjunctival injection in the other. In the midazolam group, dysarthria was noted in one patient and conjunctival injection in another. In the placebo group, one patient complained of a cutaneous flush, a second showed confusional behaviour and a third moderate hypotension and bradycardia. All side effects were of minor importance and did not last more than 2 h after administration of the drugs.

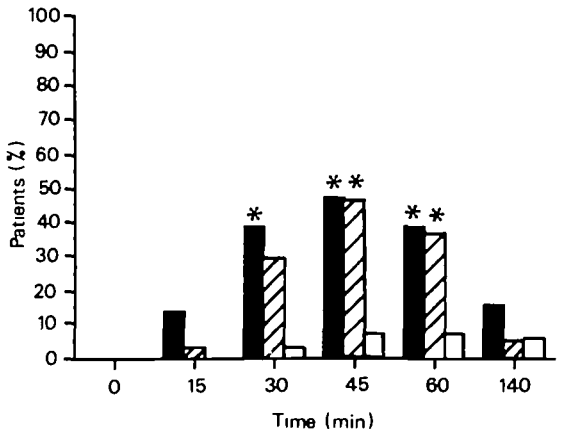

FIG. 1. Percentage of patients with anterograde amnesia after administration of zolpidem (■), midazolam (▨) or placebo (□). * Significantly different from placebo ($P < 0.05$).

The quality of premedication was better with the two active drugs, as it was qualified "good" by 60 % of the patients in the zolpidem group, 79 % in the midazolam group and 38 % in the placebo group ($P = 0.01$). The anaesthetist considered premedication excellent in 52 % of the patients with zolpidem, in 67 % with midazolam but in only 24 % with placebo ($P = 0.005$).

DISCUSSION

The purpose of the study was to compare the sedative, anxiolytic and amnesic effects of oral zolpidem and midazolam in a controlled, double-blind manner. Our results indicated that both zolpidem and midazolam induced comparable preoperative sedation and anterograde amnesia, while psychological tension was improved significantly after zolpidem when compared with midazolam.

When compared with placebo, zolpidem and midazolam produced significant and comparable sedation 45 min after administration, confirming their rapid onset of action. Patient co-operation was not impaired by any of the drugs. After operation, 140 min after administration of the drugs, mean sedation scores in all groups returned to baseline values, confirming their short duration of action. However, a previous study using the same doses [11] found a residual sedative effect for up to 240 min after drug administration. This difference may be explained by the fact that all the patients in our study were evaluated after regional anaesthesia, while general anaesthesia was used in the other study.

Anxiolysis is a subjective phenomenon which is

TABLE IV. *Alertness and concentration scores before and 60 min after drug administration (Clyde Mood Scale) (mean (SEM)). * Significantly different from placebo (P < 0.05). Maximum score = 16*

	Concentration		Alertness	
Group	Before	After	Before	After
Placebo ($n = 31$)	14.3 (0.5)	13.9 (0.6)	10.6 (0.4)	9.8 (0.6)
Midazolam ($n = 30$)	15.0 (0.3)	13.4 (0.5)	10.7 (0.4)	8.9 (0.6)
Zolpidem ($n = 32$)	14.8 (0.3)	12.2 (0.5)*	10.8 (0.4)	8.1 (0.6)*

difficult to define and evaluate. Patient rather than observer assessment was thought to be a more valid indicator of anxiolysis, as it reduces observer error in distinguishing between drowsiness and anxiolysis. The Clyde mood scale was chosen to provide a more precise evaluation of psychological tension. The degree of psychological tension was comparable between the groups on the night preceding the operation and before receiving premedicant drugs on the day of surgery. This suggests that the more extensive preoperative explanation given to the patient because of the design of the study may have contributed to the decreased anxiety. However, the patient's concentration and alertness were reduced 60 min after administration of zolpidem, suggesting that it was more effective than midazolam and placebo in decreasing psychological tension, even though the patient's anxiety level was low.

Animal studies have suggested that zolpidem does not affect memory [8], although a study in man reported that zolpidem produced anterograde amnesia in a dose-related fashion [11]. These findings are confirmed by our data, as zolpidem 20 mg produced a duration of anterograde amnesia similar to that obtained with midazolam 15 mg [12], but with a significantly shorter onset time. The main aim of premedication for regional anaesthesia is to relieve patient anxiety while maintaining co-operation. The preanaesthetic visit alone is effective in reducing patient apprehension [13], but this may not remove the need for medication. Our results demonstrated that, after a preanaesthetic visit where a good relationship was established between the patient and the physician, placebo was as effective as zolpidem 10 mg and midazolam 7.5 mg in decreasing anxiety the night before surgery.

In a previous study [7], there were no residual effects 9 h after administration of zolpidem 10, 20 and 30 mg, assessed by digit–symbol substitution and a complex reaction time task. Our study confirmed these findings, as all the variables assessed returned to baseline values on the evening following administration of the drug.

No significant side effects were seen after zolpidem or midazolam. However, paradoxical reactions have been described occasionally following administration of benzodiazepines [14]. None occurred in our study after administration of either active compound, but the number of patients was too small to draw any definite conclusion.

In conclusion, zolpidem is a new hypnotic agent with a rapid onset and a short duration of action which may be an alternative premedicant to midazolam for regional anaesthesia, when sedation, anxiolysis and anterograde amnesia are desired.

ACKNOWLEDGEMENT

We thank J. Lopez for technical assistance with this project.

REFERENCES

1. Greenblatt DJ, Shader RI, Abernethy DR. Current status of benzodiazepines. *New England Journal of Medicine* 1983; **309**: 354–358, 410–416.
2. Pearce C. The respiratory effects of diazepam supplementation of spinal anaesthesia in elderly males. *British Journal of Anaesthesia* 1974; **46**: 439–441.
3. Gregg RV, Turner AP, Denson DD, Stuebing CR, Sehlhorst CS, Forsberg T. Does diazepam really reduce the cardiotoxic effects of intravenous bupivacaine? *Anesthesia and Analgesia* 1988; **67**: 9–14.
4. Arbilla S, Depoortere H, George P, Langer SZ. Pharmacological profile of the imidazopyridine zolpidem at benzodiazepine receptors and electrocorticogram in rats. *Naunyn-Schmiedebergs Archives of Pharmacology* 1985; **330**: 248–251.
5. Arbilla S, Allen J, Wick A, Langer S. High affinity (3H) zolpidem binding in the rat brain: an imidazopyridine with agonist properties at central benzodiazepine receptors. *European Journal of Pharmacology* 1986; **130**: 257–263.
6. Depoortere H, Zivkovic B, Lloyd KG, Sanger DJ, Perrault G, Langer SZ, Bartholini G. Zolpidem, a novel nonbenzodiazepine hypnotic. I. Neuropharmacological and behavioral effects. *Journal of Pharmacology and Experimental Therapeutics* 1986; **237**: 649–658.
7. Nicholson AN, Pascoe DA. Hypnotic activity of an imidazopyridine (zolpidem). *British Journal of Clinical Pharmacology* 1986; **21**: 205–211.
8. Sanger DJ, Joly D, Zivkovic B. Effects of zolpidem, a new imidazopyridine hypnotic on the acquisition of conditioned fear in mice. Comparison with triazolam and CL 218, 872. *Psychopharmacology* 1986; **90**: 207–210.
9. Clyde DJ. *Manual for the Clyde Mood Scale*. Miami: Clyde Computing Service Ed., 1983.
10. Guy W. *ECDEU. Assessment Manual for Psychopharmacology*. N.I.M.H., Rockville (USA): U.S. Department of Health, Education and Welfare Eds, 1976.
11. Cashman JN, Power SJ, Jones RM. Assessment of a new hypnotic imidazo-pyridine (zolpidem) as oral premedication. *British Journal of Clinical Pharmacology* 1987; **24**: 85–92.
12. Dundee JW, Wilson DB. Amnesic action of midazolam. *Anaesthesia* 1980; **35**: 459–461.
13. Egbert LD, Battit GE, Turndorf H, Beecher HK. The value of the preoperative visit by an anesthetist. *Journal of the American Medical Association* 1963; **185**: 553–555.
14. Hall RCW, Zisook S. Paradoxical reactions to benzodiazepines. *British Journal of Clinical Pharmacology* 1981; **11**: 99S–104S.