J Anesth (1997) 11:14–17

Journal of
Anesthesia

Effects of estazolam as a premedication in mentally retarded patients

YUICHI KANMURA[1] and MUTUMI KAMIHASHI[2]

Departments of [1]Anesthesiology and [2]Dentistry, Kagoshima City Hospital, 20-17 Kajiya-cho, Kagoshima 892, Japan

Abstract: In anesthesia for mentally retarded patients, adequate preoperative sedation is important. We have investigated the sedative effects of estazolam in 16 mentally retarded patients who were given 0.1 mg·kg^{-1} orally; its sedative effects were compared with those of hydroxyzine (50 mg intramuscularly, 6 patients). Estazolam was observed to be significantly more effective as a sedative than hydroxyzine throughout the period under study. Estazolam was clinically effective in 94% of patients, no patient needing either additional drugs for sedation or heavy restraint. The sedative effects of estazolam lasted on average 9 h and patients were still well sedated after the operation. There was no serious complication due to estazolam. Thus, it was found to be an effective drug for premedication in mentally retarded patients.

Key words: Anesthesia, Estazolam, Premedication, Hypnotics, Mental retardation

Introduction

Anesthetic management of mentally retarded patients is difficult [1]. They are unable to comprehend the purpose of any medical procedure, so medical staff cannot obtain their active cooperation. Separation from their parents or relatives often produces anxiety, and unpleasant or painful procedures may trigger aggressive and combative behavior. In severe cases, even transfer from ward to operation room proves impossible.

Address correspondence to: Y. Kanmura
Department of Anesthesiology and Critical Care Medicine, Kagoshima University School of Medicine, 8-35-1 Sakuragaoka, Kagoshima 890, Japan
Received for publication on December 13, 1995; accepted on July 1, 1996

However, with appropriate preoperative medication, it should be possible to make these patients calm, relaxed, and cooperative, perhaps asleep, without undue depression of central nervous, cardiovascular, or respiratory functions [2]. However, few studies have reported the effects of premedication in mentally retarded patients.

Estazolam (Eurozine, Takeda Pharmaceutical, Tokyo, Japan) is an effective hypnotic, as indicated by an improvement in sleep latency and maintenance time, which is also used as a premedication for pediatric patients in Japan. No severe adverse effects have been reported in its use for pediatric premedication. Moreover, it has been reported that even in high doses, estazolam does not cause ventilatory depression [3]. On the basis of its reported safety and efficacy, we assessed the effects of estazolam as a premedication in mentally retarded patients and compared them with those of hydroxyzine.

Materials and methods

With institutional approval and informed consent from patients and/or parents, we studied 22 mentally retarded adult patients (ASA physical status I and II) undergoing dental treatment. All were in the range of severe intellectual and adaptive impairment, and previous attempts at dental examinations and treatments without general anesthesia were unsuccessful due to their aggressive and combative behavior.

One hour and a half before the patients were due to be taken into the operating room, they were given hydroxyzine 50 mg intramuscularly (6 patients) or estazolam 0.1 mg·kg^{-1} orally (16 patients). Heart rate and respiratory rate were checked both at the onset and throughout the period of sedation, each patient being monitored for adverse effects.

Once the patient was in the operating room, anesthesia was induced via a face mask with sevoflurane and

nitrous oxide in oxygen. After induction, an intravenous catheter was inserted and vecuronium bromide 0.1 mg·kg^{-1} given to facilitate nasal tracheal intubation. Famotidine 20 mg was given intravenously and a gastric tube inserted to enable emptying of the gastric contents. Each dental treatment for all patients was provided by the same dentist using conventional dental therapies. After the operation, neuromuscular blockade was antagonized with neostigmine 0.05 mg·kg^{-1} and atropine 0.02 mg·kg^{-1}, intravenously.

The level of sedation was assessed using a five-point scale: 1 = agitated/combative, 2 = awake/anxious, 3 = awake/calm, 4 = sleepy/drowsy, 5 = asleep [4]. For each patient, the position on this sedation scale, heart rate, and respiratory rate were recorded (a) immediately before the drug was administered, (b) 1 h after drug administration (in the ward), (c) 1.5 h after drug administration (on arrival in the operating room), (d) at induction of general anesthesia, (e) 10 min after extubation, and (f) 1.5 h after extubation (in the ward). Patients with a score of 3, 4 or 5 were considered to have a satisfactory level of sedation, and those with a score of 1 or 2 were considered not to be satisfactorily sedated. Statistical analysis was carried out on a personal computer using StatView 4.0 software (Abacus Concepts, Berkeley, CA, USA). For each group, the sedation scores at the different times were analyzed independently using the Wilcoxon signed-rank test. Comparison between groups at each time point was made using Mann-Whitney U test. Demographic data were compared using Student's *t*-test. A P value of <0.05 was considered statistically significant.

Results

Sixteen patients (8 men and 8 women) were given estazolam, and 6 patients (4 men and 2 women) hydroxyzine as premedication before anesthesia for dental procedures. The patients in the estazolam group were 18–42 years old (mean ± SD; 24.8 ± 7.5 years) and those in the hydroxyzine group 18–42 years old (mean

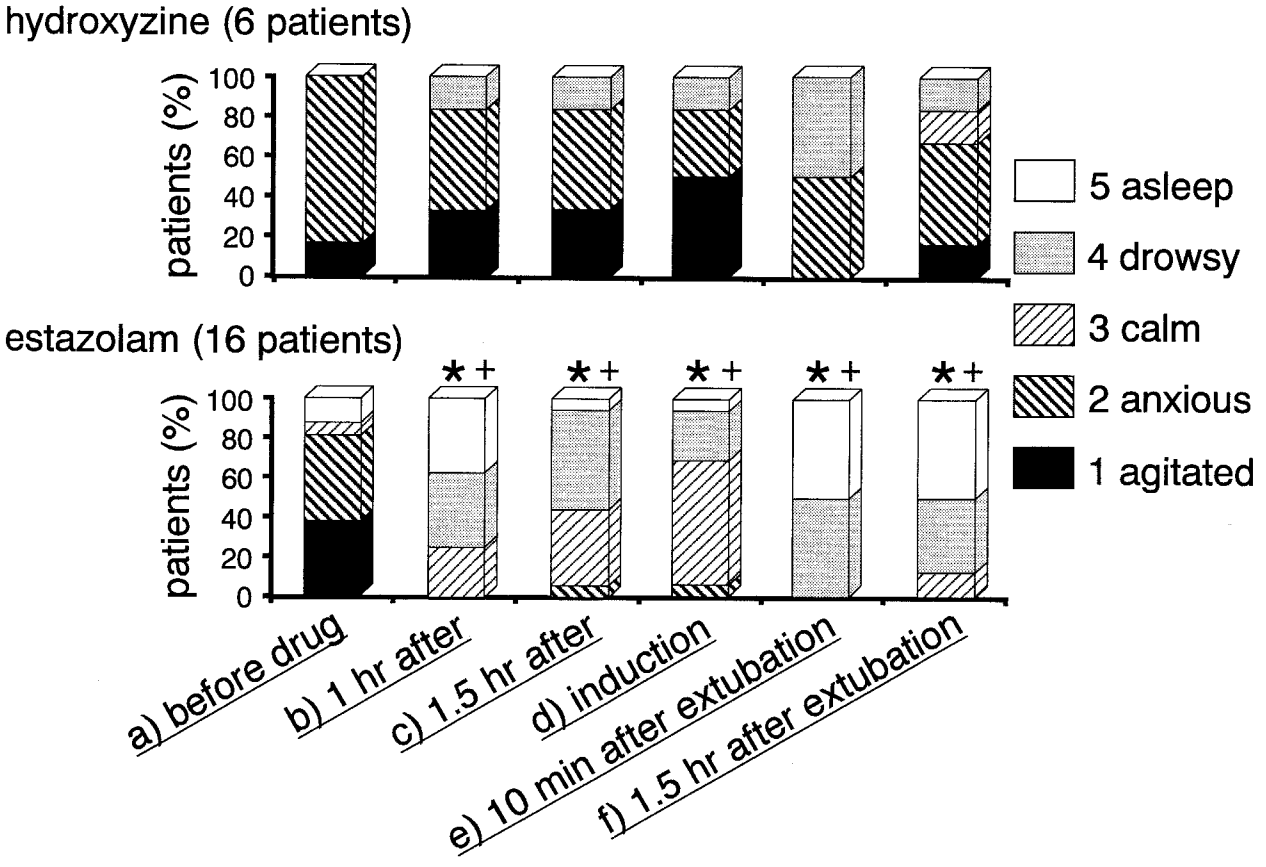

Fig. 1. Changes in sedation level following hydroxyzine or estazolam administration **a** before drug administration, **b** 1 h after drug administration (in ward), **c** 1.5 h after drug administration (on arrival at operating room), **d** at induction of general anesthesia, **e** 10 min after extubation, **f** 1.5 h after extubation (in ward). *$P < 0.01$ *vs* before drug administration (Wilcoxon signed-rank test). †$P < 0.01$ *vs* hydroxyzine group at same time (Mann-Whitney U test)

± SD; 29.0 ± 10.0 years). The body weight of the estazolam group was 33–55 kg (mean ± SD; 44.9 ± 5.8 kg) and that of the hydroxyzine group 39–52 kg (mean ± SD; 49.5 ± 4.6 kg). There was no significant difference between the two groups in terms of patients' age or weight.

The behavior of the patients during the study period is indicated in Fig. 1. In the hydroxyzine group, no significant change occurred after administration of the premedication. Five of the six patients needed physical restraint during their transfer to the operating table and at induction of anesthesia. The proportion in the "anxious" and "agitated" categories remained high (over 80% until induction). By contrast, in the estazolam group, significant improvements in behavior were already evident 1 h after administration by comparison with the period before administration; the effects continued throughout the period under study. Only one patient was considered unsatisfactorily sedated on arrival in the operating room and he was easily transferred onto the operating table with only slight restraint via his wrists. Significant differences in the level of sedation were already evident between the estazolam group and the hydroxyzine group 1 h after drug administration, and the statistical difference persisted thoughout the study period (Fig. 1).

Operation time was 55–295 min (mean ± SD; 206 ± 69 min) in the estazolam group and 100–275 min (mean ± SD; 185 ± 72 min) in the hydroxyzine group. There was no significant difference between these values. After the operation, the neuromuscular blockade was antagonized and the trachea extubated after confirmation of an arousal reaction. All patients in the estazolam group were still asleep or drowsy 10 min after extubation; their cardiovascular functions were stable and their peripheral oxygen saturation (SpO_2) in room air was over 96%. Most patients (88%) in the estazolam group were still asleep or drowsy 1 h after arrival on the ward and no patient needed physical restraint during transfer to the ward. Six patients in the estazolam group and 2 in the hydroxyzine group who had undergone extractions were given 12.5 or 25 mg diclofenac sodium rectally for pain relief just after the operation. The time to complete recovery from estazolam sedation (spontaneous eye opening) was 450–650 min (mean ± SD; 530 ± 69 min). No serious complication was experienced with estazolam.

Discussion

In mentally retarded patients, the incidence of dental disease is high due to their low level of oral hygiene. However, they cannot tolerate even conventional dental treatment which in normal patients is performed with or even without local anesthetic: their cooperation is impossible to obtain and general anesthesia is necessary [1]. Appropriate premedication is essential, both to make them calm enough to be transferred from ward to operating room without cardiovascular or respiratory depression and to facilitate the smooth induction of anesthesia.

There are several reports on premedication in mentally retarded patients. Diamond and Cochrane [1] suggested oral premedication with nitrazepam 10 mg and droperidol 20 mg, 2 h preoperatively in older children and adolescents. However, of their patients, 21% manifested evidence of aggression and 16% resisted induction of anesthesia. Consequently, they recommended an additional 10–20 mg droperidol by intramuscular injection half an hour preoperatively when patients were not adequately sedated by the initial oral premedication. As intramuscular premedication, 1.0–4.0 mg butorphanol has been suggested for dental procedures in severely and profoundly retarded patients [5]. However, while this was said to be clinically effective in 75% of patients, heavy restraint (restraining the patient's wrists, legs, chest, and head) was required in 44% of trials. The oral administration of ketamine (6–10 $mg \cdot kg^{-1}$) has been reported to be effective in agitated and combative mentally retarded patients [6,7], though to prevent excessive salivation and emergence phenomena due to ketamine, glycopyrolate 0.4 mg and diazepam 10 mg were necessary at the same time.

In the present investigation, we found that, at the doses used, estazolam had significantly greater sedative effects in mentally retarded patients than did hydroxyzine. Hydroxyzine was used because we routinely use this drug for adult patients as a premedication. Initially, we were unsure whether estazolam or hydroxyzine would prove to be the drug of choice for mentally retarded patients, but it soon became clear that hydroxyzine was inadequate for this purpose. The ineffectiveness of hydroxyzine may be explained in part by the difference in the drug administration routes. Intramuscular injection induces local pain and it may exacerbate the patients' anxiety and agitation. Therefore, we think that preanesthetic medication should be applied orally in mentally retarded patients. We also found that the effects of estazolam outlasted the operation. Following these initial findings, we decided to concentrate on testing the efficacy and safety of estazolam in these patients.

Estazolam is a triazolobenzodiazepine compound which has hypnotic and sedative properties and is currently available in Japan, Europe, and Latin America [8]. Its chemical structure is 8-chloro-6-phenyl-4H-S-triazolo-1,4 benzodiazepine. In our study, estazolam was observed to be clinically effective in 94% of patients, and no patient needed either additional drugs for

further sedation or heavy restraint. The sedative effects of estazolam lasted on average 9 h and, after the operation, patients were easily awakened, though still well sedated. It has been reported that, in healthy adults, estazolam is detectable in the blood within 30 min of oral administration, reaches maximal plasma concentration at approximately 1 to 2 h, and has a plasma half-life of 17 h [9]. The prolonged action of estazolam in our study presumably reflects its long plasma half-life.

The dose of estazolam used in this study ($0.1\,mg \cdot kg^{-1}$) is rather high, compared to the recommended dose in normal adults (2–4 mg). The most likely complication with such high doses is respiratory depression, but despite careful observation, we could find no evidence of respiratory disorder. Moreover, Skatrud et al. [3] have reported that a high dose of estazolam (6 mg) in healthy adults did not cause any ventilatory depression. In our study, there was no serious complication. Therefore, we think our dosage ($0.1\,mg \cdot kg^{-1}$) of estazolam can be used safely as a premedication for mentally retarded patients. However, careful monitoring after the operation is necessary for a considerable time and this drug may not be suitable as a premedication for day care surgery.

The route of drug administration is an important question in the premedication of mentally retarded patients [1]. Such patients are often suspicious about unfamiliar drugs and refuse to swallow them. In our study, the relationship between patient and dentist was sufficiently good that there was no problem in any patient swallowing the estazolam. We believe that the relationship between doctor (or dentist) and mentally retarded patient is an important factor in preanesthetic medication.

In conclusion, our results demonstrate the efficacy of estazolam as a premedication for mentally retarded patients. Estazolam ($0.1\,mg \cdot kg^{-1}$) was safe and effective not only as premedication, but also as a postoperative sedative.

Acknowledgment. The authors wish to thank Dr. R.J. Timms for his help in preparing the manuscript.

References

1. Diamond AW, Cochrane DF (1976) General anaesthesia for the mentally handicapped, a study based on anaesthesia for dental surgery. Anaesthesia 31:190–194
2. Kroll RG (1969) The effect of premedication on handicapped children. J Dent Child 36:103–114
3. Skatrud JB, Badr S, Begle RL, Juan D (1990) Ventilatory response to single, high dose estazolam in healthy humans. J Clin Pharmacol 30:543–548
4. Wilton NC, Leigh J, Rosen DR, Pandit UA (1988) Preanesthetic sedation of preschool children using intranasal midazolam. Anesthesiology 69:972–975
5. Jann MW, Fidone G, Gorday M, Rostedt RR (1987) Butorphanol as a dental premedication in the mentally retarded. Oral Surg Oral Med Oral Pathol 63:403–407
6. Bragg CL, Miller BR (1990) Oral ketamine facilitates induction in a combative mentally retarded patient. J Clin Anesth 2:121–122
7. Petros AJ (1991) Oral ketamine, its use for mentally retarded adults requiring day care dental treatment. Anaesthesia 46: 646–647
8. Walsh JK, Targum SD, Pergam V, Allen RP, Fillingim JM, Parwatikar S, Schweitzer PK (1984) A multi-center clinical investigation of estazolam: short-term efficacy. Curr Ther Res 36: 866–874
9. Allen MD, Greenblatt DJ, Arnold JD (1979) Single- and multiple-dose kinetics of estazolam, a triazolo benzodiazepine. Psychopharmacology 66:267–274