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Decreased intraoral secretions during sedation-analgesia with propofol-ketamine and midazolam-ketamine combinations

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Abstract

Purpose. To investigate salivary flow over time with a balanced sedation-analgesia technique using a propofol-ketamine (PK) or a midazolam-ketamine (MK) combination in human volunteers.

Methods. In the PK group, boluses of 1 mg·kg^{-1} of propofol and 0.7 mg·kg^{-1} of ketamine were initially administered. This was followed by an infusion, given over a 1-h period, of propofol (5 mg·kg^{-1}) admixed with ketamine (0.7 mg·kg^{-1}). In the MK group, 0.07 mg·kg^{-1} of midazolam and 0.7 mg·kg^{-1} of ketamine was followed by the infusion of a midazolam (0.07 mg·kg^{-1}) and ketamine (0.7 mg·kg^{-1}) admixture, also given over a period of 1 h. Salivary flow was measured prior to and at 10-min intervals during the sedation-analgesia, as well as for 30 minutes after its termination.

Results. Mixed intraoral secretions were significantly reduced, by 43% and 47%, on average, in the PK and MK groups, respectively, when compared with presedation levels, and had not returned to baseline levels 30 min after discontinuation of the infusion.

Conclusion. Sedation-analgesia with PK and MK combinations controls intraoral secretions by reducing salivary flow.

Key words Salivation · Propofol · Midazolam · Ketamine · Sedation-analgesia

Introduction

Various upper airway procedures, including endoscopic procedures and, in particular, dental and other intraoral procedures, require a dry working field that is free of salivary secretions. Various devices, such as evacuators, remove the secretions once they become present. There have been no extensive studies of the effects on salivary flow of many pharmacological agents. Some sedating agents with antisialogogue effects of varying duration include scopolamine, clonidine, diazepam, and nitrous oxide [1–4].

Ketamine is a potent nonopiod analgesic with sedative, hypnotic, and amnesic properties, and it has the additional advantage of maintaining postoperative analgesia. Administered solely, it stimulates hemodynamics and may produce nausea and dysphoria. Propofol and midazolam produce anxiolysis, sedation, and hypnosis. Propofol, in particular, also has antiemetic properties. When ketamine is used to supplement propofol or midazolam sedation, each agent attenuates the undesirable effects of the other, while reducing the hypnotic requirement and maintaining cardiorespiratory stability [5–8].

Ketamine anesthesia has been reported to cause excessive salivation, with reported rates varying from as low as less than 2% of patients [9]. Kanri et al. [10] have shown a significant increase in mixed salivary secretions associated with the sole use of ketamine. It appears that increasing the dose of ketamine increases the likelihood of salivation [11]. Schaer [12] reported that 10 of 40 patients receiving propofol anesthesia experienced salivation that, in some instances, led to coughing. Benzodiazepines are known to, infrequently, cause dry mouth; however, quantification of the effect of midazolam on salivary function could not be found in the literature. In animal experiments, the addition of midazolam after the administration of ketamine did not affect salivation [13]. The unnecessary addition of anticholinergic agents to counteract excessive salivation may have other unwanted effects, such as cardiac effects and delirium [14].

The effect of salivary flow with a balanced sedation-analgesia technique using a propofol-ketamine (PK) or midazolam-ketamine (MK) combination has not been studied previously.

The aim of the present study was to investigate the effect of a subanesthetic dose of a propofol or mida-

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zolam and ketamine combination on total intraoral mixed salivary secretions over time.

Subjects and methods

The PK group consisted of 11 healthy adults with a mean age of 25.6 ± 2.0 years and a mean weight of 62.3 ± 8.6 kg. The MK group consisted of 10 healthy adults with a mean age of 28.6 ± 5.8 years and a mean weight of 63.8 ± 10.0 kg. All the subjects were healthy, American Society of Anesthiologists (ASA) physical status I volunteers and were studied after they had provided their informed consent. The study protocol was examined and approved by the institution's investigation committee. The subjects were tested in the morning, after an overnight fast.

After the subject was placed in the supine position, oxygen was administered via a nasal mask, and routine clinical monitoring, which included noninvasive determination of arterial blood pressure and arterial oxygen saturation, tracheal auscultation, and the use of a three-lead ECG, was carried out throughout the entire study period. An intravenous infusion of 0.9% saline was established, after left forearm venipuncture, with a 20- or 22-gauge cannula.

In the PK group, a loading dose of 1 mg·kg^{-1} of propofol was initially administered slowly, over a period of 2 min. This was immediately followed by 0.7 mg·kg^{-1} of ketamine, which was also infused slowly, over a period of 2 min. Propofol (5 mg·kg^{-1}) was admixed with ketamine at the same dose as the initial dose (0.7 mg·kg^{-1}) and infused over a period of 1 h. In the MK group, midazolam was initially administered intravenously, at a loading dose of 0.07 mg·kg^{-1}, over a 2-min period and this was followed by a ketamine bolus of 0.7 mg·kg^{-1}, also administered slowly, over a 2-min period. Midazolam 0.07 mg·kg^{-1} was admixed with ketamine 0.7 mg·kg^{-1} and this was infused over a 1-h period. In both groups, saline was added to the agents to produce a standard volume of 60 ml. This was infused via a micro-mini drip over the 1-h period. Measurements were taken prior to the administration of the agents, immediately after the end of the loading doses, and every 10 min thereafter, until 30 min after the discontinuation of the infusion.

Salivary flow was measured by placing three dental cotton rolls (diameter, 8 mm; length, 25 mm; Taketora, Tokyo, Japan) in the floor of the mouth for 5 min. The first measurement during the sedation period was therefore taken 5 min post-induction. Two cotton rolls were placed in the lateral sulcus of the floor of the mouth and one in the anterior sulcus, and the mouth was closed. The cotton rolls were weighed, immediately after removal, on an electronic balance (AND, Tokyo, Japan) with an accuracy of 1×10^{-7} g. The cotton rolls were inserted and removed with the assistance of dental tweezers. Room temperature was maintained at a constant 25°C, with a relative humidity of 50%.

Data values were analyzed using analysis of variance, followed by a Bonferroni post-hoc *t*-test, with $P < 0.05$ being considered significant.

Results

The ages and weights of the subjects in the two groups were not significantly different. Salivary flow was reduced significantly at all points after the administration of the agents, except for 10 min after the initial propofol and ketamine doses. During the period of drug administration, salivary flow fell significantly, by 43% on average in the PK group and by 47% on average in the MK group, in comparison with presedation levels. The overall profiles of total intraoral mixed salivary secretions in the PK and MK groups were similar, with no significant differences between the groups (Fig. 1).

The onset of and continuing reduction in salivary levels appeared to be correlated with the deepening of sedation. Although the level of sedation may have appeared to be deep, respiration rates did not change significantly from preadministration control levels in either group, and hemoglobin oxygen saturation levels remained very high in both groups; 99.5 ± 0.8% in the PK group and 98.6 ± 1.2% in the MK group.

A change from nose to mouth breathing was also noted as the depth of sedation increased. The phenomenon of coughing was, unexpectedly, observed only in the PK group, notably during the second half of the 1-h infusion when levels of salivary secretion were lowest and sedation deepest.

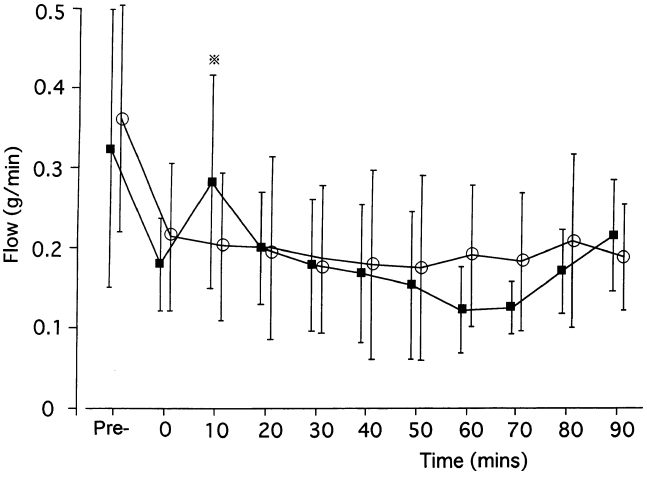

Fig. 1. Salivary flow over time. *Circles*, midazolam-ketamine; *squares*, propofol-ketamine. ※Not significantly different from presedation levels ($P < 0.05$)

At the end of the trial, all subjects reported that at no stage did they experience an uncomfortable level of dryness of the mouth.

Discussion

The results of the present study show that salivary flow was reduced after intravenous sedation-analgesia with propofol-ketamine or midazolam-ketamine.

To date, the methods used for testing the antsialogogue effect of various agents have been completely subjective, or they have measured parotid flow via a suction cup or cannulization. The last two measures assume the unproven assertion that parotid flow is directly proportional to the total level of salivary secretions. Salivation into a container or tube requires subject cooperation and is not a precise technique [15]. Our technique for collecting saliva provides a simple and effective method for measuring salivary flow.

Total intraoral mixed secretion levels fell significantly and to a similar extent after the administration of the agents in both groups, and had not returned to baseline levels 30 min after the discontinuation of the agents. The subanesthetic doses chosen for this study were approximately half of those commonly used during general anesthesia.

Salivary levels appeared to be related to depth of sedation. This has been particularly noted with benzodiazepine sedation, in which sedation is significantly correlated with saliva levels [16]. This phenomenon was noted particularly in the PK group and could explain the transient increase in salivary levels to baseline levels that was seen, 10 min after the bolus administration of propofol and ketamine, when the level of sedation appeared to lighten.

We attempted to keep our subjects' mouths closed, but the effect of mouth breathing on intraoral salivary levels is not known. Schaer [12] noted salivation with propofol anesthesia, which led to coughing. Coughing in the present study was observed in the PK group, notably in the second half of the 1-h infusion, when levels of salivary secretion were lowest and sedation deepest. Shibazaki et al. [17] noted coughing in 60% of patients receiving propofol sedation and none in patients receiving midazolam sedation. It appears that subject positioning did not effect coughing rates. In their study, coughing occurred on average 33 min after the commencement of the infusion, but no severe adverse effects were noted. The mechanism of cough induced by propofol is not clearly understood, and may be independent of salivation. Similarly, glycopyrrolate will diminish salivation, but does not affect the stridor seen with ketamine administration [18].

Roelofse et al. [19] showed a twofold increase in excessive salivation in patients receiving an oral midazolam-ketamine combination, compared with findings in those receiving midazolam alone. A possible explanation for this result may be the disproportionately higher level of midazolam when used alone and the high dose of ketamine used in the midazolam-ketamine combination. Similarly, Saint-Maurice et al. [20] also reported a high rate of salivation (25%) in pediatric patients who received nasally administered midazolam ($0.2\,mg\cdot kg^{-1}$) followed by rectally administered ketamine ($9.0\,mg\cdot kg^{-1}$).

The present study was carried out in human volunteers, and more research is required to investigate the clinical situation, in which other factors, such as stress and anxiety, premedication, and other drugs may affect salivary secretions.

In conclusion, mixed intraoral secretion levels were significantly reduced over time, compared with presedation levels, with subanesthetic doses of propofol and ketamine or midazolam and ketamine. This technique may be clinically important during dental and other upper airway procedures that require sedation-analgesia.

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