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H_1- and H_2-receptor antagonists prevent histamine release in allergic patients after the administration of midazolam-ketamine. A randomized controlled study

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Abstract. *Objective*: The prophylactic effects of H_1- and H_2-receptor antagonist against histamine release and clinical symptoms (e.g. skin reactions, hemodynamic changes) were examined in 80 allergic patients after the administration of midazolam-ketamine.
Subject: We examined 80 allergic patients undergoing oral surgery.
Methods: A prospective randomized controlled study was performed in four groups of 20 patients who received either hydroxyzine (H_1-receptor antagonist), chlorpheniramine (H_1-receptor antagonist), a combination of chlorpheniramine and famotidine (H_1- and H_2-receptor antagonist) or a placebo (control) as premedications. Venous blood samples were obtained before introduction as a control and 0.5, 1, 3, 5 min after the administration of midazolam-ketamine in order to measure the plasma histamine level. In addition, any observed hemodynamic changes were simultaneously recorded. The plasma histamine level was measured using the HPLC (high performance liquid chromatography) post-label system.
Results: The patients who were treated with both chlorpheniramine and famotidine demonstrated a high level of basal plasma histamine compared to the patients who were treated by hydroxyzine alone ($p < 0.05$), and they also showed less histamine release and anaphylactoid reactions during midazolam-ketamine anesthesia. Allergic patients demonstrated a high percentage of eosinophils, with an average of $4.79 \pm 3.78\%$.
Conclusion: The administration of midazolam-ketamine in allergic patients demonstrated no significant problems. The combined premedication with chlorpheniramine and famotidine was thus found to have the most prophylactic effect against histamine release after the administration of midazolam-ketamine in allergic patients in spite of a high level of basal plasma histamine.

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Key words: H_1-receptor antagonist – H_2-receptor antagonist – Midazolam – Ketamine – Allergic disease

Introduction

The induction of anesthesia is considered to be the most dangerous period for the reaction of histamine release. Many drugs (e.g. muscle relaxants, intravenous anesthetics) and infusion materials, which are used for the induction of anesthesia, may cause an increase in the plasma histamine level by non-immunologic mechanisms and unwanted reactions due to histamines such as skin reactions, hemodynamic changes and other clinical symptoms may thus occur. Previous studies have reported the prophylactic use of histamine receptor antagonists to attenuate many of the histamine mediated side effects [1–3]. Moreover, Lorenz et al. strongly recommended its combination treatment as a general premedication before anesthesia in patients with a history of adverse reactions or a history of allergy, a high risk of histamine release during surgery, a high age and a poor physical status due to other systemic diseases [4–7]. The use of the combination of H_1- and H_2-receptor antagonist is well known to have a good prophylactic effect on anaphylactoid reactions during the perioperative period for non-allergic patients, however, its clinical efficacy for allergic patients has yet to be elucidated. Ketamine is useful for asthmatic patients [8], and its effectiveness and successful use in the anesthetic management of the asthmatic patients have both been reported [9–11]. The combination of midazolam with ketamine has also been previously recommended for total intravenous anesthesia in military surgery, general civilian practice and cardiac surgery [12–14].

The purpose of this study was to evaluate its prophylactic effect against histamine release and the clinical symptoms of H_1- and H_2-receptor antagonist used either in combination with other drugs or alone during the induction of midazolam-ketamine anesthesia for allergic patients.

Patients and methods

Patients and groups

A prospective randomized controlled study was performed in 80 adult patients undergoing oral surgery at the Dental Hospital of Kyushu University, Fukuoka, Japan. Each patient received information about this trial and gave their consent. All 80 patients had to meet the following criteria: patients with a history of allergy, and/or the percentage of eosinophils in the leukocytes was more than 3%. Eighty patients were allocated randomly to one of four premedication groups of 20 patients each, for the prospective randomized controlled study of the effects of H_1- and/or H_2-receptor antagonist. The four premedication groups included group 1: who received a placebo as a control, group 2: who received chlorpheniramine (H_1-receptor antagonist), group 3: who received hydroxyzine (H_1-receptor antagonist) and group 4: who received chlorpheniramine (H_1-receptor antagonist) and famotidine (H_2-receptor antagonist), respectively. In order to randomize the list of premedications, chlorpheniramine 0.12 mg/kg, famotidine 0.4 mg/kg and hydroxyzine 1 mg/kg were given orally 120 minutes before, and atropine sulfate 0.01 mg/kg was injected in all patients intramuscularly 30 min before the induction of anesthesia.

The patients showed an anesthetic risk of ASA class I-II and ranged in age from 14 and 83 years (average 34.8), weighing from 41.0 to 95.6 kg, and the male to female ratio was 39 to 33. Eight patients out of 80 were excluded from this study because of the inability to obtain a sufficient blood sample. The demographic data in each group are summarized in Table 1.

Methods

After arriving at the operating theater, intravenous infusion was started from the cephalic vein. In addition, the median cubital vein on the other arm was cannulated for blood sampling to determine the level of plasma histamine by the HPLC (high performance liquid chromatography). All patients were monitored by electrocardiography, automated blood pressure and pulse oximetry (Life Scope 14, Nihonkohden, Tokyo, Japan).

Midazolam 0.1 mg/kg and ketamine 1 mg/kg were administered for over 1 minute in all patients for the induction of anesthesia. The patients were ventilated with 4 litre/min. oxygen. Vecuronium, 0.1 mg/kg, was continuously administered to facilitate tracheal intubation. Tracheal intubation was performed 5 minutes after midazolam-ketamine. Anesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen in all patients.

Venous blood samples (4 ml each) were obtained before induction as a control and 0.5, 1 3, 5 min after the administration of midazolam-ketamine in order to measure the plasma histamine level by a heparinized plastic syringe, and then were transferred to a plastic tube in an ice box. The heart rate and blood pressure were simultaneously recorded. Skin reactions (e.g. skin flushing, urticaria) were evaluated by two anesthesiologists. Blood samples were centrifuged at 10,000 r.p.m. for 10 min at 4 °C immediately to obtain a plasma layer (1 ml). Perchloric acid (50 μl) was added to the plasma layer. All samples were stored at −25 °C until the plasma histamine level was measured using the HPLC post-label system.

Table 1. Demographic data in each group. Values are the mean ± SD.

	Group 1	Group 2	Group 3	Group 4
Number (n)	19	18	18	17
Age (yr)	36.1 ± 14.1	30.4 ± 18.1	33.2 ± 17.2	35.4 ± 16.3
Weight (kg)	53.1 ± 8.1	57.8 ± 8.5	58.0 ± 7.3	61.6 ± 14.5
Sex (M/F)	7/12	14/4	10/8	8/9

Measurement of the plasma histamine level

Plasma histamine assays were performed using the HPLC (high-performance liquid chromatography) post-label system as previously reported [15, 16]. This system was composed of an Intelligent pump (Hitachi, L-6200), a Reaction pump (Hitachi, 655-A-13), a Fluorescence spectrophotometer (Hitachi, F-1150), an Autosampler (Hitachi, AS-4000), a Chromato-integrator (Hitachi, D-2500) and a 6 ø, 15 cm column (Catecholepak, Toyosoda, Tokyo, Japan) warmed at 50 °C by Column oven (Hitachi, L-5020). The measurement of the concentration of plasma histamine was evaluated by the external standard method, the limit of which was 1 pg/ml [16]. The stored plasma was centrifuged at 3,000 r.p.m. for 25 min at 15 °C. Each supernatant 100 μl was injected into the HPLC for each sample. The excitation wavelength used was 340 nm and the emission 450 nm and the retention time was approximately 10 minutes 40 s.

None of the drugs or drug formulations interfered with the HPLC assay.

Criteria for the histamine release and hemodynamic changes

Histamine release was regarded as positive (i.e. a positive responder), when the level of plasma histamine increased by more than 50% [17] from the control value 5 min after the administration of midazolam-ketamine. An increase in the heart rate and a decrease in the systolic blood pressure by more than 20% from the control level were defined as positive.

Statistical analysis

The data are presented as the mean ± SD. The demographic data were compared using one factor ANOVA. The Chi-square test and Fisher's exact probability test were used to compare the incidence of each reaction between the groups. A comparison of plasma histamine level between the groups was analyzed by one factor ANOVA with Bonferroni's correction as post hoc testing, and a repeated measure ANOVA was used to compare any differences within a group. Values of $p < 0.05$ were considered to be statistically significant.

Results

The number of the patients as well as the age, body weight and sex distribution in each group are summarized in Table 1. No significant differences were observed between the groups regarding the demographic data.

The number of allergic diseases, the basal plasma histamine level and the percentage of eosinophils in each group are shown in Table 2. The incidence of allergic diseases between the groups did not reach statistical significance. The mean basal plasma histamine level in group 4 (0.51 ± 0.24 ng/ml) was much higher than that in group 3 (0.32 ± 0.15 ng/ml) ($p < 0.05$). The percentage of eosinophils was similar between the groups, the average of which in all patients was 4.79 ± 3.78%.

The frequency of histamine release were similar between the groups (Table 3). The highest incidence of skin reaction was observed in the placebo group, and the lowest incidence was found in the group either with hydroxyzine alone or a combination of chlorpheniramine and famotidine. However, no significant differences were seen between the groups. Although no statistically significant differences were seen between the groups, the highest increase in the heart rate, namely more than 20% from the control value, was observed

Table 2. Number of allergic diseases, basal plasma histamine level and eosinophil in each group. Values are the means ± SD. Basal plasma histamine level in group 4 was higher than in group 3 (*$p < 0.05$).

	Group 1 (n = 19)	Group 2 (n = 18)	Group 3 (n = 18)	Group 4 (n = 17)
Allergic disease				
asthma	2	4	4	2
hay fever	3	2	3	3
atopic dermatitis	3	1	1	1
drug allergy	6	0	1	3
food allergy	4	3	2	2
allergic rhinitis	3	1	0	2
contact-type dermatitis	0	1	2	0
cold urticaria	0	0	1	1
Basal plasma				
histamine level (ng/ml)	0.39 ± 0.19	0.45 ± 0.23	0.32 ± 0.15	0.51 ± 0.24*
Eosinophil (%)	5.2 ± 5.0	4.1 ± 3.4	5.5 ± 3.7	4.3 ± 2.9

in the placebo group (52.6%). The decrease in the systolic blood pressure, namely more than 20% from the control value, was similar between the groups.

The combination of skin reactions with histamine release was observed in 3 patients from the control group and in none of the patients in group 4, however, the incidence was not statisically significant between the groups. (Data are not shown.) The change in the mean plasma histamine level from the control value in the responders is shown in Fig. 1. After the administration of midazolam-ketamine, the plasma histamine level at 1 min in group 1 (placebo) was much higher than that in group 4 (H_1- and H_2-receptor antagonist). In this study, the peak plasma histamine level was observed at either 0.5 or 1 min after the administration of midazolam-ketamine.

No patient demonstrated any severe adverse reactions which required treatment after the administration of H_1- and/or H_2-receptor antagonist and also during midazolam-ketamine anesthesia.

Discussion

Anesthesiologists still cannot clearly agree on the best anesthetic method including premedication for allergic patients, because patients with some susceptibilities to various drugs may also develop adverse reactions. Many previous clinical trials have excluded patients with any history of allergy. For this reason, we decided to focus our study on patients with a history of allergy.

Since Betts and Parkin [8] first described the use of ketamine for an asthmatic patients, its effectiveness and successful use regarding the anesthetic management of the asthmatic patients has been reported [9–11]. Moreover the usefulness of ketamine, which produces significant cardiovascular stimulation and unpleasantness, including vivid dream-like experiences [18] has been also assessed in vitro [19, 20]. In contrast, midazolam attenuated both the cardiostimulatory responses and unpleasant emergence reaction associated with ketamine [21].

For these reasons, the combination of midazolam and ketamine has been previously recommended for total intravenous anesthesia [12–14], however, there are few reports on whether or not it is also useful for patients who have a history of allergy. Nevertheless, it is well known that combined H_1- and H_2-receptor antagonist reduces the number of histamine-related side effects [1–3]. Lorenz et al. has strongly recommended this combination treatment as a premedication before anesthesia and surgery in patients with either an allergic history or other systemic diseases [4–7]. Many previous studies have shown the use of i.v. antihistamine to have an effective prophylactic effect.

For these reasons, we examined the prophylactic effect against the histamine release reaction for a strong H_1-receptor antagonist hydroxyzine, a weaker H_1-receptor antagonist chlorpheniramine and the combination H_1- and H_2-receptor antagonist (chlorpheniramine and famotidine), which was administered orally before midazolam-ketamine anesthesia for allergic patients. Chlorpheniramine administered at an oral dose of 0.12 mg/kg was rather low, compared to other studies in the same field which normally administered 0.3 mg/kg intravenously [22, 23].

Regarding the patient with asthma, the number of eosinophils in the blood increased [24, 25], and there was a significant correlation between the peripheral blood eosinophil counts and the severity of asthma [26, 27]. The eosinophil count in the peripheral blood was well reflected in the pathophysiologic process, which was responsible for bronchial asthma, moreover, the relationship between allergic diseases and eosinophils has also been suggested. Our results showed that allergic patients demonstrated a high percentage of eosinophils.

Table 3. The incidence of histamine release, skin reactions and hemodynamic changes.

	Group 1 (n = 19)	Group 2 (n = 18)	Group 3 (n = 18)	Group 4 (n = 17)
Histamine release (responder)	7 (36.8%)	6 (33.3%)	6 (33.3%)	6 (35.3%)
Skin reactions	7 (36.8%)	6 (33.3%)	2 (11.1%)	2 (11.8%)
Heart rate ≧ 205	10 (52.6%)	7 (38.9%)	5 (27.8%)	8 (47.1%)
S.B.P. ≦ 20%	2 (10.5%)	2 (11.1%)	4 (22.2%)	2 (11.8%)

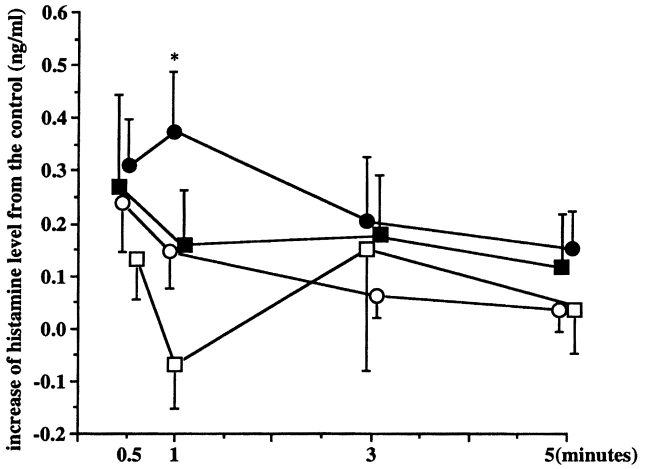

Fig. 1. The change in the plasma histamine level from the control value in each responder in each time. All data are presented as the mean ± SE. Premedication groups: ● = Group 1 (n = 7); ○ = Group 2 (n = 6); ■ = Group 3 (n = 6); □ = Group 4 (n = 6). *P < 0.05 vs. group 4.

Different premedications demonstrated different basal plasma histamine levels according to our results. The mean basal histamine level in group 4 (0.51 ± 0.24 ng/ml) was much higher than that in group 3 (0.32 ± 0.15 ng/ml ($p < 0.05$). In a previous study, the first-generation histamine H_1-receptor antagonist, chlorpheniramine, was reported to possibly activate histamine release from mast cells [28]. In another study, chlorpheniramine was also shown to be a histamine releaser in man, particularly when it was used with cimetidine [22]. In contrast, H2-receptor antagonist famotidine demonstrated a dose-dependent inhibition of histamine release [29]. The combination of H_1-receptor antagonist (chlorpheniramine) and H_2-receptor antagonist (famotidine) has also been shown to cause histamine release by itself.

Moreover, our findings suggested that the difference in the basal plasma histamine level may reflect each histamine receptor antagonism in each premedication group. Since histamine receptors in the whole body were blocked by H_1- and H_2-receptor antagonists in group 4, few residual receptors are known to combine with free histamine in blood. Therefore, the mean basal histamine level in group 4 (H_1- and H_2-receptor antagonist) was higher than in the other groups.

In this study, histamine release and clinical symptoms were evaluated up to 5 minutes after the administration of midazolam-ketamine. According to Lorenz et al. [4], the stress hormone released by such physical stimulation as intubation induced histamine release. For that reason, we ruled out any other reactions except for induction agents to histamine release, hemodynamic changes and other clinical symptoms.

Although the basal plasma histamine level did differ between the groups (Table 2), the frequency of histamine release after the administration of midazolam-ketamine was similar between the groups, as shown in Table 3. Doenicke et al. reported that cutaneous manifestations could be prevented by the administration of H_1- and H_2-receptor antagonist [2]. Similar findings were also observed in our results. Hemodynamic changes after the administration of induction agents were considered to be due to the effects of ketamine, because they are associated with catecholamine release which induces an increase in both the heart rate and systolic blood pressure [30, 31].

Histamine release events do not correlate with clinical symptoms, however, 6 out of 9 patients who showed a high level of plasma histamine namely more than 1 ng/ml showed either skin reactions or hemodynamic changes after the administration of midazolam-ketamine. (Data are not shown). A high level of plasma histamine is thus considered to correlate to skin reactions or hemodynamic changes.

Patients given a combination of H_1- and H_2-receptor antagonist showed the smallest change in histamine release after the administration of midazolam-ketamine, as shown in Fig. 1. Doenicke et al. suggested that antihistamine might thus significantly inhibit drug-induced histamine release [3].

While the peak plasma histamine level was seen at either 0.5 or 1 min after the administration of midazolam-ketamine in most patients, it soon returned to the baseline level within 5 minutes, which was a a little earlier than that described in a previous report [17].

The induction of anesthesia by midazolam-ketamine is thus considered to be useful in allergic patients without any significant problems. Moreover, we also consider the combined H_1- and H_2-receptor antagonist used as a premedication to have the greatest prophylactic effect for allergic patients against histamine release reaction (i.e. the increase of plasma histamine, skin reactions, hemodynamic changes) after the administration of midazolam-ketamine in spite of a high level of basal plasma histamine.

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