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Effects of a mixture of medetomidine, midazolam and butorphanol on anesthesia and blood biochemistry and the antagonizing action of atipamezole in hamsters

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ABSTRACT. Syrian golden hamsters (*Mesocricetus auratus*) are useful laboratory rodents for studying human infectious diseases, metabolic diseases and cancer. In other rodents, such as mice and rats, a mixture of medetomidine, midazolam and butorphanol functions as a useful anesthetic, although it alters some blood biochemical parameters. In this study, we examined the effects of this mixture on anesthesia and blood biochemical parameters, and the action of atipamezole, a medetomidine antagonist, in hamsters. Intramuscular injection of a mixture of medetomidine, midazolam and butorphanol at doses of 0.15, 2.0 and 2.5 mg/kg, respectively, had a short induction time (within 5 min) and produced an anesthetic duration of approximately 100 min in hamsters. We also demonstrated that 0.15 mg/kg of atipamezole, corresponding to the same dose as medetomidine, made hamsters recover quickly from anesthesia. The anesthetic agent markedly altered metabolic parameters, such as plasma glucose and insulin; however, 0.15 mg/kg of atipamezole returned these levels to normal range within approximately 10 min after the injection. The anesthetic also slightly altered mineral levels, such as plasma inorganic phosphorus, calcium and sodium; the latter two were also improved by atipamezole. Our results indicated that the mixture of medetomidine, midazolam, and butorphanol at doses of 0.15, 2.0 and 2.5 mg/kg, respectively, functioned as an effective anesthetic, and atipamezole was useful for antagonizing both anesthesia and biochemical alteration in hamsters.

KEY WORDS: atipamezole, butorphanol, hamster, medetomidine, midazolam

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Syrian golden hamsters (*Mesocricetus auratus*) are small rodents possessing cheek pouches and a well-characterized animal model for oral mucosal irritation studies and research on human oral cancers [8, 10]. Hamsters are essential animal models in biomedical studies, in addition to mice and rats, as they display many similar features to human physiology and are used also as models for human diseases, such as infectious diseases, atherosclerosis, pancreatitis, pancreatic cancer and nonalcoholic fatty liver disease [2, 3, 9, 19, 22]. Moreover, recently, it has become possible to generate transgenic or knockout hamsters [4, 7].

In hamsters, an adequate anesthetic is the inhalation of isoflurane [6]. However, since it is supplied through oral airway, use of isoflurane disadvantages the experiments using cheek pouches. Although the injection of a combination of ketamine and xylazine also works well in hamsters [6], ketamine has been categorized as a narcotic drug in Japan, whereas the injection of pentobarbital is no longer used because of its poor analgesic activity and narrow safety margins [5]. Therefore, the identification of suitable injectable anesthetics will facilitate the use of hamsters as animal models in biomedical experiments. Recently, the mixture of

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medetomidine, midazolam and butorphanol (MMB) has been recognized as favorable anesthetic in laboratory rodents, such as mice, rats and cotton rats [12, 13, 15, 17]. Although the MMB mixture provides sufficient anesthesia and is counteracted by atipamezole, a medetomidine antagonist, this anesthetic agent alters some biochemical parameters in mice and rats [18, 21].

This study examined the anesthetic effect of the MMB mixture in hamsters. The influence of the anesthetic agent and its antagonizing action of atipamezole on the biochemical parameters, were also examined.

MATERIALS AND METHODS

Animals

Animal experimentation was performed in accordance with the guidelines issued by Chitose Laboratory, Japan Food Research Laboratories (approval no. 20161208). Male Syrian hamsters were obtained from Japan SLC (Hamamatsu, Japan). Hamsters, weighing between 133 and 188 g, were used in this study. The animals were allowed free access to tap water and a commercial diet (CRF-1, Oriental Yeast, Tokyo, Japan). The animal room was maintained at 20 to 26°C with relative humidity from 30 to 70% and a 12-hr light and dark cycle.

Anesthetic protocol

Medetomidine hydrochloride (Domitor®, Nippon Zenyaku Kogyo, Tokyo, Japan), midazolam (Midazolam Sandoz®, Sandoz, Tokyo, Japan) and butorphanol (Vetorphale®, Meiji Seika Pharma, Tokyo, Japan) were diluted with sterile saline (Hikari Pharmaceutical, Tokyo, Japan) and were mixed at doses of 0.3, 4.0 and 5.0 mg/kg body weight of hamsters, respectively (high dose MMB). In addition, the high dose MMB was diluted with the same volume of sterile saline to make the low dose MMB (0.15 mg/kg of medetomidine, 2.0 mg/kg of midazolam and 2.5 mg/kg of butorphanol). The anesthetic mixture was prepared at time of use and was injected intramuscularly at 0.25 ml/100 g. The administration route was chosen according to the manufacturers' instructions. After the injection, the animals were kept on the wood chip, and each anesthetic score was measured using a grading system described in a previous study [15]. The score was based on 5 reflexes: a front paw reflex, a hind paw reflex, a tail reflex, a corneal reflex and a body righting reflex. If an animal lacked one of the aforementioned reflexes, it was given a score of 1. If it reacted, it was given a score of 0. The total anesthetic score was graded from 0 to 5. A hamster that scored 4 or more was considered to be under anesthesia. The induction time was defined as the time from injection to the onset of anesthesia. The duration for which a hamster showed a score of either 4 or 5 was considered to be the anesthetic duration. The time required for the anesthetic score to return to 0 from the end of anesthetic condition was defined as the recovery time. For the assessment of the recovery from anesthesia, animals receiving MMB low dose were intramuscularly injected with 0.15 mg/kg of atipamezole (Antisedan®, Nippon Zenyaku Kogyo) immediately after reaching anesthetic condition. The dose of atipamezole was the same as that of medetomidine, which has previously been shown to be sufficient to recover from the anesthesia in mice, rats and cotton rats [14, 15, 17].

Blood biochemistry

The group settings are summarized in Fig. 1. In hamsters receiving a high and low dose MMB, blood was collected from the vena cava under anesthesia with isoflurane when the anesthetic score returned to 0. Hamsters receiving low dose MMB

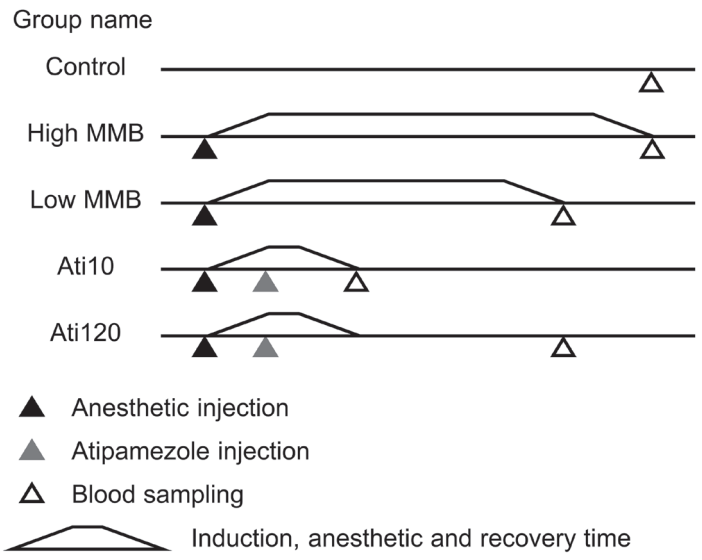

Fig. 1. Scheme of blood sampling.

Table 1. Evaluation of the anesthetic effect in hamsters

Group	High MMB	Low MMB	Low MMB + ATI
Number of animals	5	6	8
Body weight (g)	147.1 ± 5.5	167.4 ± 5.8	159.3 ± 6.3
Induction time (min)	4.4 ± 0.5 (3–6)	4.0 ± 1.1 (3–9)	5.4 ± 1.0 (3–10)
Anesthetic time (min)	162.0 ± 11.7 (118–182)	106.2 ± 7.9 (74–123)[a)]	-
Recovery time (min)	40.2 ± 3.6 (29–48)	27.8 ± 4.0 (14–41)	10.5 ± 2.5 (4–25)[b,c)]

Data are presented as means ± standard error. The range is given between parentheses. Differences were analyzed using the Mann-Whitney *U* test between two groups and the Kruskal-Wallis test followed by Scheffé's method among three groups. a) $P<0.05$, b) $P<0.001$ vs. high MMB group, c) $P<0.05$ vs. low MMB group.

and atipamezole were divided into two groups. In one group, blood was collected about 10 min after atipamezole injection, corresponding to the time when anesthetic score returned to 0 (Ati10); in another group, blood was collected about 120 min after atipamezole injection, corresponding to the time when the anesthetic score of MMB low group returned to 0 (Ati120). For untreated animals, served as a control group, blood was collected from the vena cava under anesthesia with isoflurane. Blood was anticoagulated with heparin, and plasma was prepared by centrifugation. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), blood urea nitrogen (BUN), creatinine (CRE), amylase (AMY), lipase (LIP), glucose (GLU), triglyceride (TG), total cholesterol (TCHO), total protein (TP), albumin (ALB), calcium (Ca), inorganic phosphorus (IP), sodium (Na), potassium (K) and chloride (Cl) were measured using a Fuji Dri-Chem 7000v instrument (Fujifilm, Tokyo, Japan). Plasma insulin concentration was analyzed by enzyme-linked immunosorbent assay (Morinaga, Yokohama, Japan).

Statistical analysis

The results are expressed as mean ± standard error. The Mann-Whitney *U* test was used to compare data between two groups. The Kruskal-Wallis test was used for comparing data among three or more groups, and multiple comparisons were performed using Scheffé's method when a significant difference was noted.

RESULTS

Effect of anesthetic agents in hamsters

None of the hamsters died during anesthesia, and all of them showed anesthetic scores of 4 or more. The induction time was 4.4 ± 0.5 min in the high dose MMB group, 4.0 ± 1.1 min in the low dose MMB group and 5.4 ± 1.0 min in the group receiving the low dose MMB and atipamezole, showing no significant differences among groups (Table 1). The anesthetic duration was 162.0 ± 11.7 min in the high dose MMB group and 106.2 ± 7.9 min in the low dose MMB group, showing a significant difference (Table 1). The recovery time was 40.2 ± 3.6 min in the high dose MMB group and therefore slightly longer compared to 27.8 ± 4.0 min of recovery time in the low dose MMB group (Table 1). Atipamezole induced a quick recovery after 10.5 ± 2.5 min from anesthesia in the animals receiving the low dose MMB, which was significantly shorter than that of the high and low dose MMB groups (Table 1). These results indicated that low dose MMB induced sufficient anesthesia for hamsters.

States of biochemical parameters by administration of MMB anesthesia and atipamezole

The MMB anesthetic altered several metabolic parameters in hamsters. In high and low dose MMB groups, GLU was markedly elevated, while insulin levels were significantly lower than in control group (Table 2). The high dose of MMB significantly increased AMY and decreased TG compared to control group in a dose dependent manner (Table 2). The MMB anesthetic also altered plasma mineral levels. In MMB-treated groups, IP increased, while Ca and Cl decreased dose-dependently compared to the control group (Table 2). Na levels were lower in the low dose MMB group than in the control group without dose dependence (Table 2). The other biochemical levels were not affected by the MMB anesthetic (Table 2).

Then, we examined whether atipamezole was able to counteract the MMB-induced biochemical alterations. Specifically, the plasma GLU, insulin, Ca, IP and Na values, which were altered by low dose MMB, were compared among the control group, low dose MMB group, Ati10 group and Ati120 group (Fig. 1). In both the ATI10 and ATI120 groups, plasma levels of GLU markedly decreased with respect to the levels of the low MMB dose group. The level of ATI10 group, however, remained significantly higher than that of the control group (Fig. 2). The insulin and Na levels returned to the control value within 10 min after atipamezole injection (Fig. 2). The Ca value was significantly decreased in the ATI10 group compared to the control group, but returned to the control value in the ATI120 group (Fig. 2). IP value did not show clear tendencies (Fig. 2).

DISCUSSION

Generally, the anesthetic effects of agents are influenced by their dosage, the drug sensitivity of the animals and the route of administration. The adequate dosage of medetomidine, midazolam and butorphanol depends on animal species. For mice, the high

Table 2. Blood biochemical levels after recovery from anesthesia in hamsters

Group	Control	Low MMB	High MMB
Number of animals	5	6	5
AST (IU/m*l*)	31.6 ± 2.1	55 .7 ± 11.1	43.4 ± 5.6
ALT (IU/m*l*)	73.0 ± 10.1	141.2 ± 38.4	70.2 ± 11.1
GGT (IU/m*l*)	<10	<10	<10
ALP (IU/m*l*)	305 ± 18	324 ± 15	323 ± 40
TBIL (mg/d*l*)	0.14 ± 0.02	0.15 ± 0.02	0.16 ± 0.02
BUN (mg/d*l*)	21.3 ± 0.8	24.3 ± 1.0	28.6 ± 2.9
CRE (mg/d*l*)	0.14 ± 0.02	0.15 ± 0.02	0.22 ± 0.04
AMY (IU/m*l*)	3,257 ± 92	3,550 ± 103	4,020 ± 130[a)]
LIP (IU/m*l*)	65 ± 17	138 ± 22	137 ± 25
GLU (mg/d*l*)	86 ± 8	568 ± 8[b)]	568 ± 127[a)]
Insulin (ng/m*l*)	2.05 ± 0.95	0.12 ± 0.05[a)]	0.11 ± 0.03[b)]
TG (mg/d*l*)	484 ± 73	287 ± 91	163 ± 42[a)]
TCHO (mg/d*l*)	186 ± 13	174 ± 11	171 ± 29
TP (g/d*l*)	6.6 ± 0.2	6.2 ± 0.2	6.0 ± 0.2
ALB (g/d*l*)	2.9 ± 0.1	2.9 ± 0.1	2.6 ± 0.1
Ca (mg/d*l*)	11.8 ± 0.1	11.3 ± 0.1[a)]	11.1 ± 0.2[b)]
IP (mg/d*l*)	5.7 ± 0.3	6.9 ± 0.2[a)]	7.3 ± 0.5[a)]
Na (mEq/*l*)	141.4 ± 0.4	135.0 ± 0.5[b)]	137.4 ± 1.9
K (mEq/*l*)	6.7 ± 0.4	7.4 ± 0.2	6.7 ± 0.4
Cl (mEq/*l*)	99.8 ± 1.2	95.7 ± 1.3	94.6 ± 0.9[a)]

Data are presented as means ± standard error except for those of GGT in which all data are lower than detection limit (10 IU/m*l*). Differences were analyzed using the Kruskal-Wallis test followed by Scheffé's method. a) $P<0.05$, b) $P<0.01$ vs. control group.

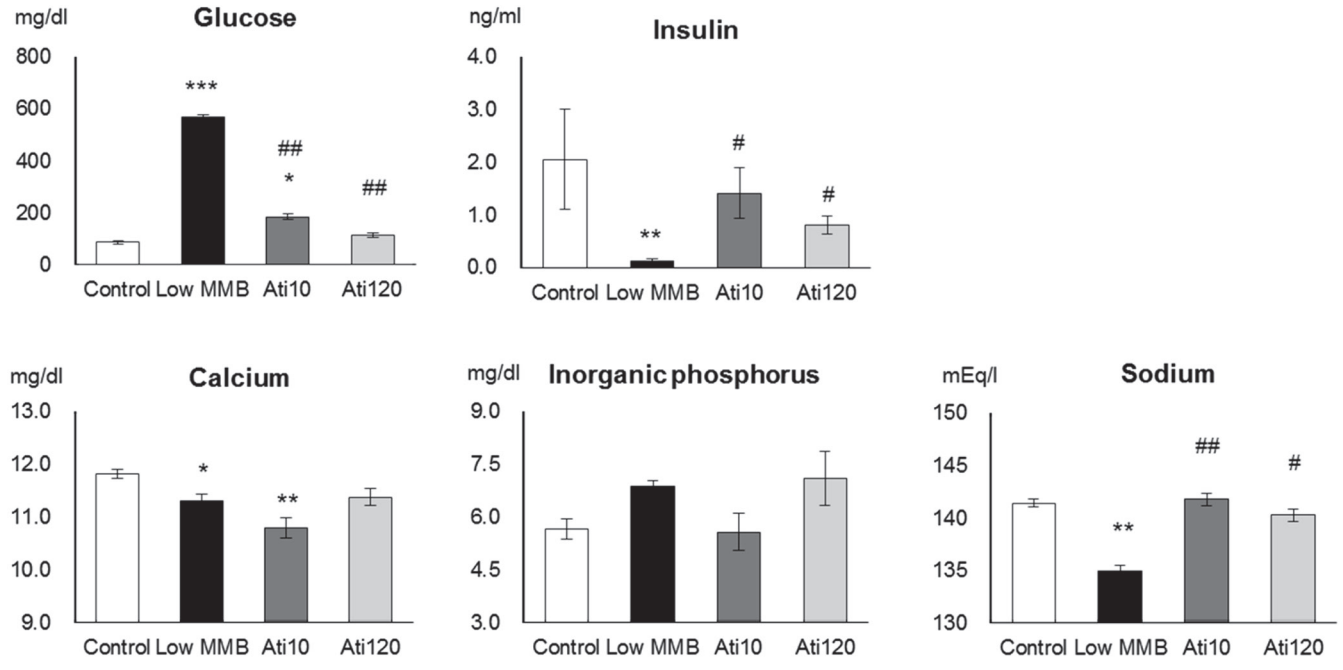

Fig. 2. Ameliorating effect of atipamezole on blood biochemical parameters by anesthetic mixture. Values represent means ± standard error. n=5 (control group), n=6 (low MMB group), n=4 (Ati10 group), n=4 (Ati120 group). Statistical differences were analyzed using the Kruskal-Wallis test followed by Scheffé's method. *$P<0.05$, **$P<0.01$, ***$P<0.001$ vs. control group. $^{\#}P<0.05$, $^{\#\#}P<0.01$ vs. low MMB group.

dose MMB results in approximately 40–50 min of anesthetic time [12, 13], while for rats and cotton rats, the low dose MMB is sufficient for a similar effect [15, 17]. In hamsters, the low dose MMB, corresponding to 0.15, 2.0 and 2.5 mg/kg body weight of medetomidine, midazolam and butorphanol, respectively, produced an anesthetic time of approximately 100 min, which was enough for short-time surgery, indicating this dosage is sufficient for male hamsters. If hamsters would show low responses

to the low dose MMB, an additional injection of the anesthetic mixture might be applicable since the high dose MMB did not result in death. Future research should address the anesthetic effect in female hamsters, since sex differences might exist in some animal species [17]. In the present study, we used intramuscular injection as administration route. Although tail veins are the most accessible for intravenous injection in mice and rats, they are not available in hamsters due to their short tails. The intraperitoneal route has relatively higher failure rate and additional stress than other routes [14]. In addition, the intramuscular route is less irritative compared to the intraperitoneal and the subcutaneous ones [11]. Thus, the intramuscular route might be preferable for the MMB anesthetic in hamsters rather than intravenous or intraperitoneal one. The subcutaneous route has also been recognized as effective for MMB anesthetic [14]. Although anesthetic duration of the MMB anesthetic has not been compared between the intramuscular route and the others, absorption rate of the intramuscular route is higher than that of the subcutaneous one and lower than that of the intraperitoneal one, and the latter two routes produce similar anesthetic duration [11, 14]. Therefore, the subcutaneous route might be also effective for the MMB anesthetic in hamsters as well as the intramuscular route.

The MMB anesthetic drastically altered plasma GLU and insulin levels in hamsters as well as in mice and rats [18, 21]. These alterations by the MMB mixture are exclusively due to an α2-adrenoreceptor agonist, medetomidine, which inhibits insulin secretion from the pancreatic β-cells and therefore increases the blood GLU levels [1, 18]. However, Ochiai *et al.* [18] demonstrated that atipamezole at a dose twice the one of medetomidine, required a long time to bring back the GLU level within the normal range in mice receiving the high dose of MMB anesthetics. Similar tendencies are observed when yohimbine, an α2-adrenoreceptor antagonist, was injected into acute hyperglycemic rats receiving ketamine and xylazine [20]. In hamsters, atipamezole at the same dose as medetomidine (0.15 mg/kg) quickly brought plasma GLU and insulin values within the normal range. Although the strain differences were not clarified in this study, our results highlighted that anesthesia with the low dose MMB and antagonization with atipamezole was applicable for experiments related to metabolic disorders, such as diabetes, in hamsters. However, we propose that an excess dose of MMB should be avoided for the metabolic experiments in hamsters, since a long time might be required for the levels of GLU and insulin to return to the normal range, as was the case for mice [18]. The low dose MMB also affected mineral parameters (IP, Ca and Na) as in other rodents [18, 21]. These changes were not considered to be physiologically harmful, since they were within the reference ranges [16], and the latter two parameters returned to the control value by injecting atipamezole.

In conclusion, our study indicated that a mixture of medetomidine, midazolam and butorphanol at a dose of 0.15, 2.0 and 2.5 mg/kg, respectively, was a favorable anesthetic agent in hamsters. Atipamezole at the same dose as medetomidine improved biochemical parameters that were altered by the MMB anesthetic and returned them within the normal range. This anesthetic agent will facilitate the use of hamsters as animal models in a wide range of biomedical experiments.

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