Inflamm. res. 54 (2005) 256–260
1023-3830/05/060256-05
DOI 10.1007/s00011-005-1352-y

Inflammation Research

Effect of H_1- and H_2-receptor antagonists on the hemodynamic changes induced by the intravenous administration of ketamine in sevoflurane-anesthetized cats

C. Costa-Farré [1], F. García [1], A. Andaluz [1], R. Torres [2] and F. de Mora [2]

[1] Department of Medicine and Surgery – Veterinary School –, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain
[2] Department of Pharmacology, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain, Fax: ++34 93 5812006, e-mail: fernando.demora@uab.es

Received 22 October 2004; returned for revision 5 January 2005; accepted by A. Falus 14 February 2005

Abstract. *Objective:* The anesthetic ketamine has been reported to cause both an increase of the plasma histamine concentration, notably in cats, and a cardiovascular depression. The latter has been described in humans and in other species. However the relevance of the histamine fluctuation for the ketamine-induced hemodynamic changes has not been determined.
Subjects and treatment: We studied the contribution of histamine to the hemodynamic effects induced by IV ketamine (7 mg/kg) in 12 sevoflurane anesthetized cats, of which half had been pre-treated with combined H_1- and H_2 -receptor antagonists.
Methods: The mean arterial pressure (MAP) and the heart rate (HR) from both untreated (group C) and pre-treated (group AH) cats were recorded before and after the ketamine administration. The plasma histamine concentration was also measured.
Results: Plasma histamine fluctuations in the control and the antihistamine-treated group followed a similar pattern (no statistical differences); an initial rise that peaked 2 min after ketamine injection (from 0.63 ± 0.11 ng/ml to 2.22 ± 0.69 ng/ml in the C group, and from 0.71 ± 0.10 ng/ml to 1.09 ± 0.28 ng/ml in the AH group) followed by an immediate decrease in plasma concentrations. As for the hemodynamic variables under analysis, in the control group ketamine administration was followed by an early 30.3 ± 8.1% reduction ($p < 0.005$) in the MAP with no associated changes in the HR. In the antihistamine pre-treated group, ketamine caused a further decrease of the MAP (41.7 ± 2.3%), and a significant ($p < 0.01$) 11.6 ± 2.9% reduction of the HR.
Conclusion: Ketamine in anesthetized cats triggers histamine release and induces cardiovascular depression. The depression is more pronounced under the blockade of histamine activity through histamine receptor antagonists.

Correspondence to: F. de Mora

Key words. H_1-receptor antagonist – H_2-receptor antagonist – Histamine – Ketamine – Sevoflurane

Introduction

Ketamine is a dissociative anesthetic widely used in human and veterinary anesthesiology. In conscious individuals, whether human or veterinary patients [1, 2], ketamine stimulates the cardiovascular activity. Conversely, when the drug is rather administered in combination with other anesthetics (i.e. unconscious individuals), or to critically ill patients, it substantially decreases the arterial blood pressure and the cardiac output [3–5]. When used under these clinical circumstances, a major concern when injecting ketamine is its potential depressor effects on the cardiovascular system. Thus, the understanding of the mechanisms that drive the ketamine-induced changes on the cardiovascular system is of outmost relevance to diminish the risk associated to ketamine-based anesthesia.

Although considered in principle a low histamine releaser [6], ketamine has been shown to induce mast cells' histamine release in vitro [7], and more recently to trigger histamine release well above baseline levels in vivo in anesthetized cats [8]. Cardiovascular reactions to histamine include systemic arterial hypotension, and other hemodynamic changes in humans [9, 10] as well as in cats when administered by infusion at similar doses [10]. Therefore we hypothesized that histamine contributes to the ketamine-associated cardiovascular effects. Since the anesthetized cat might help understand the ketamine-caused cardiac depression, we used such species as a model to study the potential role of histamine in ketamine-mediated adverse effects in critically ill or anesthetized individuals.

Therefore the purpose of this study was to assess the impact of the blockade of the histamine activity through H_1- and H_2- receptors antangonists, on the ketamine-induced cardiovascular changes in sevoflurane anesthetized cats.

Material and methods

Cats

Twelve healthy adult male cats weighing 4.39 ± 0.22 kg (mean ± SEM) were used. Cats were selected upon agreement from a pool undergoing elective minor surgery at the Veterinary Teaching Hospital of the Universitat Autònoma de Barcelona (UAB). The experimental protocol was approved by the official Ethical Committee for Animal Research, and was carried out under the owners' consent. Cats were selected for the study on the basis of the results of the physical examination and a complete blood count. Only animals revealing no signs of any disease were included in the study. Food was withheld for 12 h before each trial.

Groups

Cats were randomly allocated to one of the two following groups. Group AH (n = 6) included antihistamines pre-medicated cats, and group C (n = 6) included controls, i.e. non pre-medicated cats. Cats from group AH received chlorphenamine maleate and cyproheptadine chlorhydrate (Alergia-N ®, Neosan, Barcelona, Spain), 1 mg/kg and 0.2 mg/kg IM for H_1-receptor antagonism, and ranitidine (Zantac ®, Glaxosmithkline, Madrid, Spain), 2 mg/kg IM as an H_2-receptor antagonist. The choice of the antihistamines and the dose was done on the basis of the clinical use of these drugs in such species. Cats from group C received saline (IM). The animals from both groups were manipulated identically except for the administration of either antihistamines or saline solution 1 h before the induction of anesthesia.

Study design

Anesthesia was induced within a chamber filled with 7% sevoflurane delivered in 100% oxygen. The trachea was intubated and the end-tidal sevoflurane concentration was maintained at 1.2 times the minimum alveolar concentration (MAC) in 2 l/min oxygen under spontaneous breathing using a non-rebreathing system. A 22-gauge polyethylene catheter was inserted into the cephalic vein to administer saline 0.9% throughout the anesthetic period at 10/ml/kg/h with an infusion pump (perfusor fm, Braun Medical, Barcelona, Spain). A 24-gauge polyethylene catheter was inserted into the femoral artery to measure the blood pressure continuously, and for the collection of blood samples. After a 20 min stabilization period, 7 mg/kg of ketamine (Imalgene ®, Merial, Lyon, France), a therapeutic dose used to prolong anesthesia, were administered intravenously through the cephalic vein catheter as a 5s bolus injection.

Monitoring

The variables under study, HR and MAP, were recorded before (baseline data), and 2, 5, 10, 15, 20, 25 and 30 min after the ketamine injection, with a multicanal equipment (cardiocap II, Datex-Ohmeda, Helsinki, Finland) that was calibrated before each trial. This equipment was also used for pulsoximetry, and to continuously monitor the oesofageal temperature. In addition, to ensure that either the ketamine or the antihistamines administration would not alter blood gas, electrolytes (Istat, Heska, NJ, US), end-tidal sevoflurane, end-tidal carbon dioxide tension, and respiratory rate (RGM infrared gas analyzer, Ohmeda, Helsinki, Finland), a routine determination of those variables was carried out in both groups.

Measurement of plasma histamine concentration

Blood samples (1 ml) collected through the femoral artery were also used for the determination of histamine at baseline, and 2, 5, and 10 min after the ketamine injection. The samples were transferred to refrigerated EDTA tubes, centrifuged over a 10 min period at 900 g at 4 °C (Omnifuge 2.ORS, Heraeus, Germany) to obtain plasma, and stored in propylene tubes at –20 °C. The plasma histamine concentration was determined using an ELISA kit (Immunotech, France). Briefly, histamine from samples and standards was acylated and added to labeled histamine-specific antibody coated wells. Concomitantly, histamine-alkaline phosphatase was added to compete for the limited number of antibody binding sites. The bound enzymatic activity was then measured by the addition of a chromogenic substance. A standard curve was constructed to assess the histamine concentration through non-linear regression.

Statistical analysis

The actual raw hemodynamic data (HR and MAP) were analysed statistically through a 2-way repeated measures analysis of variance (RM-ANOVA) in order to compare the results among the different time-points within each experimental group. When either of the 2 factors, i.e. time or treatment, affected the response ($p < 0.05$), a Bonferroni post-test was performed in order to determine which time-point values were statistically significantly different from baseline ($p < 0.05$). Although statistics was applied to the raw data, for an easier interpretation of the results the HR and MAP data are graphed as the percent change from the baseline value (prior to ketamine injection), i.e. we express the magnitude of the change of HR and MAP upon ketamine injection. Baselines from both experimental groups (C and AH) were also compared through a 2-way RM-ANOVA to assess the potential effect of the antihistamine pre-treatment on the studied variables. So were the histamine concentration fluctuations of both groups.

Results

No differences in pulsoximetry, oesofageal temperature, blood gas, electrolytes, end-tidal sevoflurane, end-tidal carbon dioxide tension, and respiratory rate were observed between the C and the AH group after the ketamine administration.

Ketamine-associated histamine release

In group C, the average baseline plasma histamine concentration was 0.63 ± 0.11 ng/ml (mean ± SEM). As depicted in Figure 1 where individual and average data from this group are shown, the histamine concentration increased in all the cats 2 min after the ketamine injection. The histamine concentration reached at 2 min was over 1ng/ml in 5 out of the 6 cats. After 5 min, the histamine levels started to shift back towards baseline values, with possibly a slight upturn at 10 min. A similar trend was observed in the group AH after ketamine injection although the increase of histamine concentrations was lower in the antihistamines pre-treated animals. Histamine concentrations fluctuated from 0.71 ± 0.10 ng/ml (vs. 0.63 ± 0.11 ng/ml in the C group) before ketamine injection up to 1.09 ± 0.28 ng/ml (vs. 2.22 ± 0.69 ng/ml in the C group) after 2 min, and back to 0.73 ± 0.13 ng/ml (vs. 1.42 ± 0.58 ng/ml in the C group) at 5 min. No statistical differences of the histamine levels data were observed between the C and the AH group.

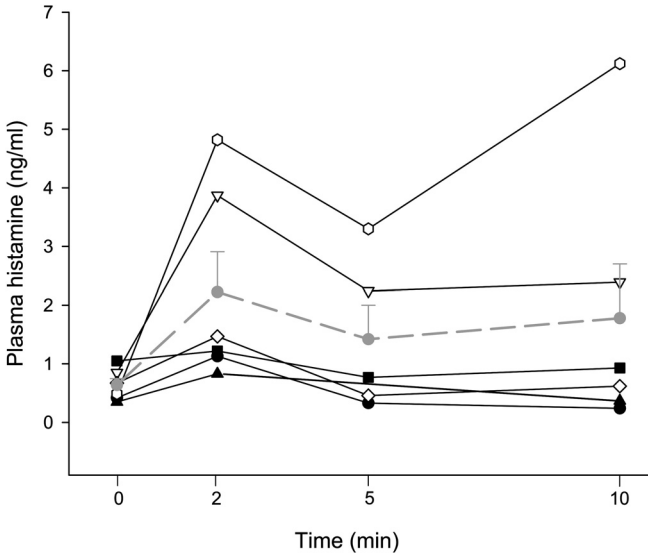

Fig. 1. Plasma histamine concentrations before, and 2, 5 and 10 min after ketamine injection in control cats (n = 6). Individual results for each cat[1] (solid lines) and mean ± SEM (dash line) are depicted. As shown, the histamine concentration raised over baseline levels 2 min after ketamine administration in all 6 cats, and thereafter started to shift back towards normal levels but appeared to slightly recover at min 10.
[1] (except for cat ▲ at min 5).

Antihistamines effect on the ketamine-associated cardiovascular changes

Figures 2 and 3 show the changes of HR and MAP respectively upon ketamine injection in the groups C and AH. In those graphs the fluctuations of the HR and the MAP are expressed as the percent change versus baseline, i.e. the increase or decrease with respect to baseline levels, yet statistics was applied to the actual raw data. It is noteworthy that as for the 2-way RM-ANOVA, the interaction between the

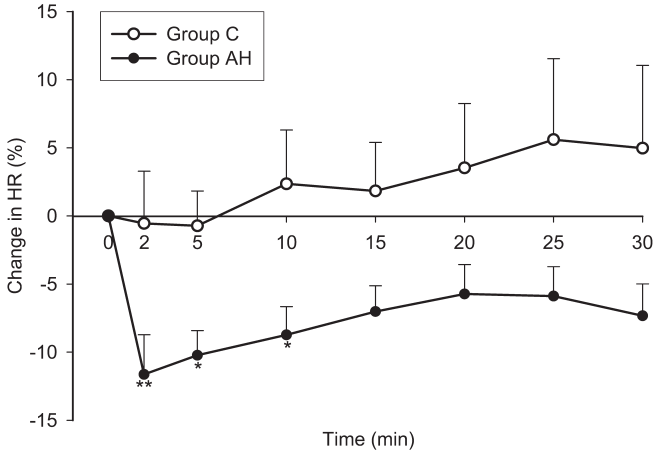

Fig. 2. Heart rate percent changes (mean ± SEM) after ketamine administration in the C group (n = 6), and the AH group (n = 6). Significant differences (*p < 0.05, **p < 0.01) were observed upon comparison of raw time-point HR values to baseline values within each experimental group (2-way RM-ANOVA).

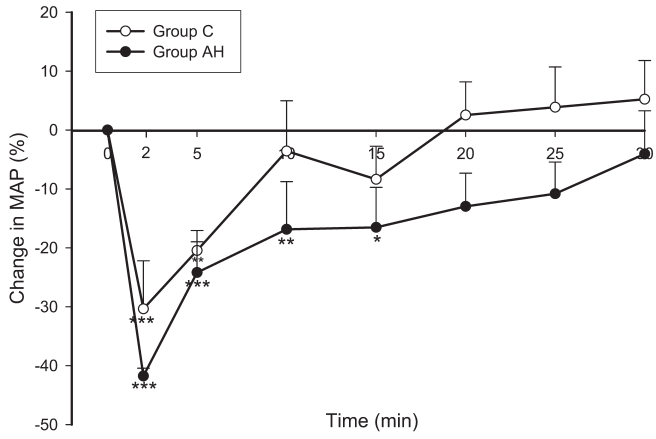

Fig. 3. Mean arterial blood pressure percent changes (mean ± SEM) after ketamine administration in the C group (n = 6) and the AH group (AH) (n = 6). Significant differences (*p < 0.05, **p < 0.01, ***p < 0.005) were observed when raw time-point MAP values are compared to baseline within each experimental group (2-way RM-ANOVA).

2 factors (time and treatment) was not significant, i.e. the differences between time-points are consistent for pre-treated and untreated animals.

The average baseline or starting HR value (mean ± SEM) of the cats from the C (128.6 ± 9.5 bpm), and the AH (136.6 ± 5.9 bpm) group were statistically similar showing that both groups were homogeneous in terms of HR, and therefore that the antihistamine pre-treatment did not shift the baseline. As for Figure 2, upon ketamine injection, the HR in the C group remained within the baseline range for up to 30 min, i.e. no differences were found within the C group between the average HR baseline value and the HR values at each time point. Conversely, when administered to antihistamine pre-treated cats, ketamine reduced the HR significantly from baseline until up to 10 min post-injection (from $p < 0.01$ to $p < 0.05$). The ketamine-induced HR decrease peaked at 2 min down to 11.6 ± 2.9% under baseline.

The MAP baseline values were identical; 68.8 ± 3.0 mm Hg and. 70.8 ± 4.4 mm Hg in the C and the AH group respectively, and therefore the antihistamine pre-treatment had no effect on such variable. The ketamine bolus administration caused hypotension, i.e. a MAP decrease, as early as 2 min after ketamine injection in both groups (Figure 3). Although the MAP decreased significantly in both the pre-treated and the untreated cats for up to 5 min as shown by the comparison of baseline and time-point values (from $p < 0.005$ to $p < 0.05$), the decrease was more pronounced in the cats that had been pre-treated with antihistamines (41.7 ± 2.3% reduction in the AH group versus 30.3 ± 8.1% reduction in the C group). Furthermore, the recovery of the MAP back to baseline levels was faster in the C than in the AH group where an abnormal MAP remained for up to 15 min.

Discussion

We have investigated the effect of histamine receptors blockade on the ketamine-induced hemodynamic changes in sevoflurane anesthetized cats, in order to assess whether plasma histamine fluctuations could mediate such effect.

Anesthetized ketamine-treated cats are being taken as a model for human and veterinary patients in which ketamine can cause a life-threatening cardiovascular depression, such as critically ill patients or patients under anesthesia.

We first analyzed baseline and post-ketamine injection histamine plasma concentrations. Ketamine induced a histamine increase above the normal baseline values in cats which was observed already 2 min after the drug injection. Such histamine level causes adverse clinical consequences in cats [10], as it does in humans [9, 10]. In most cases, shortly after the peak, the histamine plasma concentration fell back, and then might slightly recover 10 min after the ketamine administration. Although a higher n would help confirm the validity of these data, the analysis of the individual pattern suggests that such fluctuations are very consistent. Irman-Florjanc [8] reported an analogous pattern in cats under ketamine/medetomidine anesthesia. Similarly, in a more recent study, the administration of midazolam-ketamine to allergic humans caused an increase of the plasma histamine above 1 ng/ml in 6 out of 9 patients [11], a level which is considered to have an adverse clinical impact in anesthetized patients [12]. In parallel to the fluctuation of the histamine concentration, ketamine injection under sevoflurane anesthesia caused a rapid hypotension without changes in the HR in the control untreated cats. Similar results were described after midazolam-ketamine administration in isoflurane anesthetized dogs, with even one dog dying after the bolus injection [5], and very early reports pointed also towards this direction in human patients [3]. Ketamine is considered a low histamine releaser, i.e. only high concentrations appear to cause a direct significant release of histamine from human lung mast cells in vitro [7]. Those concentrations are presumably not reached under our conditions and therefore the cardiovascular effects that we report upon ketamine injection might not be directly mediated by the stimulation of the circulating basophils or the tissue mast cells by ketamine, but rather through an indirect mechanism.

The histamine levels upon ketamine injection in the untreated cats did not differ statistically from the levels in the antihistamine pre-treated ones, although the increase observed at 2 min was lower in the latter. Such trend in the AH group has also been described by other authors [11, 13, 14], and might partly explain the observed differences in the HR and the MAP among groups. However, the resemblance in the histamine fluctuation pattern in both groups allows for comparisons between the ketamine effects on the hemodynamics. To elucidate the contribution of histamine to the cardiovascular changes observed after the ketamine administration, we compared the effect of ketamine injection on normal control cats, and on cats pre-treated with H_1- and H_2-antagonists. The antihistamines were administered prior to ketamine injection and, as expected from earlier reports' data [9], the drug did not alter by themselves the baseline MAP and HR values. However, the presence of antihistamines in the ketamine-injected cats had a clear effect on the ketamine-induced cardiovascular depression even though towards an unexpected direction. Both the HR and the MAP decreased in the animals under the effect of antihistamines. Overall, both hemodynamic variables fell under normal values, and recovered more slowly in the antihistamines pre-treated than in the non pre-treated cats. The blockade of the histamine activity appears to either worsen the ketamine-induced cardiovascular effects as for the MAP, or initiate such depressor effects in the heart (HR). Therefore, antihistamines rather than prevent the ketamine-induced hemodynamic changes cause a more pronounced depression, and most probably such effect is mainly due to the actual blockade of the histamine receptors [15]. Kimura et al. [11] found a similar trend by means of a different experimental approach, since they observed that antihistamine treatment prevented the heart rate increase induced by ketamine-midazolam administration.

It should not be fully discarded that the non-antihistamine properties of the drugs used, such as the anticholinergic and the antiserotonine effects might influence the observed outcome. However, given the correlation between the ketamine-induced cardiovascular effects, and the fluctuation in the plasma histamine concentration, we believe that most of the hemodynamic changes are explained by the blockade of the histamine activity.

We conclude that ketamine induces a moderate histamine release in anesthetized cats, and that under these conditions the pre-medication with H_1- and H_2-antagonists worsens the ketamine – induced cardiovascular depressor effects.

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