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# Can Ethanolaminic $H_1$ Blockers Improve CNS Suppression Effects of Ketamine as Oral Spray in Animal Model?

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**Abstract:** Ketamine is a suitable injectable anesthetic in human and animal that has a low intestinal absorption rate. Its bioavailability in human with oral administration is 20±7% and with rectal administration in cat is 43.5±6.1%. This drug has some side effects such as hypertension, histamine releasing effects, hallucination, hyper salivation (especially with oral administration), etc. Clemastine is one ethanolaminic antihistamines with anticholinergic effects that can pass through blood-brain barrier and cause suppression of CNS. Then, it seems that co administration of clemastine and ketamine cause more effective and deep CNS depression effects. The aim of this study was evaluation of ketamine and clemastine CNS suppression effects in the manner of single and concomitant in cat. Ten free roaming male and mature cats received mentioned drugs (ketamine (20, 40 and 80 mg $kg^{-1}$) and clemastine (0.68, 1.36 and 2.5 mg/cat)) as sublingual spray manner. Each animal was monitored continually by educated expert for CNS depression signs as graded on the behavioral scales. Clemastine alone in sublingual spray administration did not show a significant CNS depression effects. But ketamine in different doses showed a significant dose dependent effect. Concomitant use of clemastine with ketamine reduced CNS depression effects of ketamine. But duration of CNS depression was longer in co administration of these two drugs. Results showed that when ketamine sprayed in mouth (as sublingual form) a strong and long CNS depression was achieved.

**Key words:** Oral ketamine, antihistamine, clemastine, CNS depression, cat

## INTRODUCTION

Ketamine (KT) is a synthetic available anesthetic that has been used in human and animal operations for almost 35 years. Several studies had showed its wide margin of safety (Krauss and Green, 2000; McCarthy *et al*., 2000). This agent blocks NMDA (N-Methyl-D-Aspartate) receptors in CNS (Freye *et al*., 2005). KT induces one form of anesthesia that called dissociative anesthesia in which there is a marked sensory loss and analgesia as well as amnesia and paralysis of movement, without actual loss of consciousness. Ketamine has some effects such as sedation, analgesia and immobility. This drug has low intestinal absorption rate. It's bioavailability in human with oral administration is 20±7% (White *et al*., 1985) and with rectal administration in cat is 43.5±6/1% (Hanna *et al*., 1988).

KT was stated to be metabolized to at least two major compounds of pharmacological interest: to Norketamine (NK) by N-demethylation which then is converted to Dehydronorketamine (DHNK) by dehydrogenation (Chang and Glazko, 1974). Its major metabolite norketamine, however is active with one-third of the potency of its parent drug as an anesthetic. Thus, the first-pass effect after oral administration results in an active metabolite that can contribute to the pharmacological effects.

Oral KT has been used sporadically as premedication for anesthesia in children (Darlong *et al*., 2004; Ghai *et al*., 2005). Also, it had been administered in fractious cats when the animal is hissing but in anesthetized cats it cause psychotic symptoms, release of histamine and induce cardiovascular system hyper activity such as increase of heart rate and hypertension (Adams, 2001; Costa-Farre *et al*., 2005).

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Clemastine is one of first age $H_1$ blocker antihistamines with ethanolaminic structure that also has anticholinergic effects and as well can pass trough blood-brain barrier and cause suppression of CNS (Hardman *et al*., 2001).

So, it seems that co administration of clemastine with ketamine improves CNS suppressing effect of KT and decreases some side effect of this drug (e.g., hyper salivation due to histamine realizing effect of KT). The main and important aim of this study was evaluation of CNS suppressing effect of orally administered ketamine and clemastine in the manner of single and together.

## MATERIALS AND METHODS

**Animals:** The cat preferred as animal model for this study. Male, mature, sturdy free roaming and mixed breed animals selected randomly and were maintained as group housing in wide space (in a big room) to exhibit a wide range of complex behaviors. Animals had free access to food and water and maintained on a 12 h light-dark cycle. Temperature 25°C with humidity between 45 and 65% provided for them allover the study. Food was withheld for 12 h and water for 2 h prior to the study to minimize the effects of gastric contents. They were kept 1 week before the examination in their room to achieve maximum adaptation to environmental situations. The numbers of cats in all of the treatment groups were ten animals.

**Drugs:** Racemic ketamine (ketamine hydrochloride, Sigma, St. Louis, MO, USA) was dissolved in normal saline and the pH of each solution was adjusted to 5. Ketamine at a dose of 20, 40 and 80 mg $kg^{-1}$) (Adams, 2001) was sprayed in sublingual area of mouth by a ordinary syringe. For comparison, a similar study was performed with clemastine. Clemastine as fumarate salt (Sigma-Aldrich, USA) was dissolved in water, in 20°C and different doses of clemastine (0.68, 1.36 and 2.5 mg/cat) (Adams, 2001) were administered as a mentioned method. In first stage, drugs administered separately. Then, in 2nd stage they are used together in treatment groups. In combination regimes high dose of each drug with low dose of other, also middle dose with other's middle dose was used. Hence, treatment groups include: ketamine 20, 40 and 80 mg $kg^{-1}$, clemastine 0.68, 1.36 and 2.5 mg $cat^{-1}$, ketamine 20 mg $kg^{-1}$) plus clemastine 2.5 mg $cat^{-1}$, ketamine 40 mg $kg^{-1}$ plus clemastine 1.36 mg/cat and ketamine 80 mg $kg^{-1}$ plus clemastine 0.68 mg/cat.

Each animal was monitored continuously by an educated expert for CNS depression as graded on the behavioral scales. Scales for CNS depression were (Daniel and Ramsay, 2000):

- Score 1: No effect
- Score 2: Impaired gait, prancing gat and some excitement
- Score 3: Lowered head, braced stance and hindquarter weakness
- Score 4: Sternal or lateral recumbency and some responsiveness to repositioning
- Score 5: Lateral recumbency, no response to movement of limbs and painful excitements

Reflex to pain in cat is evaluated by painful excitation of tail or pads with clamp (Ilkiw *et al*., 1996). Also obtained results in administration of various doses of drugs were evaluated on the base of underneath parameters for each treatment group (Shimoyama *et al*., 1996).

**Onset time of effect:** Refer to initiation first effect result from drug which generally reveals by relaxation and mild ataxia.

**Duration of effect:** Refer to drug effect length of time (from initiation of first drug effect and passing of peak score and then achieving to normal state in animal).

**Peak score:** For each dose: refer to the highest rate of CNS suppression in administrated dose.

**Percentage of animal reached peak score:** Lost the reflexes (upon scores) for each dose.

**Onset time of peak score:** Refer to peak score initiation time of each dose.

**Duration of peak score:** Refer to time that animal is in highest recordable score in administrated dose. When ever score 2 recorded we did not recognize any time to Duration of peak score and onset time of peak score. Also times >6 h was not recorded in this study. In second step clemastine co-administered with ketamine and results evaluated again on the base of mentioned method.

**Statistical analysis:** The results (onset time and duration of CNS depressant effects) are expressed as the Mean±SE. Differences between the individual mean values in different groups were analyzed by one-way Analysis of Variance (ANOVA) and differences with a $p<0.05$ were considered significant.

## RESULTS AND DISCUSSION

**Rate of CNS suppression of sublingual administration of clemastine (0.68, 1.36 and 2.5 mg/cat):** Clemastine as oral spray in mentioned doses didn't exert any significant CNS suppression effect.

**Rate of CNS suppression of sublingual administration of ketamine (20, 40 and 80 mg kg$^{-1}$):** As shown in Table 1 and 2, onset time of effect decreased with increasing dose of ketamine. In dose of 80 mg kg$^{-1}$ this time decreased to 1:24 that in comparison with ketamine 20 mg kg$^{-1}$ was considered significant ($p<0.001$). Also, peak score of CNS suppression increased dose dependently so that in dose 80 mg kg$^{-1}$) in 50% of cats, analgesia was saw (score 5). Onset time of peak score decreased dose dependently so that in dose of 80 mg kg$^{-1}$ this time reached to 2.59±0.5 min that in comparison approximately is half of group 20 mg kg$^{-1}$.

**Comparison of CNS suppression of ketamine (as sublingual administration) with it's and clemastine co-administration:** Comparison of CNS suppression effects due to ketamine in the manner of single administration and combined with Clemastine are shown in Table 1 and 2.

Administration of ketamine combined with clemastine causes tardier start and also durable CNS suppression effect than solely ketamine. Whereas as shown in Fig. 1 and 2 depth of CNS suppression (peak score) is abated whenever dose of ketamine increase in combinational protocols.

**The results of present study show some notable facts:** Clemastine didn't cause a significant CNS suppression effects when sprayed in mouth in administered doses. Intra oral (sublingual) spray of ketamine in administrated doses absolutely causes a dose dependently CNS suppression. CNS depression effect in co administration of Clemastine with ketamine improved in compare with whenever ketamine administered sporadically.

Table 1: Effect of ketamine administration (20, 40, 80 mg kg$^{-1}$ as intra oral spray

| Dose of ketamine (mg kg$^{-1}$) | Onset time of effect (min) | Duration of effect (h) |
|---|---|---|
| 20 | 2.26±0.36 | 0.65±0.09 |
| 40 | 1.65±0.13 | 1.69±0.31* |
| 80 | 1.39±0.11* | 2.63±0.36*** |

Onset time and duration of CNS suppression (since onset time of effect to the time of getting normal) were showed. Results are expressed as Mean±SE. ***p<0.001, *p<0.05 significantly different from the control group (ketamine 20 mg kg$^{-1}$)

Table 2: Effect of ketamine administration (20, 40 and 80 mg kg$^{-1}$) as intra oral spray

| Dose of ketamine (mg kg$^{-1}$) | Observed peak score | Percentage of animals reached peak score (%) | Onset time of peak score (min) | Duration of peak score (min) |
|---|---|---|---|---|
| 20 | 3 | 40 | 5.22±0.9 | 11.15±1.90 |
| | 4 | 60 | 3.5±0.50 | 23.46±6.90 |
| 40 | 3 | 40 | 4.1±0.38 | 10.87±2.60 |
| | 4 | 60 | 3.1±0.60 | 62.33±14.9 |
| 80 | 4 | 50 | 2.23±0.4 | 86.2±19.80 |
| | 5 | 50 | 2.1±0.60 | 114.4±24.80 |

The highest rate of CNS suppression (peak score) and percentage of cats reached to seen peak score in each dose, also onset time and duration of peak score were showed. Each group had at least 10 cats. Results are expressed as mean

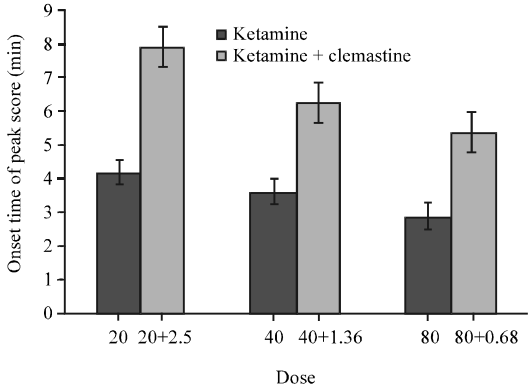


Fig. 1: The comparison onset time of CNS suppression between ketamine (20, 40 and 80 mg kg$^{-1}$) and ketamine (20, 40 and 80 mg kg$^{-1}$) + Clemastine (0.68, 1.36 and 2.5 mg/cat). Results are expressed as Mean±SE

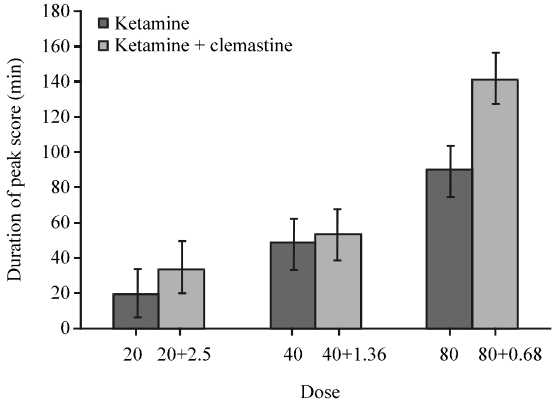


Fig. 2: The comparison duration of CNS suppression between ketamine (20, 40 and 80 mg kg$^{-1}$) and ketamine (20, 40 and 80 mg kg$^{-1}$) + Clemastine (0.68, 1.36 and 2.5 mg/cat). Results are expressed as Mean±SE

Ketamine is a drug with high lipid solubility and rapidly leaves plasma to the CNS (brain). After IV administration, maximum within 1 min it reaches to the highest brain concentration. There for this fact is compatible with its rapid onset time of effect that seems to be some seconds after IV administration (Ilkiw *et al*., 2002, 2003). The IV administration of ketamine has some obvious CNS suppression effects in cat. In the present study sublingual ketamine spray induced CNS depression effects in 2.5-3 min in cats. These effects were dose dependently so that with dose of 80 mg kg$^{-1}$ the cats

reached to score 5 (analgesia). This drug's rapid onset time of effect with oral (sublingual) administration indicates its high mucosal absorption from proximal parts of GI (oral cavity, esophagus, etc.).

This study administration of clemastine as intra oral spray didn't exert a significant CNS suppression effects. Even whenever it added to ketamine regime cause reduction in rate and depth of CNS suppression. This fact is in opposite of other antihistamines' effect such as promethazine and chlorpheniramine as these two drugs can improve accelerate depression of CNS as well as cause profound CNS depression in concomitant administration with ketamine (Issabeagloo *et al*., 2011a, b). Parameters of CNS suppression effects (onset time of effect, highest peak score in administered dose and percentage of animals reached to peak score) were severe and sensible in group ketamine 40 mg $kg^{-1}$) + Clemastine 1.36 mg/cat so as score 4 was seen in 80% of cases in this treatment group.

Clemastine is one of ethanolaminic $H_1$ blocker family so that has high oral absorption like other members of this group and usually cause partial sedation in treated cases (Hardman *et al*., 2001).

But this drug couldn't cause any significant sedation in animals may be because of species diversity or absorption disturbance in this route or low administration dose or etc. so that further studies may be needed for establish accurate mechanism of this event.

Depth of CNS suppression due to ketamine oral administration, reduced whenever clemastine Co-administrated with ketamine. Some of last studies had been showed that sometimes antihistamines can cause CNS stimulation, seizure attacks and agitation in high doses (Hardman *et al*., 2001). Diminution in depth of CNS suppression rate whenever clemastine be combined with ketamine may be pertaining to activation of some neuronal path ways due to clemastine administration.

## CONCLUSION

With attention to this point in present study ketamine 40 mg $kg^{-1}$) + Clemastine 1.36 mg/cat only could to induce score 4 but not analgesia (score 5) it seems that this concomitant protocol is not suitable for anaesthetization. But solely ketamine in dose 80 mg $kg^{-1}$ can cause an explicit analgesia and anesthesia and suggested as non invasive rout of administration to induce anesthesia in cat. Also more studies with other antihistamines and or other drugs with sedative properties as sublingual route in the manner of single and combine with ketamine is necessary to achieve a suitable noninvasive anesthetic protocol.

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