Evaluation of Carbinoxamine effect on improvement of orally ketamine influence on CNS suppression in animal model

[1]Ramin Aminabad*, [2]Eilyad Issabeagloo, [3]Deepmala Verma

1. Food and Drug Association, Medical sciences university of Tabriz, Tabriz, Iran.
2. Department of pharmacology, Medical Sciences Faculty, Tabriz branch, Islamic Azad University, Tabriz, Iran.
3. Director, Society of Education, Agra, India
Ramin.Abad@yahoo.com

Abstract: Ketamine is a suitable injectable anesthetic in human and animal that has a low intestinal absorption rate. It's 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) and etc. Carbinoxamine is one potent antihistamines with anticholinergic effects that can pass trough blood-brain barrier and cause suppression of CNS. Then it seems that co administration of Carbinoxamine and ketamine cause more effective and deep CNS depression effects. The aim of this study was evaluation of ketamine and Carbinoxamine CNS suppression effects in the manner of single and concomitant in cat. Ten mixed bred male & mature cats received mentioned drugs as oral route. In 2nd stage they received concomitant doses of Carbinoxamine & ketamine in the manner of mentioned method. Each animal was monitored continuously by educated experts for CNS depression signs as graded on the behavioral scales. Carbinoxamine in sub lingual administration in high doses cause only a partial ataxia. But ketamine in different doses showed a significant dose dependent effect. Concomitant administration of Carbinoxamine with ketamine improved depth & duration of CNS depression in comparison of single administration of ketamine. Results showed that a strong and long time CNS depression is achieved when they used orally.
[Naiyereh Haerifar. **Evaluation of Carbinoxamine effect on improvement of orally ketamine influence on CNS suppression in animal model**. *Life Sci J* 2013;10(12s):293-297]. (ISSN: 1097-8135).
http://www.lifesciencesite.com. 51

Keywords: CNS depression, oral administration, ketamine, Carbinoxamine, cat

1. Introduction

Ketamine (KT) is a synthetic available anesthetic that has been used in human & animal operations for almost 35 years. Several studies had showed its wide margin of safety (2, 5). This agent blocks NMDA (N-methyl-D-Aspartate) receptors in CNS (4). 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 (7). 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(15) and with rectal administration in cat is %43.5±6/1 (16).

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 (17). 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 (18, 1). Also In fractious cats, is administered by squirting the drug into the mouth with a syringe when the animal is hissing (8, 3). KT in anesthetized cats cause psychotic symptoms, release of histamine and induce cardiovascular system hyper activity such as increase of heart rate and hypertension.

Carbinoxamine is one of first age antihistamines that are one group of sedative-hypnotic drugs which used to reduce hallucination induced by Ketamine.

It was first launched in the United States. It is approved by the U.S. Food and Drug Administration (FDA) (specifically at the 4 mg dose/strength) for hay fever (a.k.a. allergic rhinitis, SAR and PAR); vasomotor rhinitis; mild urticaria; angioedema, dermatographism and allergic conjunctivitis. Carbinoxamine is a histamine antagonist, specifically an H1-antagonist. The maleic acid salt of the Levorotatory isomer is sold as the prescription drug Rotoxamine. Carbinoxamine is available in various countries around the world by itself, combined with decongestants such as pseudoephedrine, and also with other ingredients including paracetamol, aspirin, codeine hydrochloride &c.

In June 2006 the FDA announced that more than 120 branded pharmacy products containing carbinoxamine were being illegally marketed, and demanded they be removed from the marketplace. This action was precipitated by twenty-one reported deaths in children under the age of two who had been administered carbinoxamine-containing products. Despite the fact that the drug had not been studied in this age group, a multitude of OTC preparations containing carbinoxamine were being marketed for infants and toddlers. At present, all carbinoxamine-containing formulations are approved only for adults or children ages 3 or older. It has anticholinergic effects and also can pass trough blood-brain barrier and cause suppression of CNS (6). So it seems that co administration of Carbinoxamine and ketamine bring about more effective and deep CNS depression effects. Also presumably this drug can prevent some of KT side effects such as hyper salivation & hallucination particularly in oral administration.

The main and important aim of this study was evaluation of CNS suppressing effect of orally administered Ketamine & Carbinoxamine in the manner of single and together.

2. Material and method

Animals: Male, mature, sturdy free roaming and mixed breed cats 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-hour light-dark cycle. Temperature 25^{oc} 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 one 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, U.S.A.) was dissolved in normal saline and the pH of each solution was adjusted to 5. Ketamine at a dose of 20, 40, 80 mg/kg (9), was administered orally to with a ordinary syringe in sublingual area of mouth.

For comparison, a similar study was performed with Carbinoxamine. Carbinoxamine as maleate (Palgic, USA) was dissolved in water, in 20°C and different doses of Carbinoxamine (2, 4, 8 mg/kg) (8), were administered as a mentioned method.

In first stage, drugs administered separately. In second step Carbinoxamine co-administered with Ketamine 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.

Each animal was monitored continuously by educated experts for CNS depression as graded on the behavioral scales shown as fallow.

Scales for CNS depression were (14):

1) No effect

2) impaired gait, prancing gat, some excitement

3) Lowered head, braced stance, hindquarter weakness

4) Sternal or lateral recumbency, some responsiveness to repositioning

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 (10).

Also obtained results in administration of various doses of drugs were evaluated on the base of underneath parameters for each treatment group: (13).

- 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 & onset time of Peak Score. Also Times more than 6 hours was not recorded in this study.

3. 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.

4. Results

Rate of CNS suppression of oral administration of Carbinoxamine (2, 4, 8 mg/kg):

Carbinoxamine solely as oral route in mentioned doses didn't develop any significant and clear CNS suppression effect.

Rate of CNS suppression of oral administration of ketamine (20, 40, 80 mg/kg):

As shown in Tables 1 & 2, Onset time of effect decreased with increasing dose of ketamine. In dose of 80 mg/kg this time decreased to 1':24" that in comparison with ketamine 20 mg/kg was considered significant (P<0.001).

Also peak score of CNS suppression increased dose dependently so that in dose 80 mg/kg, in 50% of cats analgesia was saw (Score5). Onset time of peak score decreased dose dependently so that in dose of 80 mg/kg this time reached to 2.59±0.5 minute that in comparison approximately, is half of group 20 mg/kg.

Table 1: Effect of ketamine administration (20, 40, 80 mg/kg as as oral route).

Dose Of Ketamine (mg/kg)	Onset Time Of Effect (min)	Duration Of Effect (hour)
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 20mg/kg).

Table 2: Effect of ketamine administration (20, 40, 80 mg/kg as oral route).

Dose Of Ketamine (mg/kg)	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±1.9
	4	60 %	3.5±0.5	23.46±6.9
40	3	40 %	4.1±0.38	10.87±2.6
	4	60 %	3.1±0.6	62.33±14.9
80	4	50 %	2.23±0.4	86.2±19.8
	5	50 %	2.1±0.6	114.4±24.8

The highest rate of CNS suppression (Peak Score) & 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±SE.

Rate of CNS suppression in co-administration (as oral administration) of ketamine (20, 40, 80 mg/kg) with Carbinoxamine (2, 4, 8 mg/kg):

Results of CNS suppression effects of co administration of ketamine 20 mg/kg + Carbinoxamine 8 mg/kg, ketamine 40 mg/kg + Carbinoxamine 4 mg/kg, ketamine 80 mg/kg + Carbinoxamine 2 mg/kg has been showed in tables 3 & 4.

As shown in table 3, onset time of effect (onset time of CNS suppression) in ketamine 40 mg/kg + Carbinoxamine 4 mg/kg group is faster than other two groups but duration of effect (CNS depression duration) in ketamine 80 mg/kg + Carbinoxamine 2 mg/kg group is longer than other two groups so that in 6 hours monitoring, all animals shown various degrees of CNS suppression.

On the other hand, in concomitant administration of ketamine and Carbinoxamine with mentioned doses, in all animals full anesthesia was established. Anesthesia initiation time (onset time of peak score = score 5) in ketamine 40 mg/kg + Carbinoxamine 4 mg/kg group was faster than other two groups (more than 6 hours). Also when ketamine 20 mg/kg plus Carbinoxamine 8 mg/kg, 40% of animals that where under treatment established seizure attacks.

Table 3. Effect of ketamine (20, 40, 80 mg/kg) & Carbinoxamine (2, 4, 8 mg/kg) co administration as oral route.

Ketamine (mg/kg) + Carbinoxamine (mg/kg)	Onset Time Of Effect (min)	Duration Of Effect (hour)
20 + 8	1.33 ± 0.14	4.17 ±0.21
40 + 4	1 ± 0.2	3.5 ± 0.27
80 + 2	1.32 ± 0.11	> 6 hr ***

Onset time and duration of CNS suppression (since onset time of effect to the time of getting normal) has been mentioned. Results are expressed as Mean±SE. *** p<0.001 significantly different from the control group (Ketamine 20mg/kg + Carbinoxamine 8 mg/kg). †Times more than 6 hours was not recorded.

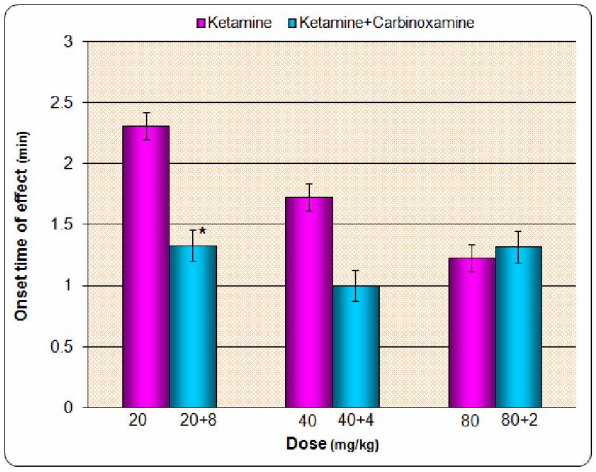
Comparison of CNS suppression of ketamine (as oral administration) with co administration of it & Carbinoxamine:

Comparison of CNS suppression effects due to ketamine in the manner of single administration and combined with Carbinoxamine are shown in graphs 1 & 2. Concomitant use of high doses of Carbinoxamine with Ketamine causes faster onset time and longer lasting effects than solely Ketamine group. It seems that Carbinoxamine in concomitant administration with high dose of Ketamine (40 and 80 mg/kg) has strong performance in accelerating of CNS depression onset time than to solely administrating of Ketamine but in low doses (20 mg/kg) had not this performance.

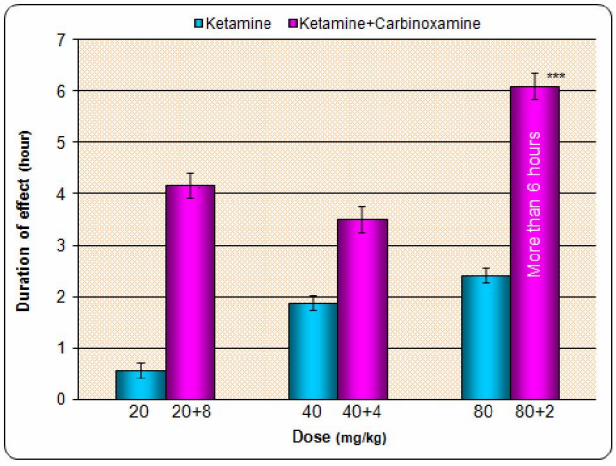
Table 4: Effect of ketamine (20, 40, 80 mg/kg) & Carbinoxamine (2, 4, 8 mg/kg) co administration as oral route.

Duration Of Peak Score (hour)	Onset Time Of Peak Score (min)	Percentage Of Animals Reached Peak Score	Observed Peak Score	Ketamine + Carbinoxamine (mg/kg) (mg/kg)
3.25±0.19	1.74±0.21	100%	5	**20 + 8**
2.47±0.28	1.22±0.23	100 %	5	**40 + 4**
> 6 hr ***	2.13±0.39	100%	5	**80 + 2**

The highest rate of CNS suppression (Peak Score) & percentage of cats reached to this value in each dose, also onset time (the time needed to initiation) and duration of peak score (duration of animals remains in this scale) were showed. Each group had at least 10 cats. Results are expressed as Mean±SE. *** $p<0.001$ significantly different from the control group (Ketamine 20mg/kg + Carbinoxamine 8mg/kg). †Times more than 6 hours was not recorded**.**



Graph 1. The comparison onset time of CNS suppression between ketamine (20, 40, 80 mg/kg) & ketamine (20, 40, 80 mg/kg) + Carbinoxamine (2, 4, 8 mg/kg). Results are expressed as Mean±SE. * $p<0.05$.



Graph 2. The comparison duration of CNS suppression between ketamine (20, 40, 80 mg/kg) & Ketamine (20, 40, 80 mg/kg) + Carbinoxamine (2, 4, 8 mg/kg). Results are expressed as Mean±SE. *** $p<0.001$

5. Discussion

The current study results showed that:

1- Carbinoxamine cannot establish CNS depression effects via oral spray.

2- Oral spray of Ketamine can induce a significant CNS depression dose-dependently.

3- CNS depression rate in concomitant administration of Ketamine and Carbinoxamine was increased than solely Ketamine administration.

4- Common complication in Ketamine administration is hyper salivation that didn't observed in concomitant administration of Carbinoxamine with Ketamine.

Ketamine is lipid soluble drug and rapidly reaches in brain via plasma. After intra venous administration, in less than 1 minute, reaches to maximum peak score in brain. This matter is compatible with drug's onset time of effect that is initiated several second after intra venous administration (11, 12). Ketamine intra venous administration in cat has clear CNS depression effects. In current study, oral Ketamine spray caused CNS depression after 2.5-3 minute.

This effect was dose-dependently so that, cats can reaches to score 5 (significant analgesia plus deep sedation) in Ketamine 80 mg/kg. Drug's Rapid effect in oral spray is due to mucosal absorption from upper gastrointestinal mucosa (sublingual and esophagus mucosa).

Also, in current study, oral Carbinoxamine administration didn't establish significant depression. This is probably due to drug's low CNS distribution at used doses or because of its low efficacy for induction deep sedation. But, when added into Ketamine regime as oral spray it cause acceleration of CNS depression as well as causes profound CNS depression. Rapid CNS depression onset time in concomitant administration of Carbinoxamine with Ketamine in compared with Ketamine group alone is probably due to high Carbinoxamine mucosal absorption thus, after entering of both drugs to CNS owing to synergism among these two drugs, depth

and duration of depression was increased. Carbinoxamine is a member of first age H_1 blockers family thus, like other members of this family has high oral absorption and in most under treatment peoples is capable to induce partial sedation (6). But in this study, cats has showed weak CNS depression when Carbinoxamine solely was administrated.

With due attention to that in present study, whenever Ketamine 40 mg/kg plus Carbinoxamine 4 mg/kg administrated, onset time and duration of effect was more proportionate and also deep sedation plus analgesia (anesthesia) was seen in allover of cases (100%) and likewise seizure attacks was not seen in any under treatment animals, it seems that this regime is a suitable protocol to induction sedation mid analgesia as noninvasive rout of drug administration in an unrestrainable animal such as cat.

Corresponding Author:
Ramin Aminabad. Food and Drug Association, Medical sciences university of Tabriz, Tabriz, Iran.
E-mail: Ramin.Abad@yahoo.com

References

1. B. Ghai, R.P. Grandhe , A. Kumar , P. Chari. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Paediatr Anaesth.15:554-9 (2005).
2. B. Krauss, S.M. Green. Sedation and analgesia for procedures in children. N. Engl. J. Med. 342: 938–45 (2000).
3. C. Costa-Farre , F. Garcia , A. Andaluz , R. Torres , F. de Mora . Effect of H1- and H2-receptor antagonists on the hemodynamic changes induced by the intravenous administration of ketamine in sevoflurane-anesthetized cats. Inflamm Res.54:256-60 (2005).
4. E. Freye , L.B. Partecke , J.V. Levy . Increase in delta- and beta-wave activity of the EEG during rapid opiate detoxification (ROD)-reversal by administration of the non-specific NMDA-antagonist S+ ketamine-. Neurophysiol Clin. 35:25-32 (2005).
5. E.C. McCarthy, G.A. Mencio, L.A. Walker et al. Ketamine sedation for the reduction of children's fractures in the emergency department. J. Bone Joint Surg. Am. 82-A: 912–8 (2000).
6. Hardman, Limbird, gilman. 2001. The Pharmacological Basis of Therapeutics.10th edition. Mc Graw Hill. section:4.654,656.
7. H. P. Rang, M. M. Dale, J. M. Ritter, and P. K. Moore. Pharmacology. Fifth Edition. Churchill Livingstone, 2007, pp: 533, 547, 607.
8. H. Richard Adams. 2001. Veterinary Pharmacology and Therapeutics. Iowa State University. Press / AMES, section:3, pp: 252.
9. H. Richard Adams. 2001. Veterinary Pharmacology And Therapeutics. Iowa State University Press / AMES.section:9. 301
10. JE. Ilkiw , CM. Suter , D. McNeal , TB. Farver, EP. Steffey. The effect of intravenous administration of variable-dose midazolam after fixed-dose ketamine in healthy awake cats. J Vet Pharmacol Ther.Jun;19(3):217-24, (1996).
11. JE. Ilkiw, PJ. Pascoe , LD. Tripp. Effect of variable-dose propofol alone and in combination with two fixed doses of ketamine for total intravenous anesthesia in cats. Am J Vet Res. 64:907-12 (2003).
12. JE. Ilkiw , TB. Farver, C. Suter , D. McNeal , EP. Steffey. The effect of intravenous administration of variable-dose flumazenil after fixed-dose ketamine and midazolam in healthy cats. J Vet Pharmacol Ther.25:181-8 (2002).
13. M. Shimoyama, N. Shimoyama, CE. Inturrisi, K. Elliott. Oral ketamine produces a dose-dependent CNS depression in the rat. Life Sci. 60(1): PL9-14 (1997).
14. M.G. Daniel, C. E. Ramsay. Sedative and physiologic effects of orally administered α2-adrenoceptor agonists and Ketamine in Cats. JAVMA, Vol 216, NO. 12, June. 15, (2000).
15. P.F. White, J. Schuttler, A. Shafer. D.R. Stanski, Y. Horai, A.J. Trevor. Comparative pharmacology of the ketamine isomers. Br. J. Anaesth. 57:197-203 (1985).
16. R.M. Hanna, R.E. Borchard, S.L. Schmidt. Pharmacokinetic of ketamine HCL and metabolite I in the cat: a comparison of i.v., i.m., and rectal administration. J Vet Pharmacol Ther. Mar; 11(1); 84-93 (1988).
17. T. Chang, A. J. Glazko. Biotransformation and disposition of ketamine. International Anesthesiology Clinics. 12:157-177 (1974).
18. V. Darlong , D. Shende , M.S. Subramanyam , R. Sunder , A. Naik. Oral ketamine or midazolam or low dose combination for premedication in children. Anaesth Intensive Care. 32:246-9 (2004).

9/22/2013