Comparison of Sedative Effects of Oral Ketamine & Chlorpheniramine in the Manner of Single and Concomitant administration in Cat

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ABSTRACT

Ketamine is a suitable injectable anesthetic in human and animal that has a low intestinal absorption rate. It's bioavailability in human by oral administration is %20±7 and by rectal administration in cat is %43.5±6.1. this drug has some side effects such as hypertension, histamine releasing effects, hallucination, hyper salivation (specially with oral administration) and etc. Chlorpheniramine is an antihistamine agent that can pass through blood-brain barrier and causes CNS suppression. Therefore it seems that co-administration of Chlorpheniramine and ketamine cause more effective and deep CNS depression effects. The aim of this study was evaluation of ketamine and chlorpheniramine CNS suppression effects in the manner of single and together in cat. Ten free roaming male & mature cats received drugs [ketamine (20, 40, 80mg/kg) & chlorpheniramine (4, 8, 16mg/cat)] first in mixture of milk (40ml) or meat (30g) or sublingual spray route. In 2nd stage they received concomitant doses of chlorpheniramine & ketamine by the method mentioned above. Each animal was observed continually by educated observer for CNS depression as graded on the behavioral scales. Almost all of the animals rejected receiving drugs in mixture of milk and meat. So sublingual spray route used for oral administration of drugs. Chlorpheniramine, alone in sublingual spray administration did not show any significant CNS depression effects with administered doses. But ketamine showed dose dependent effects in different administered doses. Concomitant use of chlorpheniramine with ketamine improved depth and duration of ketamine's CNS depression effects. So results of this study showed this fact that administration of ketamine & chlorpheniramine in mixture of milk & meat is not a suitable method of administration in cats. But a strong and long time CNS depression is achieved when ketamine sprayed in mouth (as sublingual form). These effects are more effective in co-administration of these two drugs.

Key words: Ketamine, chlorpheniramine, Sublingual administration, CNS depression, Cat

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 [3,6]. This agent blocks NMDA (N-methyl-D-Aspartate) receptors in CNS [5]. 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. Its 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 dehydrodornoketamine (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 [2,18]. Also it had been administered in fractious cats, when the animal is hissing [4,8]. KT in anesthetized cats cause psychotic symptoms, release of histamine and induce cardiovascular system hyper activity such as increase of heart rate and hypertension.

Chlorpheniramine is one first generation H₁ blockers that not only prevent systemic effects due to release of histamine but also can induce suppression of CNS [1]. So it seems that co administration of Chlorpheniramine with ketamine improves CNS suppressing effect of KT and decreases some side effect of this drug (e.g. hyper Salivation). The main and important aim of this study was evaluation of CNS suppressing effect of orally administered ketamine & Chlorpheniramine in the manner of single and together.

Material and method

Animals: Male & mature stray cats were caged with free access to food and water, and maintained on a 12-hour light-dark cycle. The animals were fasted for 12 hours prior to the study to minimize the effects of gastric contents on drug absorption rate. The numbers of cats in 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 [8], was administered orally to cats in mixed with milk (40 cc) or meat (30 g) or sprayed in sublingual area of mouth by a ordinary syringe (when animals were rejects the drug in mixture with milk or meat). For comparison, a similar study was performed with chlorpheniramine. Chlorpheniramine as maleate salt (sigma-aldrich, USA) was dissolved in water as 0.55g/100mL, in 20° and different doses of Chlorpheniramine (4, 8, 16mg/cat) (Lowe, 2010) were administered as a mentioned method. In first stage, drugs administered separately. Then in 2nd stage they be used together in treatment groups. Each animal was monitored continuously by an 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 [9]. 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, Duration of effect (time from treatment to recovery), Peak score for each dose, Percentage of animal reached peak score (lost the reflexes (upon scores) for each dose), Onset time of peak score and Duration of peak score.

When ever score 2 recorded we did not recognize any time to Duration of Peak Score and onset time of Peak Score.

In second step Chlorpheniramine co-administered with Ketamine and results evaluated again on the base of mentioned method. In combination regimes high dose of each drug with low dose of other, also middle dose with other's middle dose was used.

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:

CNS suppression effect in orally administered ketamine (20, 40, 80 mg/kg) & Chlorpheniramine (4, 8, 16 mg/cat) in mixture with milk and meat in cat: In these routes almost all of cats did not accept drugs in mixture with milk & meat or ice cream or chocolate. Therefore sublingual method was used throughout study time.

Rate of CNS suppression of sublingual administration of Chlorpheniramine (4, 8, 16 mg/cat):

Chlorpheniramine 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, 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.

Rate of CNS suppression in co-administration (as sublingual method) of ketamine (20, 40, 80 mg/kg) with Chlorpheniramine (4, 8, 16 mg/cat):

Results of CNS suppression effects of co administration of ketamine 20 mg/kg + Chlorpheniramine 16 mg/cat, ketamine 40 mg/kg + Chlorpheniramine 8 mg/cat, ketamine 80 mg/kg + Chlorpheniramine 4 mg/cat has been showed in tables 3 & 4. As saw in table 3 co administration of Chlorpheniramine with ketamine cause dose dependently and meaningful accelerating in onset time of effect & increasing duration of effect in compare with group ketamine 20mg/kg + chlorpheniramine 16 mg/cat. Also in compare of group ketamine 40mg/kg + chlorpheniramine 8mg/cat with group ketamine 80mg/kg + chlorpheniramine 4mg/cat there is a meaningful accelerating in onset time of CNS suppression effect so that this effect depends on ketamine's dose ($P<0.05$). This effect is also seen in regard to duration of CNS suppression within these two groups ($P<0.001$). Beside peak score be intensive when ketamine administered dose increase so that there is a complete anesthesia in almost 80% of animals in group ketamine 80mg/kg + chlorpheniramine 4mg/cat. Also duration of peak score prolonged whenever ketamine's administered dose increased.

Comparison of CNS suppression of ketamine (as sublingual administration) with its and chlorpheniramine co-administration:

Comparison of CNS suppression effects due to ketamine in the manner of single administration and combined with chlorpheniramine are shown in graphs 1 & 2.

Administration of ketamine combined with chlorpheniramine causes tardier start and also durable CNS suppression Effect than solely ketamine.

It seems that the administration of ketamine in combination with higher doses of chlorpheniramine shows stronger performance in prolonging of onset time of CNS suppression effect.

Discussion and conclusion:

The results of present study show some notable facts:

1) Administration of ketamine or chlorpheniramine as mixed with milk, meat, ice cream or chocolate is not an appropriate route of administration of these drugs in cat.

2) Chlorpheniramine didn't cause a significant CNS suppression effects when sprayed in mouth in administered doses.

3) Intra oral (sublingual) spray of ketamine in administrated doses absolutely causes a dose dependently CNS suppression.

4) CNS depression effect in co administration of Chlorpheniramine with ketamine improved in compare with whenever ketamine administered sporadically.

Ketamine is a drug with high lipid solubility and rapidly leaves plasma to the CNS (brain). After i.v. administration, maximum within 1 minute 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 [10,11]. 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 minutes in cats. These effects were dose dependently so that with dose of 80 mg/kg the cats reached to score5 (analgesia). This drug’s Rapid onset time of effect with oral (sublingual) administration, indicates its high mucosal absorption from proximal parts of GI (e.g. oral cavity and esophagus).

In other section of this study administration of chlorpheniramine as intra oral spray didn't exert a significant CNS suppression effects. This occurrence is may be due to low or slow distribution of the drug trough CNS in used doses, low efficacy of drug in CNS suppression, or etc. so to discover distinct mechanism of this occurrence further studies may be needed.

But whenever it added to ketamine's regime (as oral spray), this drug decreased KT's onset time of CNS suppression effect. Also severity of CNS suppression effect (peak score) increased whenever chlorpheniramine co administered with ketamine.

Parameters of CNS suppression effects (highest peak score in administered dose and percentage of animals reached to peak score) were severe and sensible in group ketamine 80mg/kg + chlorpheniramine 4mg/cat so as score 5 was seen in 80% of cases in this treatment group. May be slow onset time of CNS suppression effect in animals that
Table 1: Effect of ketamine administration (20, 40, 80 mg/kg as intragastric spray). 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.

<table>
<thead>
<tr>
<th>Dose Of Ketamine (mg/kg)</th>
<th>Onset Time Of Effect (min)</th>
<th>Duration Of Effect (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2.26 ± 0.36</td>
<td>0.65 ± 0.09</td>
</tr>
<tr>
<td>40</td>
<td>1.65 ± 0.13</td>
<td>1.69 ± 0.31</td>
</tr>
<tr>
<td>80</td>
<td>1.39 ± 0.11 *</td>
<td>2.63 ± 0.36 ***</td>
</tr>
</tbody>
</table>

*** 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 intragastric spray). 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.

<table>
<thead>
<tr>
<th>Dose Of Ketamine (mg/kg)</th>
<th>Observed Peak Score</th>
<th>Percentage Of Animals Reached Peak Score</th>
<th>Onset Time Of Peak Score (min)</th>
<th>Duration Of Peak Score (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>3</td>
<td>40 %</td>
<td>5.22±0.9</td>
<td>11.15±1.9</td>
</tr>
<tr>
<td></td>
<td>60 %</td>
<td>3.5±0.5</td>
<td>23.46±6.9</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>40 %</td>
<td>4.1±0.38</td>
<td>10.87±2.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3.1±0.6</td>
<td>2.66 ±0.31*</td>
<td>62.33±14.9</td>
</tr>
<tr>
<td>80</td>
<td>4</td>
<td>50 %</td>
<td>2.23±0.4</td>
<td>86.2±19.8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>50 %</td>
<td>2.1±0.6</td>
<td>114.4±24.8</td>
</tr>
</tbody>
</table>

Table 3: Effect of ketamine (20, 40, 80 mg/kg) & Chlorpheniramine (4, 8, 16 mg/cat) co-administration as sublingual spray. 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.

<table>
<thead>
<tr>
<th>Ketamine + chlorpheniramine (mg/kg)</th>
<th>Onset Time Of Effect (min)</th>
<th>Duration Of Effect (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 + 16</td>
<td>3.73 ± 0.31</td>
<td>1.35 ±0.22</td>
</tr>
<tr>
<td>40 + 8</td>
<td>3.20 ± 0.28</td>
<td>2.66 ± 0.31*</td>
</tr>
<tr>
<td>80 + 4</td>
<td>1.45 ± 0.23**</td>
<td>4.85± 0.42 ***</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001 significantly different from the control group (Ketamine 20 mg/kg + Chlorpheniramine 16 mg/cat).

Table 4: Effect of ketamine (20, 40, 80 mg/kg) Chlorpheniramine (4, 8, 16 mg/cat) co-administration as sublingual spray.

<table>
<thead>
<tr>
<th>Ketamine + chlorpheniramine (mg/kg)</th>
<th>Observed Peak Score</th>
<th>Percentage Of Animals Reached Peak Score</th>
<th>Onset Time Of Peak Score (min)</th>
<th>Duration Of Peak Score (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 + 16</td>
<td>3</td>
<td>20%</td>
<td>9.40±1.1</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>40 + 8</td>
<td>4</td>
<td>80%</td>
<td>7.14±0.57</td>
<td>0.71±0.18</td>
</tr>
<tr>
<td>80 + 4</td>
<td>4</td>
<td>40%</td>
<td>6.03±0.45</td>
<td>1.7±0.3</td>
</tr>
<tr>
<td>20 + 16</td>
<td>3</td>
<td>20%</td>
<td>9.40±1.1</td>
<td>0.4±0.1</td>
</tr>
<tr>
<td>40 + 8</td>
<td>4</td>
<td>80%</td>
<td>7.14±0.57</td>
<td>0.71±0.18</td>
</tr>
<tr>
<td>80 + 4</td>
<td>4</td>
<td>80%</td>
<td>2.51±0.58</td>
<td>3.87±0.62</td>
</tr>
</tbody>
</table>

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.

Graph 1: Comparison onset time of CNS suppression between ketamine (20, 40, 80 mg/kg) & Ketamine (20, 40, 80 mg/kg) + Chlorpheniramine (4, 8, 16 mg/cat). Results are expressed as Mean±SE, **P<0.01, ***P<0.001.
received combination of ketamine & chlorpheniramine in compare with cases treated with ketamine alone is due to challenge of chlorpheniramine with ketamine in mucosal absorption. But when they reached in brain, CNS suppression effect is severe due to their synergism.

Chlorpheniramine is one of alkylaminic H1 blockers so that has high oral absorption like other members of this group and usually cause partial sedation in treated cases (11). 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. with attention to this point in present study ketamine and chlorpheniramine have better results in CNS suppression in regime ketamine 80mg/kg + chlorpheniramine 4mg/cat, it seems that this protocol is suitable to induction deep sedation of cat as non invasive route of administration. 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.

References


