(RS)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone has forcefully effect on CNS whenever be administrated Enterally with Diphenhydramine as a potent classic antihistamine

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Abstract: (RS)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone with generic name of Ketamine is a drug used in human and veterinary medicine, primarily for the induction and maintenance of general anesthesia, usually in combination with a sedative in addition to it's sedative, analgesic anti bronchospasm and anti depressant effects. Diphenhydramine is a influential first-generation antihistamine possessing anticholinergic, antitussive, antiemetic, and sedative properties which is mainly used to treat allergies. It also has a powerful hypnotic effect, and for this reason is often used as a non-prescription sleep aid. Thereupon it seems that co administration of Diphenhydramine and ketamine cause more effective & deep CNS depression effects and also alleviate some of ketamine adverse effects. The aim of this study was evaluation of ketamine and Diphenhydramine CNS suppression effects in the manner of single and concomitant administration. Ten free roaming male & mature cats as animal model received mentioned drugs via enteral route. Each animal was monitored continually by educated expert for CNS depression signs as graded on the behavioral scales. Diphenhydramine alone in oral administration of any Doses could induce only suitable sleep with Immobility in animals. But ketamine in different doses showed a significant dose dependent CNS suppression effect. Concomitant use of Diphenhydramine with ketamine promoted CNS depression effects of ketamine.

[Eilyad Issabeagloo, Ali Rezaei. **(RS)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone has forcefully effect on CNS whenever be administrated Enterally with Diphenhydramine as a potent classic antihistamine.** *Life Sci J* 2013;10(1):886-894]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 139

KEY WORDS: Ketamine, Diphenhydramine, CNS depression, enteral route, Animal model

1. Introduction

Ketamine (KT) with chemical name: (RS)-2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone was originally developed in 1965 as a derivative of phencyclidine (PCP), which was synthesized in 1926, a feat made possible by the discovery of a new organic Grignard reaction by Parke-Davis scientist Harold Maddox (17). Initially known as CI-581, ketamine was first synthesized by Parke-Davis scientist Calvin Stevens. Pharmacological investigations in human subjects began in 1964 (17). These investigations demonstrated that ketamine's shorter duration of action and lesser psychotomimetic profile made it favorable over PCP as a "dissociative" anesthetic (11). Following FDA approval in 1970, ketamine anesthesia was first given to American soldiers during theVietnam War.

Ketamine is a drug used in human and veterinary medicine, primarily for the induction and maintenance of general anesthesia, usually in combination with a sedative. Other uses include sedation in intensive care, analgesia (particularly in emergency medicine), and treatment of bronchospasm. Ketamine has a wide range of effects in humans, including analgesia, anesthesia, hallucinations, elevated blood pressure, and bronchodilation (46). It has been shown to be effective in treating depression in patients with bipolar disorder who have not responded to antidepressants (8). In persons with major depressive disorder, it produces a rapid antidepressant effect, acting within two hours as opposed to the several weeks taken by typical antidepressants to work (43). It is also a popular anesthetic in veterinary medicine.
Its hydrochloride salt is sold as Ketanest, Ketaset, and Ketalar. Pharmacologically, ketamine is classified as an NMDA receptor antagonist (5). At high, fully anesthetic level doses, ketamine has also been found to bind to opioid μ receptors type 2 in cultured human neuroblastoma cells – however, without agonist activity (22) and to sigma receptors in rats (25). Also, ketamine interacts with muscarinic receptors, descending monoaminergic pain pathways and voltage-gated calcium channels (44). Like other drugs of this class such as tiletamine and phencyclidine (PCP), it induces a state referred to as "dissociative anesthesia" (47) and is used as arecreational drug. Ketamine is a chiral compound. Most pharmaceutical preparations of ketamine are racemic; however, some brands reportedly have (mostly undocumented) differences in enantiomeric proportions. The more active enantiomer, (S)-ketamine, is also available for medical use under the brand name Ketanest S (36). Ketamine is a 'core'

medicine in the World Health Organization's "Essential Drugs List", a list of minimum medical needs for a basic healthcare system (58).

Nonmedical use of ketamine was documented in the early 1970s in underground literature (see The Fabulous Furry Freak Brothers). It was used in psychiatric and other academic research through the 1970s, culminating in 1978 with the publishing of psychonaut John Lilly's The Scientist and Marcia Moore and Howard Alltounian's Journeys into the Bright World, which documented the unusual phenomenology of ketamine intoxication (2). The incidence of nonmedical ketamine use increased through the end of the century, especially in the context of raves and other parties (7, 13, 20, 31, 33). However, its emergence as a club drug differs from other club drugs (e.g. MDMA) due to itsanesthetic properties (e.g., slurred speech, immobilization) at higher doses (33); in addition, reports of ketamine being sold as "ecstasy" are common (45). The use of ketamine as part of a "post-clubbing experience" has also been documented (42). Ketamine's rise in the dance culture was most rapid in Hong Kong by the end of the 1990s (33). Diphenhydramine (DPH) is a first generation antihistamine possessing anticholinergic, antitussive, antiemetic, and sedative properties which is mainly used to treat allergies. Like most other first-generation antihistamines, the drug also has a powerful hypnotic effect, and for this reason is often used as a non-prescription sleep aid; especially in the form of diphenhydramine citrate. It is produced and marketed under the trade name Benadryl by McNeil-PPC (a division of Johnson & Johnson) in the U.S., Canada and South Africa (other trade names in other countries: Dimedrol, Daedalon). It is also available as a generic or store brand medication. It is also found in the name-brand products Nytol,Unisom, Tylenol PM, Excedrin PM, Midol PM, Zzzquil and Advil PM, though some Unisom products contain doxylamine instead. It is available as an over-the-counter (OTC) or prescribed HCl injectable. It may also be used for the treatment of extrapyramidal side-effects of many antipsychotics, such as the tremors that haloperidol can cause. In addition, injectable diphenhydramine can be used for life-threatening reactions (anaphylaxis) to allergens such as bee stings, peanuts, or latex, rather than risking the side-effects of epinephrine. It is a member of the ethanolamine class of antihistaminergic agents.

Diphenhydramine was one of the first known antihistamines, invented in 1943 by Dr. George Rieveschl, a former professor at theUniversity of Cincinnati (24). In 1946, it became the first prescription antihistamine approved by the U.S. Food and Drug Administration (FDA) (52).

Diphenhydramine is an inverse agonist of the histamine H1 receptor (59). By blocking histamine in the capillaries it can reduce the intensity of allergic symptoms. Diphenhydramine crosses the blood–brain barrier (BBB) and antagonizes the H1 receptors centrally. Its effects on central H1 receptors causes drowsiness (50). Like many other first-generation antihistamines, diphenhydramine is also a potent competitive antagonist of muscarinic cholinergic receptors, and, as such, at high doses can cause anticholinergic syndrome (3). Diphenhydramine can also act as a antiparkinson agent as a result of the blocking properties to the muscarinic acetylcholine receptors in the brain.

In the 1960s, diphenhydramine was found to inhibit reuptake of the neurotransmitter serotonin (16). This discovery led to a search for viable antidepressants with similar structures and fewer side-effects, culminating in the invention of fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI) (16, 6). A similar search had previously led to the synthesis of the first SSRI, zimelidine, from brompheniramine, also an antihistamine. Diphenhydramine also acts as an intracellular sodium channel blocker, which is responsible for its actions as a local anesthetic (35). Diphenhydramine acts as an analgesia potentiator with morphine in rats (9). It is used recreationally as a deliriant, or as a potentiator of alcohol and some opiates (54). CNS effects occur within the limbic system and hippocampus, causing confusion and temporary amnesia. Like its chemical relatives, diphenhydramine has mild to moderate euphoriant actions of its own. Toxicology also manifests in the autonomic nervous system, causing urinary retention, pupil dilation, tachycardia, irregular urination, and dry skin and mucous membranes. Severe restlessness or akathesia can also be a side effect that is made worse by increased levels of diphenhydramine (26). Considerable overdosage can lead to cardiac arrest, serious ventricular dysrhythmias, coma, and death. Such a side-effect profile is commonly thought to give ethanolamine-class antihistamines a relatively low abuse liability. The specific antidote for diphenhydramine poisoning (similar to that of Datura or Atropa belladonna poisoning) isphysostigmine.

2. Materials and Methods

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. Animals had not be implicated any healthy problem allover the study. The numbers of cats in all of the treatment groups were ten animals. The procedure has been approved by research organization Islamic Azad University ethic committee and was conducted in conformity with the NIH guidelines for the care and use of 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 (51), was sprayed in mouth by a ordinary syringe. For comparison, a similar study was performed with DPH. Diphenhydramine (Benadryl®) (Parke-Davis) was dissolved in normal saline and different doses of Diphenhydramine (1, 2, 4 mg/kg) (57) were administered as a mentioned method. To prevent absorption of the drugs from lower parts of gastrointestinal tract such as stomach or intestine, thus mentioned doses were balanced no exceed of 0.5 ml in treatment groups.

In first stage, drugs administered separately. In second step Diphenhydramine 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. Hence treatment groups include:

1) ketamine 20 mg/kg, 2) ketamine 40 mg/kg, 3) ketamine 80mg/kg, 4) Diphenhydramine 1 mg/kg, 5) Diphenhydramine 2 mg/kg, 6) Diphenhydramine 4 mg/kg, 7) ketamine 20 mg/kg plus Diphenhydramine 4 mg/kg, 8) ketamine 40 mg/kg plus Diphenhydramine 2 mg/kg, 9) ketamine 80 mg/kg plus Diphenhydramine 1 mg/kg.

Each animal was observed continuously by an educated expert 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 (29).

Also obtained results in administration of various doses of drugs were evaluated on the base of underneath parameters for each treatment group: (55')

- 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.

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.

3. Results

- Rate of CNS suppression of ketamine in oral administration:

As shown in Tables 1, Onset time of effect decrease with increasing dose of KT. In dose of 80 mg/kg this time decrease to 1':44" that in comparison with KT 20 mg/kg was considered significant ($P<0.05$). Duration of effect was lasted with increasing dose of KT so that the longest time seen in group ketamine 80mg/kg (2:36') in order that in compare with control group (20 mg/kg) this parameter shows a significant elevation ($P<0.001$).

Also peak score of CNS suppression increased dose dependently so that in dose 80 mg/kg, in 60% of cats analgesia was sow (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 with almost in comparison, is half of 20 mg/kg. For evaluation of probability and rate of mortality, we used 120, 160 and 240 mg/kg doses in separate groups. There wasn't seen any mortality in very high doses (120-240 mg/kg) in oral administration of KT. So it seems that this drug has a significant safety whenever administered orally. But very inconsistent results obtained in duration of peak score and duration of effect in these high doses as duration of peak score was fluctuated between 8 – 17 hours and duration of effect between 25-49 hours. Some of data about mortality or onset and duration

times of CNS suppression in mentioned very high doses has not specified in the table.

Table 1. Effect of ketamine (20, 40, 80 mg/kg as oral administration).
Onset time and duration of CNS suppression; 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. Results are expressed as Mean±SE.

Dose Of Ketamine (mg/kg)	Onset Time Of Effect (min)	Duration Of Effect (hour)	Observed Peak Score	Percentage Of Animals Reached Peak Score	Onset Time Of Peak Score (min)	Duration Of Peak Score (min)
20	2.37 ± 0.53	0.49 ± 0.07	3	30 %	4.8±0.5	12.11±1.4
			4	70 %	3.55±0.9	22.67±5.4
40	1.85 ± 0.78	1.63 ± 0.31 *	3	50 %	4.43±0.21	11.36±3.3
			4	50 %	3.79±0.08	59.21±13.1
80	1.26 ± 0.16 *	2.61 ± 0.17 ***	4	40 %	2.71±0.46	81.5±15.18
			5	60 %	2.36±0.6	111.4±25.1

*** p<0.001, * p<0.05 significantly different from the control group (Ketamine 20mg/kg).

Rate of CNS suppression of Diphenhydramine in oral administration:

As regards to tables 2 Onset time of CNS suppression decrease with increasing dose of DPH. So that in dose 4 mg/kg this time is nigh half of 1 mg/kg (lowest administered dose) (P<0.001). Also duration of CNS suppression was lasted with increasing dose of DPH so as seen in table this time almost reached to 8:42' so in compare with control group (1 mg/kg) this parameter shows a significant elevation (P<0.05). DPH in the highest administered dose mainly could create score 3 in cats (70%) but 10 % of cats represented score 4 proofs.

Table 2. Effect of Diphenhydramine (1, 2, 4 mg/kg as oral administration).
Onset time and duration of CNS suppression; 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. Results are expressed as Mean±SE.

Dose Of Diphenhydramine (mg/kg)	Onset Time Of Effect (min)	Duration Of Effect (hour)	Observed Peak Score	Percentage Of Animals Reached Peak Score	Onset Time Of Peak Score (min)	Duration Of Peak Score (min)
1	21.81 ± 0.27	4.23 ± 0.41	2	100 %	†	†
2	13.49 ± 0.11 ***	7.81 ± 0.7	3	100 %	.21±0.45	.3±0.17
4	10.57 ± 0.47 ***	8.4 ± 0.37*	3	70 %	.45±0.07	.5±0.25
			4	30 %	.19±0.42	.2±0.41

*** p<0.001, * p<0.05 significantly different from the control group (Diphenhydramine 1mg/kg).
†: Whenever score 2 recorded we did not recognize any time to Duration of Peak Score & onset time of Peak Score.

Rate of CNS suppression in co-administration of ketamine with DPH:

So as saw in table 3, onset time of CNS suppression in group ketamine 80 + DPH 1 is faster than other two groups in comparison.

In addition duration of CNS suppression (duration of peak score & duration of effect) in this group is considered significant more long-lasting in compare with other two groups (P<0.001). Beside peak score accompanied by further frequency (100%) again was seen in same group in comparison with other treatment groups. Besides highest duration of peak score (280 min.) was seen still in mentioned group.

Table 3. Effect of ketamine & Diphenhydramine co administration as oral administration. Onset time and duration of CNS suppression; 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. Results are expressed as Mean±SE.

Ketamine + Diphenhydramine (mg/kg) (mg/kg)	Onset Time Of Effect (min)	Duration Of Effect (hour)	Observed Peak Score	Percentage Of Animals Reached Peak Score	Onset Time Of Peak Score (min)	Duration Of Peak Score (min)
20 + 4	3.55 ± 0.39	4.95 ±0.9	3	40 %	9.1±0.21	54.24±2.7
			4	60 %	8.7±0.15	58.61±4.21
40 + 2	2.69 ± 0.24	5.63 ±0.24	4	20 %	9.48±0.05	175.44±14.1
			5	80 %	8.34±0.1	189.33±10.58
80 + 1	⁂⁂⁂1.47 ± 0.2***	✠✠†***	5	100 %	6.78±0.42	280.8±19.53

†: Times more than 6 hours was not recorded.
*** p<0.001 significantly different from the control group (Ketamine 20mg/kg+ DPH 4mg/kg).
⁂⁂⁂ p<0.001 significantly different from the group Ketamine 40mg/kg+ DPH 2mg/kg).
✠✠ p<0.05 significantly different from the group Ketamine 40mg/kg+ DPH 2mg/kg).

4. Discussion

Ketamine is absorbable via intravenous, intramuscular, oral, and topical routes due to both its water and lipid solubilities (4). When administered orally, it undergoes first-pass metabolism, where it is biotransformed in the liver by CYP3A4 (major), CYP2B6 (minor), and CYP2C9 (minor) isoenzymes into norketamine (through N-demethylation) and finally dehydronorketamine (56). Intermediate in the biotransformation of norketamine into dehydronorketamine is the hydroxylation of norketamine into 5-hydroxynorketamine by CYP2B6 and CYP2A6. Dehydronorketamine, followed by norketamine, is the most prevalent metabolite detected in urine (40). As the major metabolite of ketamine, norketamine is one-third to one-fifth as potent anesthetically, and plasma levels of this metabolite are three times higher than ketamine following oral administration (4, 21). Bioavailability through the oral route reaches 17-20%; bioavailability through other routes are as follows: 93% intramuscularly, 25-50% intranasally, 30% sublingually, and 30% rectally (48, 56). Peak plasma concentrations are reached within a minute intravenously, 5–15 min intramuscularly, and 30 min orally (21). Ketamine's duration of action in a clinical setting is 30 min to 2 h intramuscularly and 4–6 h orally (48). Plasma concentrations of ketamine are increased by diazepam and other CYP3A4 inhibitors (48).

Ketamine is a drug with high lipid solubility and rapidly leaves plasma to the CNS (brain) and has various properties such as sleep induction, anaesthetic, analgesic and anti depressant (55). 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 (28, 30). This agent can also induce anaesthesia in I.P. route in addition to its essential routes of drug administration I.V or I.M. by dose of 0.5 ml in rat (38). But I.v. administration of ketamine has some obvious CNS suppression effects in cat. In the present study oral ketamine administration induced CNS depression effects within 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).

- Oral ketamine is more potent than SC ketamine (due to liver metabolism). Many patients require a dose reduction of 25-50% when changing to oral ketamine. Some specialists stop the SC infusion when the first dose of oral ketamine is given. Others gradually reduce the infusion dose as the oral dose is increased (27).

KT has various indications for use as an anaesthetic:

- Pediatric anesthesia (as the sole anesthetic for minor procedures or as an induction agent followed by muscle relaxant and endotracheal intubation);
- Asthmatics or patients with chronic obstructive airway disease;
- As part of a cream, gel, or liquid for topical application for nerve pain — the most common mixture is 10% ketoprofen, 5%lidocaine, and 10% ketamine. Other ingredients found useful by pain specialists and their patients, as well as the compounding pharmacists who make the topical mixtures, include amitriptyline, cyclobenzaprine, clonidine, tramadol, andmepivacaine and other longer-acting local anaesthetics.

- In emergency medicine if an entrapped patient is suffering severe trauma (12);
- Emergency surgery in field conditions in war zones;
- To supplement spinal/epidural anesthesia/analgesia using low doses;

In medical settings, ketamine is usually injected intravenously or intramuscularly (39). Since it suppresses breathing much less than most other available anaesthetics (23), ketamine is still used in human medicine as an anesthetic; however, due to the hallucinations it may cause, it is not typically used as a primary anesthetic, although it is the anaesthetic of choice when reliable ventilation equipment is not available. Ketamine tends to increase heart rate and blood pressure. Because it tends to increase or maintain cardiac output, it is sometimes used in anesthesia for emergency surgery when the patient's fluid volume status is unknown (*e.g.*, from traffic accidents). Ketamine can be used in podiatry and other minor surgery, and occasionally for the treatment of migraine. Research is ongoing in France, the Netherlands, Russia, Australia and the US into the drug's usefulness in pain therapy, depression (60) and for the treatment of alcoholism (37) and heroin addiction (34).

In veterinary anesthesia, ketamine is often used for its anesthetic and analgesic effects on cats, dogs, rabbits , rats, and other small animals. Veterinarians often use ketamine with sedative drugs to produce balanced anesthesia and analgesia, and as a constant-rate infusion to help prevent pain wind-up. Ketamine is used to manage pain among large animals, though it has less effect onbovines. It is the primary intravenous anesthetic agent used in equine surgery, often in conjunction with detomidine and thiopental, or sometime guaifenesin.

Ketamine may be used in small doses (0.1–0.5 mg/kg·h) as a local anesthetic, particularly for the treatment of pain associated with movement and neuropathic pain (41). It may also be used as an intravenous coanalgesic with opiates to manage otherwise intractable pain, particularly if this pain is neuropathic (pain due to vascular insufficiency or shingles are good examples). It has the added benefit of counteracting spinal sensitization or wind-up phenomena experienced with chronic pain. At these doses, thepsychotropic side effects are less apparent and well managed with benzodiazepines (18). Ketamine is a coanalgesic, so is most effective when used alongside a low-dose opioid; while it does have analgesic effects by itself, the higher doses required can cause disorienting side effects (18). The combination of ketamine with an opioid is, however, particularly useful for pain caused by cancer (53).

The effect of ketamine on the respiratory and circulatory systems is different from that of other anesthetics. When used at anesthetic doses, it will usually stimulate rather than depress the circulatory system (1). It is sometimes possible to perform ketamine anesthesia without protective measures to the airways. Ketamine is also a potent analgesic and can be used in subanesthetic doses to relieve acute pain; however, its psychotropic properties must be taken into account. Patients have reported vivid hallucinations, "going into other worlds" or "seeing God" while anesthetized, and these unwanted psychological side effects have reduced the use of ketamine in human medicine. They can, however, usually be avoided by concomitant application of a sedative such as a benzodiazepine (18).

Low-dose ketamine is recognized for its potential effectiveness in the treatment of complex regional pain syndrome (CRPS) (10). Although low-dose ketamine therapy is established as a generally safe procedure, reported side effects in some patients have included hallucinations, dizziness, lightheadedness and nausea. Therefore, nurses administering ketamine to patients with CRPS should do so only in a setting where a trained physician is available if needed to assess potential adverse effects on patients (55).

In some neurological intensive care units, ketamine has been used in cases of prolonged seizures. Some evidence indicates the NMDA-blocking effect of the drug protects neurons from glutamatergic damage during prolonged seizures (19).

In other section of this study, orally administration of Diphenhydramine in different doses induced almost a suitable but short-lasting CNS depression effects (maximum scores 4 in highest dose). This effect maybe in result of its mechanism of action, low & slow distribution trough CNS in administered doses or etc. For clarify of its exact mechanism need further studies.

But when this drug added to ketamine regime in mentioned doses (oral administration), all of recorded parameters improved in comparison with ketamine and Diphenhydramine alone. So that it seems due to synergistic effects between them in suppression of CNS.

These effects in group ketmanie80+ Diphenhydramine1 were considered significant ($p<0.001$) in compare with other combination protocol so that we could achieve anaesthesia in this combination protocol.

Diphenhydramine is a first-generation antihistamine possessinganticholinergic, antitussive, antiemetic , and sedative properties which is mainly used to treat allergies. Like most other first-

generation antihistamines, the drug also has a powerful hypnotic effect, and for this reason is often used as a non-prescription sleep aid; especially in the form of diphenhydramine citrate.

Diphenhydramine is a first generation antihistamine used to treat a number of conditions including allergic symptoms anditchiness, the common cold, insomnia, motion sickness, and extrapyramidal symptoms (15). Diphenhydramine is also used to treat Parkinson's disease by antagonizing acetylcholine in the muscarinic receptors; thus correcting the neurotransmitter imbalance of dopamine that also controls motor function in the brain; similar to otherantimuscarinic agents such as atropine. Since diphenhydramine has potent anticholinergic properties, recent clinical evidence revealed this medication can be helpful in treating asthma and chronic obstructive pulmonary disease, allowing the bronchi to relax and causing airflow obstruction to subside.

Despite being one of the oldest antihistamines on the market, it is more effective than even some of the latest prescription drugs (49). Consequently, it is frequently used when an allergic reaction requires fast, effective reversal of the often dangerous effects of a massive histamine release. Diphenhydramine has sedative properties and is widely used in nonprescription sleep aids, with a maximum recommended dose of 50 mg (as the hydrochloride salt) being mandated by the U.S. FDA.

Diphenhydramine also has antiemetic properties which make it useful in treating the nausea that occurs in motion sickness. As it causes marked sedation in many individuals, the less sedating drug dimenhydrinate may be preferred for this purpose. The drug is an ingredient in several products sold as sleep aids, either alone or in combination with other ingredients such as acetaminophen (paracetamol).

There are also topical formulations of diphenhydramine available, including creams, lotions, gels, and sprays. They are used to relieve itching, and have the advantage of causing much less systemic effect (i.e. drowsiness) than oral forms. As diphenhydramine is extensively metabolized by the liver, caution should be exercised when giving the drug to individuals with hepatic impairment. Diphenhydramine acts as an analgesia potentiator with morphine in rats (9). It is used recreationally as a deliriant, or as a potentiator of alcohol and some opiates (54). CNS effects occur within the limbic system and hippocampus, causing confusion and temporary amnesia. Like its chemical relatives, diphenhydramine has mild to moderate euphoriant actions of its own.

Toxicology also manifests in the autonomic nervous system, causing urinary retention, pupil dilation, tachycardia, irregular urination, and dry skin and mucous membranes. Severe restlessness or akathesia can also be a side effect that is made worse by increased levels of diphenhydramine (26). Considerable overdosage can lead to cardiac arrest, serious ventricular dysrhythmias, coma, and death. Such a side-effect profile is commonly thought to give ethanolamine-class antihistamines a relatively low abuse liability. The specific antidote for diphenhydramine poisoning (similar to that of Datura or *Atropa belladonna* poisoning) isphysostigmine.

It seems that improvement of CNS suppression effect in co-administration of Diphenhydramine & ketamine is due to high mucosal absorption of Diphenhydramine (as ketamine) and whenever these two drugs reached to CNS, depth and duration of CNS suppression effect be invigorated because of synergism existence between these two drug.

With due attention to that in present study, in group ketamine 80 plus Diphenhydramine 1 onset time and duration of CNS suppression was more suitable so that chiefly anesthesia was seen in allover the animals; it seems that this protocol is a appropriate non-invasive method to induce anaesthesia in cat.

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12/20/2012