

Ketamine anaesthesia following premedication of rabbits with vitamin C

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The effects of vitamin C on ketamine anaesthesia was studied. In normal rabbits the onset and duration of ketamine induced anaesthesia were 6.0 ± 0.5 and 36.0 ± 0.9 min, respectively. Pre-treatment of rabbits with 30, 60 and 240 mg/kg, i.m. of vitamin C followed by ketamine 40 mg/kg i.m. resulted in significant ($p < 0.05$) decrease in the onset and increase in duration of ketamine anaesthesia to 5.0 ± 0.06 and 37.0 ± 0.7 ; 4.0 ± 0.5 and 39.0 ± 0.6 ; 2.0 ± 0.3 and 44.0 ± 0.8 min, respectively. There was also significant ($p < 0.05$) decrease in the heart rates in the animals treated with vitamin C and ketamine combinations. Serum analysis showed a significant ($p < 0.05$) increase in blood glucose. The observed decrease in serum calcium and phosphorous following ketamine injection was prevented by pretreatment with vitamin C. These results suggest that vitamin C at higher doses could potentiate ketamine anaesthesia in rabbits.

Key words: ketamine, rabbits, vitamin C

Introduction

Vitamin C possesses properties that exert modulating influence on the central nervous system either physiologically or pharmacologically. It is believed that vitamin C is an important regulator of mood and behaviours from reports of observed symptoms of insomnia and anxiety [11,12]. High amount of vitamin C probably has similar physiological properties as amphetamine in the central nervous system. Depression and impairment of nervous system functions have been reported due to deficiency of this water-soluble vitamin [10,13]. In spite of several studies, the actual physiological role of vitamin C in the normal function of central nervous systems remains unclear, though it is known to be highly concentrated in the brain [11]. High doses of vitamin C have been reported to induce sleep disturbances, headache and gut upset [4,8].

Combined effects of stress and anaesthesia can result in cardio-respiratory arrests. Rabbits are prone to be easily stressed by improper pre-operative handling and/or induction of anaesthesia especially with volatile anaesthetics [3]. In rabbits, recovery from anaesthesia is often slow particularly following the use of barbiturates. The prolonged inappetence characterized by frequent postoperative complication in rabbits can result in gastro-intestinal disturbances.

Ketamine produces a most useful state of dissociative anaesthesia with the patient rapidly entering a trance like state with eyes wide open and nystagmus [7]. A patient is unconscious, amnesic and deeply analgesic. Ketamine has made many operations possible that otherwise wouldn't have been impossible because of scarcity of trained anaesthetists [6,9]. Based on this background, this study was designed to determine the effects of vitamin C on ketamine anaesthesia in rabbits.

Materials and Methods

Experimental animals

Twenty-five adult rabbits (California white breed) of either sex aged between 10 to 19 months and weighing 1.5 to 2.1 kg were used for this study. They were divided into five groups (A, B, C, D and E) of five rabbits each and housed in the animal house of the Faculty of Veterinary Medicine, Usmanu Danfodiyo University. They were fed with rabbit pellets, onions and spinach, and fresh water was provided *ad libitum*. The rabbits were allowed to acclimatize for two weeks before the experiment commenced.

Experimental procedure

Ketamine (40 mg/kg) was administered intramuscularly into each rabbit in group E. The vital parameters such as body temperature, heart and respiratory rates were taken and recorded after ketamine anaesthesia. The onset and duration of sleep were also observed and recorded. Onset of anaesthesia was evident by dropping of ears, recumbency, decrease respiratory rate, loss of pedal and pupillary reflexes and loss of external stimuli. Ketamine anaesthesia in rabbit produces a deep plane of surgical anaesthesia characterized by complete loss of consciousness and good muscle

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relaxation. Five rabbits each in groups B, C and D received 30, 60 and 240 mg/kg of vitamin C by intramuscular injection, respectively. Five minutes after premedication with vitamin C, the animals were treated with ketamine. The onset and duration of sleep as well as vital parameters were observed and recorded. The animals in groups A as control were neither treated with vitamin C nor ketamine.

Blood samples from the ear vein were collected using clean plain test tubes for each rabbit in groups A, B, C, D, and E after drug administration. The blood samples were allowed to coagulate and serum were harvested and taken to the laboratory for blood glucose, calcium, phosphate and bicarbonate ion assay [14].

Statistical analysis

Mean and standard error were used in analyzing the experimental data. Changes in the control and experimental values were compared for statistical significance using ANOVA and a probability level at 5% as levels of significant.

Results

In normal rabbits the onset and duration of ketamine-induced anesthesia was 6.0 ± 0.5 min and 36.0 ± 0.9 min, respectively. Pretreatment of rabbits with 30, 60 and 240 mg/kg i.m. of vitamin C followed by ketamine 40 mg/kg i.m. resulted in significant ($p < 0.05$) decrease in the onset and increase in the duration of ketamine anaesthesia (Table

1). The decrease in onset and increase in the duration of anaesthesia appear to be dose dependent. Administration of vitamin C prior to administration of ketamine also significantly ($p < 0.05$) decreased the heart rate and respiratory rates. The decrease in the temperature of rabbits treated with vitamin C prior to ketamine anaesthetic administration was insignificant.

Administration of vitamin C prior to ketamine treatment resulted in significantly ($p < 0.05$) increased serum glucose when compared to the control and ketamine treatment alone (Table 2). Vitamin C treatment prior to ketamine administration appear to prevent the reduction in serum calcium ion concentration observed with ketamine treatment alone. Phosphate ion concentration of the blood decreased significantly ($p < 0.05$) with the administration of ketamine alone. However, the administration of vitamin C prior to ketamine resulted in improvement of serum phosphate ion levels in rabbits. Bicarbonate ion levels was not altered by ketamine treatment alone or with its combinations with vitamin C.

Discussion

The results obtained from the experiment showed that vitamin C treatment prior to ketamine administration affected the onset and duration of sleep of ketamine anaesthesia in rabbits. The decrease in the time of onset as well as the increase in the duration of anaesthesia showed

Table 1. Effect of vitamin C on ketamine anesthesia and vital parameters of rabbits pre-treated with different doses of vitamin C

Drug treatment	Anaesthesia		Vital Parameter		
	Onset of action (min)	Duration of sleep (min)	Heart rate (beats/min)	Temperature (°C)	Respiratory rate (cycles/min)
Control	-	-	230.0 ± 1.8	39.3 ± 0.2	166.0 ± 2.8
30 mg/kg vit.C + ketamine	5.0 ± 0.6	37.0 ± 0.7	$139.0 \pm 1.8^*$	39.3 ± 1.8	$92.0 \pm 1.8^*$
60 mg/kg vit.C + ketamine	$4.0 \pm 0.5^*$	39.0 ± 0.6	$123.0 \pm 2.0^*$	39.1 ± 0.4	$122.0 \pm 2.5^*$
240 mg/kg vit.C + ketamine	$2.0 \pm 0.3^*$	$44.0 \pm 0.8^{**}$	$142.0 \pm 2.0^*$	38.8 ± 0.3	$105.0 \pm 3.1^*$
Ketamine alone	6.0 ± 0.5	36.0 ± 0.9	214.0 ± 1.8	38.9 ± 0.4	$109.0 \pm 3.1^*$

*Significantly decrease ($p < 0.05$)

**Significantly increase ($p < 0.05$)

Table 2. Changes in the level of blood glucose, Ca^{2+} , PO_4^{2-} and bicarbonate ion following administration of vitamin C prior to ketamine injection

Drug treatment	Parameters			
	Glucose (mmol/l)	Ca^{2+} (mg/dl)	PO_4^{2-} (mg/dl)	Bicarbonate (mg/dl)
Control	5.5 ± 0.5	10.3 ± 0.4	5.9 ± 0.3	23.0 ± 0.6
30 mg/kg vit. C + ketamine	$7.8 \pm 0.8^*$	9.1 ± 0.4	4.0 ± 0.4	23.6 ± 0.5
60 mg/kg vit. C + ketamine	$9.6 \pm 0.8^*$	10.1 ± 0.6	4.8 ± 0.3	23.0 ± 0.6
240 mg/kg vit. C + ketamine	$10.4 \pm 0.8^*$	10.4 ± 0.5	5.7 ± 0.3	23.8 ± 0.6
Ketamine alone	4.7 ± 0.7	$4.6 \pm 0.6^{**}$	$3.1 \pm 0.4^{**}$	22.8 ± 0.6

*Significantly increase ($p < 0.05$)

**Significantly decrease ($p < 0.05$)

that at low doses the changes were insignificant but significant at high doses. Laurence *et al.* [8] reported that high dose of vitamin C may cause sleep disturbances, headache and gut upset. The present findings appear to be in agreement with those reported by Ezewanne and Anuka [1] on behavioral excitation noticed in rats with low doses (5-80 mg/kg, i.p.) of vitamin C, while the animals were sedated at higher doses (160-320 mg/kg, i.p.). This may be explained by the fact that vitamin C acts by exerting modulating influences on the central nervous system inducing depression and impairment of the functions of central nervous system when administered at high doses [10,11].

Ketamine and vitamin C combination caused significant ($p < 0.05$) decrease in the heart rates and respiratory rates when compared to the control. The decrease in heart rates following vitamin C and ketamine administration is worthy of note since ketamine alone did not significantly reduce the heart rates. The observed decrease may have resulted from vitamin C induced central nervous system depressant activity. Li [9] was of the opinion that normal dose of ketamine does not cause significant respiratory depression. However, in the present study ketamine at 40 mg/kg in rabbits with or without vitamin C induced significant respiratory depression. Ketamine in this present study did not significantly reduce the body temperature. Body temperature is known to be decreased following the administration of general anaesthetics like barbiturates by reduction of muscular activity and depression of thermoregulatory center [5,6]. Administration of ketamine alone to rabbits was observed to induce significant ($p < 0.05$) decreases in the levels of blood glucose, calcium and phosphate ions. However, administration of ketamine with vitamin C caused significant increase ($p < 0.05$) in the levels of blood glucose and calcium ions, while there was no significant change in phosphate and bicarbonate ion level in the blood. These findings appear to agree with those of Fauci and Braunwald [2]. Vitamin C appears to be similar in structure to glucose and many animals convert the intermediate gluconic acid to vitamin C. Furthermore, vitamin C is involved in the metabolism of many substances such as iron, folic acid and histamine and can maintain the blood vessels integrity and immune function [14]. The maintenance of the integrity of the blood vessels may explain presence of normal levels of calcium and phosphorous present in blood following vitamin C and ketamine treatment as opposed to those of ketamine alone. These results suggest that vitamin C administration prior to ketamine treatment could be used to increase the duration of

anaesthesia. This combination may be useful in animals suffering from hypoglycemia that are meant for surgery.

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