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Effects of Chloramphenicol on Ketamine Anaesthesia in Rabbits

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ABSTRACT

The effect of chloramphenicol on ketamine anaesthesia was investigated in rabbits. In a 3-phased study, the rabbits were administered intramuscularly with 50 mg/kg body weight (bw) of ketamine alone, same dose of ketamine 30 minutes after intramuscular administration of a single dose of chloramphenicol (30 mg/kg bw) or same dose of ketamine 30 minutes after intramuscular administration of multiple dose (7 consecutive daily doses) of chloramphenicol (30 mg/kg bw). There was a significant decrease in the rabbits body temperature when ketamine was administered alone ($p<0.05$) but a significant increase in temperature was recorded when ketamine was combined with chloramphenicol ($p<0.05$). Significant decrease in respiratory rate was recorded for all the three treatments; however, the combination of ketamine and chloramphenicol produced.a higher decrease in respiratory rate than when ketamine was used alone. The combination of ketamine and chloramphenicol produced a significant higher heart rate than when ketamine was used alone (when compared to control) ($p<0.05$). The duration of ketamine anaesthesia was increased in rabbits administered single dose of chloramphenicol, while it was decreased in rabbits administered multiple dose of chloramphenicol. This study showed that chloramphenicol altered the temperature, respiratory and heart rates as well as onset and duration of anaesthesia, when used prior to ketamine anaesthesia in rabbits.

Key words: Chloramphenicol, ketamine, anaesthesia, microsomal, haemodynamics, induction

INTRODUCTION

Ketamine hydrochloride, 2-(o-chloriphenyl)-2-(methylamino)-cyclohexanone hydrochloride (Ketalar®, ketaset®, Vetalar®) has since its introduction been approved for use as an anaesthetic agent in sheep, swine and laboratory animals. Although ketamine has been used as sole anaesthetic agent for major surgeries in the cat, such is not considered to be prudent or recommended (Evans *et al.,* 1972), hence in practice, it is used in combination with other agents.

Many anaesthetic agents demonstrate direct activity in modulating haemodynamics, myocardial blood flow and oxygenation, and myocardiac energy supply and utilization (Muir, 1977), all of which influence heart and respiratory rates and temperature of the subject. Ketamine was reported to potentiate respiratory depression (Bovil *et al.,* 1971), increase cardiac output and arterial blood pressure with little alteration in peripheral resistance (Evans *et al.,* 1972). The attempt to reduce the side effects of ketamine has necessitated its combination with other agents (Irwin *et al.,* 1959).

Chloramphenicol is a broad spectrum antibiotic that may be used to suppress bacterial infection prior to induction of anaesthesia in preparation for some surgeries. It is reported to inhibit hepatic microsomal enzyme (Adams and Dixit, 1970; Teske and Carter, 1971) and cause aplastic anaemia (Manyan and Yunis, 1970). *In vitro* studies with microsomal fractions of the liver have revealed that chloramphenicol suppresses the metabolism of hexobarbital and other drugs (Adams and Dixit, 1970). Chloramphenicol was reported to prolong pentobarbital anaesthesia in dogs (Teske and Carter, 1971). This study, was therefore, aimed at investigating the effects of chloramphenicol on ketamine-induced anaesthesia in rabbits.

MATERIALS AND METHODS

Experimental animals

The ten healthy rabbits of different sexes used were obtained from the Maiduguri Monday Market, Nigeria.

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The animals weighed between 1 - 2 kg. They were kept in a fly proof house in separate cages and fed daily with green grass and wheat grains. The rabbits were administered amprolium at 5 g/ 4 litres of clean drinking water daily for 7 days, two weeks before the commencement of the experiment. Water was thereafter provided *ad libitum*.

Investigational drugs

ketamine hycdrochloride (Ketaset®) was supplied by Rotex Medica, Trittan, Germany, while Michael Pharmaceuticals, India, supplied chloramphenicol (Merchlor®). They were reconstituted immediately before use to the desired concentrations with distilled water.

Methodology

Ten rabbits were used in each of the three phases of the study. In the first phase, the rabbits were administered 50 mg/kg body weight (bw) ketamine alone on the first day by intramuscular route. Values of the vital parameters (temperature, respiratory and heart rates) were recorded before and after administration of the agent. The onset and duration of anaesthesia were also determined. In phase two, a week later, the rabbits received the same intramuscular dose (50 mg/kg bw) of ketamine 30 minutes after chloramphenicol (30 mg/kg bw) was administered intramuscularly. Values of the vital parameters, and the onset and duration of anaesthesia in relation to ketamine treatment were recorded as in the first phase. Two weeks after phase two, the third phase commenced in which chloramphenicol was administered intramuscularly to the animals daily for a period of one week at the dose of 30 mg/kg bw. Ketamine was administered to the rabbits intramuscularly 30 minutes after the last dose of chloramphenicol at the rate of 50 mg/kg bw. Values of the vital parameters and the onset and duration of anaesthesia in relation to ketamine treatment were determined as in the earlier phases. The respiratory rates were taken by placing stethoscope between the 5^{th} and 6^{th} ribs of the lateral aspect of the thorax, while the heart rates were taken by placing stethoscope between the 3^{rd} and 6^{th} ribs just around the cardiac notch and the temperatures were monitored by using rectal digital thermometer for one minute. The onset and duration of anaesthesia were monitored using EC/time controls (Alarm Timer, Germany).

Statistical analysis

Values determined from the study were presented as mean ± standard deviation. The data were subjected to analysis of variance (ANOVA) and Student's *t*-test was used to compare the means.

RESULTS

The administration of ketamine alone to rabbits significantly decreased the temperature by 5.6% ($p<0.05$), while the same dose of ketamine administered 30 minutes after a single dose of chloramphenicol resulted in 1.5% increase in temperature. However, when chloramphenicol was administered daily for 7 days followed by ketamine administration after the last dose of chloramphenicol, there was a 8.2% increase in temperature (Table 1).

The respiratory rate of the rabbits was depressed after administration of ketamine alone from 99.02 ± 0.2 to 74.78 ± 0.17 cycles per minute, a 24.5% decrease. The administration of a single dose of chloramphenicol 30 minutes before ketamine administration decreased the respiratory rate by 69% (from 127.92 ± 0.2 to 39.30 ± 0.17 cycles per minute). When chloramphenicol was administered daily for 7 days before ketamine administration, the respiratory rate decreased from 107.52 ± 0.2 to 39.26 ± 0.17 (i.e., a 63% decrease) (Table 1).

The heart rate of the rabbits was not significantly altered by the administration of ketamine alone ($p>0.05$). However, daily administration of chloramphenicol for 7 days prior to ketamine administration significantly increased the heart rate from 120 to 156 beats per minute (i.e., a 31% increase) ($p<0.05$). A single dose of chloramphenicol administered 30 minutes prior to ketamine administration resulted in heart rate increase of 9% (Table 1).

Ketamine administration alone resulted in a more onset of anaesthesia compared to chloramphenicol and ketamine combinations. Ketamine administered alone resulted in an onset of anaesthesia of 2.92 ± 0.28 minutes. The administration of a single dose of chloramphenicol before ketamine administration resulted in 4.96 ± 0.23 minutes onset of anaesthesia, while chloramphenicol when administered daily for 7 days before ketamine administration resulted in 4.10 ± 0.19 minutes onset of anaesthesia. The longest duration of anaesthesia of 36.90 ± 0.27 minutes was recorded when a single dose of chloramphenicol was administered prior to ketamine administration. However, when chloramphenicol was administered daily for 7 days before ketamine administration, the duration of anaesthesia was 20.30 ± 0.37 minutes, while the administration of ketamine alone resulted in 23.08 ± 0.56 minutes duration of anaesthesia (Table 2).

DISCUSSION

Chloramphenicol administered prior to ketamine administration altered the vital parameters (temperature, respiratory and heart rates) as well as the onset and duration of anaesthesia in rabbits. The decrease in temperature when ketamine was used alone may have resulted from central nervous system (CNS) depression. Hypothermia could result from CNS depression (Irwin *et al.,* 1959). Increase in body temperature was recorded when

chloramphenicol was administered prior to ketamine administration. Chloramphenicol was reported to cause allergic/anamnestic reactions (Adams and Dixit, 1970); Teske and Carter, 1971). The attendant fever to the allergic reactions (Laurence *et al.,* 1997) may be responsible for the increase in temperature.

Table 1. Effects of chloramphenicol on mean ± SD temperature, respiratory and heart rates of rabbits on ketamine anaesthesia

Drug dose (mg/kg bw)	No. of rabbits	Parameters	
		Pre-drug treatment	Post-drug treatment
			Temperature (°C)
Ketamine (50)	10	40.24 ± 0.1	38.06 ± 0.19[d] (−5.42%)
Single dose chloramphenicol (30) + ketamine (50)	10	39.62 ± 0.1	40.22 ± 0.19[bc] (+1.51%)
Multiple dose chloramphenicol (30) + ketamine (50)	10	37.90 ± 0.1	40.04 ± 0.19[bc] (+5.65%)
			Respiratory rate (cycles/min)
Ketamine (50)	10	99.02 ± 0.2	74.78 ± 0.17[d] (−24.48%)
Single dose chloramphenicol (30) + ketamine (50)	10	127.92 ± 0.2	39.36 ± 0.17[ad] (−69.23%)
Multiple dose chloramphenicol (30) + ketamine (50)	10	107.52 ± 0.2	39.26 ± 0.17[ad] (−63.49%)
			Heart rate (cycles/min)
Ketamine (50)	10	138.60 ± 0.29	137.50 ± 0.17[d] (−0.79%)
Single dose chloramphenicol (30) + ketamine (50)	10	111.10 ± 0.29	121.60 ± 0.18[ace] (−4.94%)
Multiple dose chloramphenicol (30) + ketamine (50)	10	120.10 ± 0.29	156.90 ± 0.10[be] (+30.64%)

Single dose means a day administration of chloramphenicol; multiple dose means chloramphenicol was administered daily for 7 days prior to ketamine administration; [a] = significant decrease compared to ketamine alone ($p<0.05$); [b] = significant increase compared to ketamine alone ($p<0.05$); [c] = significant decrease compared to multiple dose of chloramphenicol administration ($p<0.05$); [d] = significant decrease compared to control ($p<0.05$); [e] = significant increase compared to control ($p<0.05$); figures in brackets represent percentage increase (+) or decrease (−) compared to control

Table 2. Effects of chloramphenicol on the onset and duration and recovery from ketamine anaesthesia in rabbits

Drug dose (mg/kg bw)	No. of rabbits	Onset of anaesthesia (min)	Duration of anaesthesia (min)
Ketamine (50)	10	2.92 ± 0.28	23.08 ± 0.56[z]
Single dose chloramphenicol (30) + ketamine (50)	10	4.62 ± 0.23[y]	36.90 ± 0.27[y]
Multiple dose chloramphenicol (30) + ketamine (50)	10	4.12 ± 0.19[x]	20.30 ± 0.37

Single dose means a day administration of chloramphenicol; multiple dose means chloramphenicol was administered daily for 7 days prior to ketamine administration; [x] = significant higher compared to ketamine alone ($p<0.05$); [y] = significant higher compared to ketamine alone and chloramphenicol (multiple dose) - ketamine combination ($p<0.05$); [z] = significant higher compared to multiple dose of chloramphenicol administration ($p<0.05$)

Respiratory depression was recorded in all the treatments. Earlier report (Bovill *et al.,* 1971) indicated that ketamine caused respiratory depression in humans. The higher respiratory depression noticed when chloramphenicol was used prior to ketamine administration, probably reflected inhibition or suppression of hepatic microsomal

activity by the antibiotic, thereby interfering with the biotransformation and detoxification of the anaesthetic resulting in its higher concentration in the system.

The administration of chloramphenicol prior to ketamine administration resulted in increased heart rate apparently from increased concentration of ketamine in the system given the postulated inhibition of the hepatic microsomal enzyme. Traber and Priano (1970) reported that ketamine produces elevation in arterial blood pressure secondary to the acceleration in cardiac rate and cardiac output.

The duration of anaesthesia obtained when ketamine was used alone was similar to that in an earlier report (Deyoung *et al.,* 1972; Evans *et al.,* 1972). The increase in anaesthetic period following chloramphenicol administration 30 minutes prior to ketamine administration may also be associated with the inhibitory or suppressive effects of chloramphenicol on hepatic microsomal enzymes thereby sustaining ketamine in the system. However, it was noted that the duration of anaesthesia when chloramphenicol was administered for 7 days prior to ketamine administration was lower than that following ketamine alone and single dose chloramphenicol plus ketamine. It was not clear from the results of this study why the single dose chloramphenicol should induce a longer anaesthetic duration than that following the multiple chloramphenicol doses. The next study being conducted by the authors on the effect of multiple chloramphenicol doses on organs and tissues of rabbits may provide clues to these observations.

In conclusion, the administration of chloramphenicol prior to ketamine administration increased the body temperature, potentiated the ketamine-induced respiratory depression and increased the heart rate of rabbits. Chloramphenicol also prolonged the onset and duration of ketamine anaesthesia in rabbits. However, prolonged use of chloramphenicol decreased the anaesthetic duration.

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