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Effect of different anaesthetic agents on cardiovascular parameters in male Wistar rats.

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ABSTRACT

The objective of this study was to compare the effects of ketamine/thiopentone sodium/urethane on cardiovascular parameters in male Wistar rats. The male Wistar rats were taken and were anesthetized by injecting urethane (1.25 g/kg, i.p.), ketamine (80 mg/kg, i.p.), thiopentone sodium (30 mg/kg, i.p.) solution respectively. The left carotid artery was cannulated for blood pressure (BP) monitoring. BP, ECG and BPM (beats per ms) were recorded using 8 channel physiological recorder system. Ketamine (80 mg/kg) showed significant increase in BP while urethane (1.25g/kg) and thiopentone sodium (30 mg/kg) did not affected BP. Thiopentone sodium and ketamine increased heart rate than urethane. Ketamine or urethane had no effect on QT and ST interval. Thiopentone sodium increased QT and ST interval. Urethane in a dose of (1.25 g/kg i.p) induced anaesthesia at 8-10 min and anaesthesia remained for 6-7 hr and does not affects BP, heart rate, QT and ST intervals. Thus Urethane is a good anaesthetic agent to be used for blood pressure experiment when recovery of the animal is not required.

Keywords: Anaesthesia, BP, ECG, Urethane.

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INTRODUCTION

There are many studies in the literature demonstrating the effects of anesthetics on metabolic, hemodynamic and cardiovascular parameters [1-4].

Urethane and ketamine/xylazine are often used to induce anaesthesia in animals [1, 4]. Ketamine is pharmacologically a congener of phencyclidine and more lipophilic than thiopentone sodium. Ketamine hydrochloride is a dissociative anesthetic of the cyclohexylame group used for chemical restraint and for the induction and maintenance of anaesthesia in a number of species [5]. Unlike many anesthetics, ketamine usually stimulates cardiovascular function in normal animals, causing increase in heart rate and mean arterial pressure. The use of ketamine as sole anesthetics has been limited by muscle hypertonicity and myoclonus, violent recovery and occasional occurrence of convulsions [6]. In an attempt to counteract these undesirable effects, ketamine has been used in combination with various drugs including benzodiazepines, e.g. diazepam [7] and alpha-2 agonists eg. xylazine [8].

Ketamine is hepatically metabolized to norketamine and it is further metabolized and excreted in urine and bile. Elimination $t_{½}$ is 3-4 hr. Side effects associated with ketamine are increase in heart rate, BP, and elevated cardiac output due to sympathetic stimulation. It is good for the hypovolemic patients. Ketamine has been used for the operation on the head and neck in patients who have bled and in asthmatic (relieves bronchospasm) and also suitable for the burn dressing. It is usually combined with either diazepam or xylazine. It contraindicated in hypertensive and ischemic heart diseases.

Thiopentone sodium is another very popular laboratory anaesthetic agent available. It is an ultra short acting thiobarbiturate; with very high lipid solubility hence enters brain very fast. It is soluble in water; the solution is strongly alkaline and is unstable. So it must be prepared just before injection. Injected i.v. (3-5mg/kg) as a 2.5% solution, it produces unconsciousness in 15-20 sec. Consciousness is regained in 8-12 min. Elimination $t_{½}$ is 7-12 hr. Side effect associated with thiopentone sodium is CNS depression may persist for >12 hr. It is slowly metabolized and liable to accumulate in body fats may cause prolonged effect if given repeatedly [9, 10, 11]. Intra-arterial injection produce intense pain necrosis and gangrene may occur. Thiopentone sodium decreases cerebral metabolic rate, cerebral blood flow, and intracranial pressure so it can be used as a protective agent against cerebral ischemia. It is a useful anaesthetic for short surgeries [12]. Thiopentone sodium is not contraindicated in patients with coronary disease because the ratio of myocardial oxygen supply to demand appears to be adequately maintained within a patient's normal blood pressure range [13].

Urethane (ethyl carbamate) is a water-soluble compound whose molecular weight is 89.1and has been widely used as an anaesthetic in animal experiments. It is also a carcinogen, which precludes its use as a human anaesthetic. A search of PubMed indicates that more than 100 studies are published each year using "urethane-anesthetized" animals. The advantages of urethane in animal anesthesia are that it can be administered by several parenteral routes, produces a long-lasting steady level of surgical anesthesia, and has minimal effects on autonomic and cardiovascular systems [14, 15]. It is assumed that animals anesthetized with

urethane represent similar physiologic and pharmacologic behaviors to those observed in unanaesthetized animals.

This is an attempt to compare the effects of thiopentone sodium, ketamine/xylazine and urethane on cardiovascular parameters to analyze which is the good anaesthetic agent amongst the three for BP and ECG experiments. The manuscript will give an insight regarding the choice and efficiency of an anaesthetic to be used for different experimental surgeries as well as cardiovascular experiments.

MATERIALS AND METHODS

ANIMALS:

Male Wistar rats of weight range 220g ± 10g were purchased from National Toxicology Centre, Pune, India and used for the study. The animals had free access to food pellets (Chakan Oil Mills, Pune, India) and water. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Poona College of Pharmacy, Pune, India, constituted under Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA). The protocol no. was CPCSEA/31/08.

CANNULATION OF BLOOD VESSELS:

Male Wistar rats were taken and anesthetized by injecting either urethane (1.25 g/kg, i.p.), ketamine (80 mg/kg, i.p.), thiopentone sodium (30 mg/kg, i.p.) solution respectively. Body temperature was maintained at 37^{o}C. and the trachea was cannulated to maintain airways. PE-50 cannulas were inserted into the left carotid artery for blood pressure (BP) monitoring. The arterial catheter was connected to the pressure transducer to measure the blood pressure using 8 channel physiological recorder systems (Powerlab). ECG and BPM (beats per m) were also recorded simultaneously.

STATISTICAL ANALYSIS:

Arithmetic means of the values of readings were calculated for each experiment. The results obtained were used for statistical analysis using one-way analysis of variance (ANOVA) followed by Dunnett's test. The level of significance in the tests was $p<0.05$. The data were statistically analyzed using statistical software (Graph Pad Prism, USA, version 4 and 5).

RESULTS & DISCUSSION

Treatment with ketamine (80 mg/kg) showed significant increase in BP while urethane (1.25g/kg) and thiopentone sodium (30 mg/kg) did not affect BP (Figure.1). Thiopentone sodium and ketamine increased heart rate compared to urethane (Figure.2). Ketamine and urethane had no effect on QT and ST interval. Thiopentone sodium increased QT and ST interval (Figure.3 and Figure.4 respectively).

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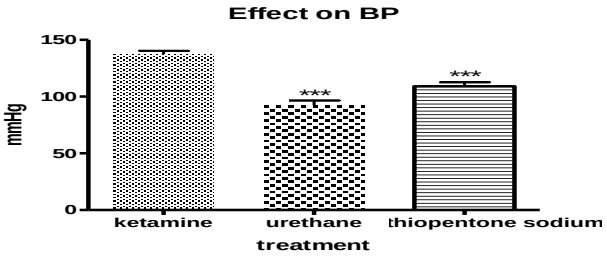

Figure 1: Effect of ketamine, urethane and thiopentone sodium on BP

Data represented are mean number of observations ± S.E.M. on blood pressure (mmHg) and was analyzed by one-way ANOVA followed by Dunnett's test. ***P< 0.001, *** P < 0.001 as compared with ketamine group.

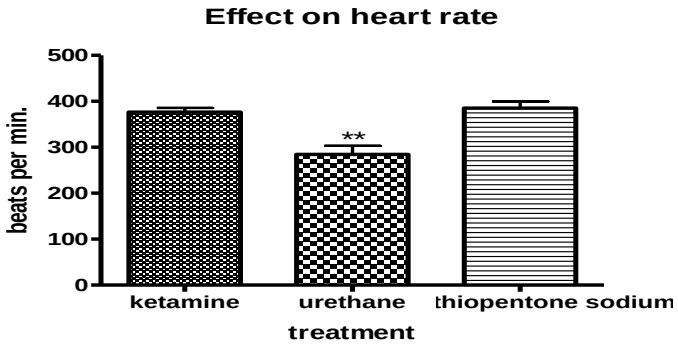

Figure 2: Effect of ketamine, urethane and thiopentone sodium on heart rate.

Data represented are mean number of observations ± S.E.M. on heart rate and was analyzed by one-way ANOVA followed by Dunnett's test. **P< 0.01 as compared with ketamine group.

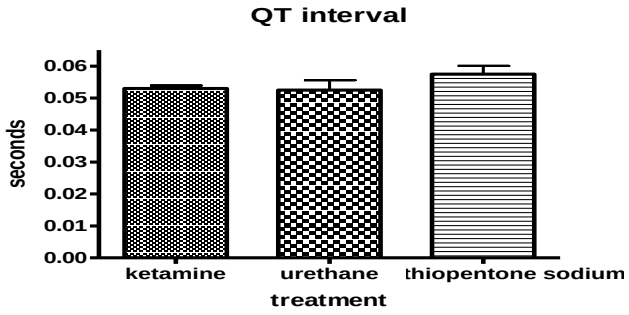

Figure 3: Effect of ketamine, urethane and thiopentone sodium on QT interval.

Data represented are mean number of observations ± S.E.M. on QT interval and was analyzed by one-way ANOVA followed by Dunnett's test.

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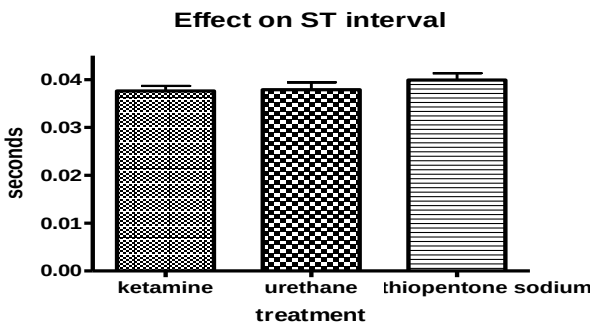

Figure 4: Effect of ketamine, urethane and thiopentone sodium on ST interval.

Data represented are mean number of observations ± S.E.M. on ST interval and was analyzed by one-way ANOVA followed by Dunnett's test.

Induction doses of ketamine typically increased blood pressure, heart rate, and cardiac output [16]. The cardiovascular effects are indirect and are most likely mediated by inhibition of both central and peripheral catecholamine's reuptake [17]. When ketamine given i.p. at a dose of (80mg/kg) induced anaesthesia at 5-8 min and the consciousness is regained in about 1hr but affects BP and heart rate (Figure 1 & Figure 2 respectively). Ketamine had no effect on QT and ST interval (Figure.3 and Figure.4 respectively). Thus ketamine should not be used for BP experiments and it should be used only for small surgeries.

The anaesthetic effect of thiopentone sodium dose depently produce blood pressure fall immediately due to vasodilatation, but recovers rapidly. Cardiovascular collapse may occurs if hypovolemia, shock or sepsis [18]. Administration of thiopentone sodium at a dose of (30 mg/kg, i.p.) induced anesthesia at 2-4 min and the consciousness is regained in about 45min., but affects QT and ST interval (Figure.3 and Figure.4 respectively). Thiopentone sodium did not affect BP (Figure.1)

Urethane is dose not inhibit the transmission of impulses is therefore, does not depress the reflex activity. The blood pressure is maintained at a lower basal level and pressor response of catecholamines are reduced compared to other anesthetics [19], thus urethane in a dose of (1.25 g/kg i.p) induced anaesthesia at 8-10 min. and the consciousness is regained in about 6-7 hr and does not affects BP, heart rate, QT and ST intervals (Figure 1, Figure 2, Figure.3 and Figure.4 respectively).. Thus Urethane is a good anesthetic agent to be used for blood pressure experiment when recovery of the animal is not required.

CONCLUSION

Ketamine if given i.p. at a dose of (80mg/kg) induced anaesthesia at 5-8 min and the consciousness is regained in about 1hr but affects BP and heart rate. Thus ketamine should not be used for BP experiments and it should be used only for small surgeries.

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