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EFFECTS OF CONCURRENT ADMINISTRATION OF BUPIVACAINE ON THE HYPNOSIS OF THIOPENTONE IN DOGS

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ABSTRACT

This study evaluated the effect of bupivacaine pretreatment on certain indices of thiopentone hypnosis in unmedicated dogs. Five healthy, unmedicated dogs underwent two series of trials one week apart. In the first series of trials, each dog received intramuscular injection of 0.5mg/kg 0.5% bupivacaine , induced, 20 min later, with the intravenous injection of 25mg/kg 2% thiopentone and then endotracheally intubated. The procedure was repeated for the second series, replacing bupivacaine with 2ml normal saline solution as control. In all trials, analgesia was assessed at 2min intervals using pedal withdrawal response to haemostatic forceps closed to the first ratchet. Calculated indices were compared with control values using student's 'T' test for paired data. Differences were considered significant at $p<0.05$. Time to intubation (11.2±2.0 min), onset of analgesia (11.1+1.9),duration of analgesia (19.4+7.2) and duration of hypnosis (50.0±5.2 min) in the experimental groups were significantly longer than the corresponding control values of 3.8±0.8 min, 3.4±0.7min, 8.4±1.5 min and 44.6±10.0 min. Duration of intubation (41.0+5.1), time to sternal posture (44.4±16.5 min) and time to standing (21.6±20.1 min) were not significantly different from corresponding control values of 8.7+7.8 min,18.2± 4.7 min and 13.4±4.5 min. It was thus concluded that the concurrent administration of bupivacaine with thiopentone resulted in prolonged hypnosis of 50.0 + 5.2 min duration.

Keywords : Bupivacaine, Dogs, Hypnosis, Thiopentone.

INTRODUCTION

A consideration of drug-drug interactions should be of particular interest to the veterinary anaesthetist who use numerous potent drugs to induce and maintain anaesthesia in animal patients commonly treated with a variety of drugs even preoperatively. Whereas some drug interactions have negligible effect on clinical outcome, others may prove to be important in the individual patient. While many of the interactions may be purposefully intended in order to achieve optimum patient safety and controllability in anaesthetic management, Others may be unfavourable, potentially dangerous and often unpredictable (Zimber,1986).A drug-drug interaction has been define as "a change in the magnitude of pharmacological action or toxicity of a drug by another drug"(Murad *et al.*,1985).

Heavner (1996) however, describe four circumstances that could result into interaction as two drugs in one formulation as a fixed drug mixture, two drugs in separate formulation simultaneously administered, a second drug adminitered during prolonged use of the first drug, and two drugs at specified time intervals.

Drug interaction may be desirable and used to clinical advantage or undesirable causing therapeutic failure, morbidity or mortality. Ben-Shomo *et al.* (1997) established in man that intramuscular injection of bupivacaine enhances the hypnosis of thiopentone.

This paper reports the effect of concurrent administration of bupivacaine on the hypnosis of thiopentone in canine anaesthesia.

MATERIALS AND METHODS

Experimental Animals

Five Nigerian local dogs (two intact male and three non-pregnant, non-lactating female), aged between 1.5 and 2.0 years old and weighing 10.0 to 12.0 kg were used for this study. Preceeding the study,the dogs were judged to be in good health based on findings at clinical examination and complete blood cell count.

Control

The dogs, each serving as their own control, were subjected to intramuscular injection of 2ml of normal saline at the thigh muscle.Two percent solution of thiopentone at a dosage of 25mg/kg was then administered intravenously 20 minutes later. The animals were then intubated, placed on lateral recumbency and allowed to breath atmospheric air.

Indices assessed

a) Analgesia

Analgesia was accessed by applying pressure at the interdigital space of the paws using an artery forcep.

b) Anaesthesia

Anesthetic indices and any side effects were recorded while the animal was monitored to recovery.
The evaluated indices for assessment are as follows :

Time to intubation : Time interval between loss of consciousness to successful intubation.

Duration of Hypnosis : Time interval between loss of consciousness and return of pharyngeal reflex.

Duration of intubation : Time interval between intubation and return of swallowing reflex.

Onset of Analgesia: Time interval between induction and loss of pedal reflex.
Duration of Analgesia: Time interval between loss and return of pedal reflex.

Time to sternal posture: Time interval between resumption of consciousness and assumption of sternal recumbency.

Time to standing: Time interval between assumption of sternal recumbency and standing postures.

Experimental Study

The procedure was repeated a week later using 0.5% solution of bupivacaine at a dosage of 0.5mg/kg intramuscularly in place of normal saline and at an interval of

40min before thiopentone administration.
Data obtained were subjected to statistical analysis by finding the Standard Error of the Mean (SEM) and student `T' test for paired data to ascertain if there is a statistically significant variation in the control result as against the bupivacaine administered results.

Five dogs were used for the two series of trials carried out. Each animal served as its own control, thereby eliminating any biological variations that could confound the study. However, the trials were carried out at one week interval to allow for the complete recovery of the dogs from an anaesthetic episode as reported by Kanto and Gepts (1989)

RESULTS

Table 1 shows the indices of the hypnosis induced by thiopentone in dogs pretreated with bupivacaine (BUP/THIO), normal saline solution (SAL/THIO) as the control. Time to intubation,onset of analgesia,duration of analgesia,duration of hypnosis,times to sternal and standing postures were longer with experimental data than the control values, there was no difference in the duration of intubation.

Table 1 : Anaesthetic indices of an intravenous injection dose of thiopentone after intramuscular injection of saline and bupivacaine.

Indices	SAL / THIO	BUP / THIO
Time to Intubation (min)	3.8 ± 0.8	11.2 ± 2.0
Duration of Intubation (min)	37.8 ± 8.7	41.0 ± 5.1
Duration of Hypnosis (min)	44.6 ±10 .0	50.0 ± 5.2
Onset of Analgesia (min)	3.4+0.7	11.0 ± 1.9
Duration of Analgesia (min)	8.4+1.5	19.4 ± 7.2
Time to sternal Posture (min)	18.2 ± 4.7	44.4 ±16.5
Time to standing (min)	13.4 ± 4.5	21.6 ± 10.1

SAL / THIO : Saline / Thiopentone.
BUP / THIO : Bupivacaine / Thiopentone.

Induction apnoea, shivering at recovery, thrashing at recovery were each noted in one or two dogs in the treatment groups.

Table 2 :Side effects associated with the intravenous induction dose of thiopentone after intramuscular injection of saline and bupivacaine.

Side effects	SAL / THIO	BUP / THIO
Induction apnoea	+ (1)	-(5)
Paddling at induction	- (5)	- (5)
Difficult intubation	+ (2)	+ (2)
Shivering at recovery	+ (2)	+ (2)
Thrashing at recovery	+ (2)	+ (2)
Vocalizing at recovery	+ (1)	- (5)
Post recovery ataxia	+ (1)	- (5)

+ : observed
- : not observed.
( ) : number of dogs involved in parenthesis
SAL / THIO : saline / thiopentone.
BUP / THIO : bupivacaine / thiopentone

DISCUSSION

The time period of 40min allowed for bupivacaine before the induction of anesthesia coincided with the time to peak plasma concentration of the local anaesthetic agent (McGrath.,198). This was intended to ensure maximum interactions of the two drugs *in vivo.*

In these trials, anaesthetic induction was adjudged adequate in the presence of satisfactory endotracheal intubation, including lack of jaw tone and absence of swallowing or coughing.

All the anaesthetic indices of bupivacaine / thiopentone group were significantly longer than the corresponding control values (Table 1). This is to be expected considering that bupivacaine is a long-acting local anaesthetic agent (Skarda,1996).This response is the result of the interaction between a large dose of thiopentone and bupivacaine. Bupivacaine is known to be slowly metabolise by hepatic microsomal enzyme (Skarda,1996) and this may explain the longer duration of the indices in BUP/THIO compared to SAL/THIO groups (Table 1).

It is noteworthy in this study that a single intravenous dose of thiopentone produced hypnosis lasting about 44min (Table 1),in contrast to 5-15min reported by Short (1983).This seemingly long duration of hypnosis may be explained by the large dose (25mg/kg) of thiopentone administered,which also produced analgesia of about 8min duration (Table 1) resulting in a state of narcosis. Normally, the induction dose of thiopentone lacks analgesic action(Hall and Clarke,1991).Since thiopentone is most often administered to provide a rapid, smooth induction of anaesthesia for tracheal intubation and maintenance with an inhalant agent (Hall and Clarke,1991),high initial vaporizer setting in the face of sustained narcosis may result in a life-threatening anaesthetic depth,even in healthy animals, if care is not taken.

CONCLUSION

The concurrent administration of bupivacaine with thiopentone resulted in a definite period of narcosis. This should be taken into account when contemplating on the maintenance of anaesthesia with a potent volatile anaesthetic agent in order to avert hazardous drug-drug interaction.

In clinical practice, the combination of bupivacaine and thiopentone can be use as a protocol to enhance the anaesthetic effect of thiopentone (short acting) in minor surgery. Anaesthesia involves the use of several drugs which are potentially toxic. The present day practice encourages minimal use of anaesthetic drugs to reduce the possibility of toxicity, this combination affords minimal use of each drug resulting in reduced possibility of toxicity and achieving the same purpose of desensitization or unconsciousness require for the proceduce.

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