ANTAGONISTIC EFFECTS OF CEFTRIAXONE AND SULPHADIMIDINE ON KETAMINE AND THIOPENTONE ANAESTHETICS IN NIGERIAN LOCAL DOG

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ABSTRACT

Antagonistic effects of ceftriaxone and sulphadimidine on ketamine and thiopentone anaesthetics were studied in Nigerian local dogs. Twenty – four Nigerian local dogs were used for the study. The dogs were divided into six groups: A, B, C, D, E, and F, with four dogs per group. Groups A and B were intravenously administered 17 mg/kg and 20 mg/kg body weight f thiopentone and ketamine respectively. But groups C and D were administered 23 mg/kg and 100mg/kg body weight of ceftriaxone and sulphadimidine respectively in addition to 20 mg/kg body weight of ketamine. However, groups E and F were administered intravenous dose of 23 mg/kg and 100 mg/kg of ceftriaxone and sulphadimidine respectively in addition to 17 mg/kg weight body of thiopentone. Vital parameters such as determination of anesthesia; onset and duration, temperature, respiratory and heart rates were recorded. The results of onset of duration of anesthesia revealed significant difference (P< 0.05) among group E, F and A animals. Although the result of onset anesthesia revealed significant difference between group A and B animals (P < 0.05). The values of respiratory rate revealed significant difference between the animals in groups D and B as well as groups F and A (P < 0.05). The values of heart rate showed significant difference between group C and D animals as well as between E and A animals (P < 0.05). Conclusively, sulphadimidine and cerftriaxone caused decreased duration of both anesthesia and onset of anesthesia when either was co-administered with ketamine or thiopentone in Nigerian local dogs. Sulphadimidine also caused increased respiratory rate, but cerftriaxone caused decreased and increased heart rate if co-administered with ketamine and thiopentone respectively. More so, thiopentone had higher durations of both anesthesia and onset of anesthesia in comparison with ketamine. So thiopentone is more potent than ketamine.

Keywords: Antagonistic, Anesthetics effect, Thiopentone, Katemine, Sulphadimidine, Cerftriaxone, Dog

INTRODUCTION

Thiopentone is a short acting barbiturate that is used for induction and/or maintenance of anesthesia, preoperative sedation and emergency management of seizure in both human and veterinary medicine (Gary and Tresznesk, 1983). It has half – life of 5 – 15 minutes by intravenous or rectal routes with between 75 and 85 % of the drug bound to plasma protein mostly albumin (Gary and Tresznesk, 1983; Tripathy, 2003). Thiopentone diffuses readily into the central nervous system (CNS); because of the lipid solubility, a small portion is excreted unchanged in urine and the terminal time is approximately 11.15 hours (Gary and Tresznesk, 1983; Laurence *et al,* 1999). Single or intermittent intravenous injection of thiopentone, concentration of 2.5 % in aqueous solution is used to reduce pain. However, injections are mostly made safe when saline or 5 % dextrose I water is used (Kennedy and Longnecker, 1996). Estimated fatal dose of thiopentone is 1g/kg body weight (Dreisbach and Robertson, 1987). Thiopentone and sulphadimidine have same binding site and hence thiopentone could easily displace sulphadimidine (Saganuwan *et al.,* 2005).

Ketamine a dissociative anesthetic induces profound analgesia, immobility, amnesia with light sleep and feeling of dissociation from ones owns body and the surrounding (Tripathy, 2003). The primary part of action is in the cortex and subcotical areas not in the reticular activating system (which is site of action of barbiturates) (Tripathy, 2003). It has rapid onset and recovery time but causes cardiovascular stimulation, increased cerebral blood flow and emergence reaction impair recovery (Trevor and white 2003). Katemine is the only intravenous anesthetic that possesses analgesic properties and produces cardiovascular stimulation. The peak increases occur in 2 – 4 minutes (*Waltzing et al.,* 2004)

Sulphadimidine has maintained an active place in the armamentry of antimicrobial drugs use in veterinary medicine (Bevill, 1982). It is 79 % plasma protein bound with half-life of 7 - 13 hours and is 60 – 90 % excreted as acetylated derivatives (Bevill, 1982). But Saganuwan *et al.* (2003) reported half-life of 15.4 ± 2.85 h in Nigerian local dogs. Sulphadimidine is known to cause decreased packed cell volume, total bilirudin and alkaline phosphate (Saganuwan, 2006a).

Cerftriaxone is a parenteral, semi synthetic third generation cephalosporin obtained from fungus cephalosporin (Tripathy, 2003) found in the sea sewage outfall in *Sardinia* (Bywater, 1991). It has activity against gram positive cocci (Prescott, 2000) but stronger activity against enterobacteriaceae, including penicillin's producing strains (Huber, 1988).

Table 1: Effects of cerftriaxone and sulphadimidine on anesthetic potency of thiopentone and katemine in Nigeria local dog

Time	Treatment groups					
	A	B	C	D	E	F
Onset of	17.50 ±	14.25 ±	11.75 ±	9.25 ±	5.33 ±	7.25 ±
Anesthesia	0.37	0.96	3.95	2.23	0.58	4.03*
Anesthesia	1872.50 ±	1440 ±	720 ±	1095 ±	1155 ±	1664.50 ±
	1077.40	189.74	259.23	79.37	552.9*	427.44*

Key: *A = thiopentone, B=ketamine, C=ceftriaxone,/ketamine, D = sulphadimidine/ketamine, E = ceftriaxone /thiopentone, F=sulphadimidine/thiopentone*

Table 2: Effects of cerftriaxone and sulphadimidine am vital parameters of Nigerian local dogs an aesthesia with katemine and thiopentone

Vital parameters	Treatment groups					
Temperature (°C)	39.35 ±	39.35 ±	37.30 ±	36.37 ±	37.38 ±	37.0 ±
	1.86	0.39	0.65	0.65	0.75	0.62
Respiratory	60.87 ±	23.4 ±	28.50 ±	33.0 ±	50.98 ±	15.05 ±
rate(/min)	15.66	2.30	5.26	11.01*	29.79	2.27*
Heart rate	85.15 ±	182.05 ±	146.12 ±	148.25 ±	143.33 ±	131.50 ±
(blat/min)	32.39	9.21	10.1*	41.33	3.05*	13.80

Keys: ** =significance difference in comprise with thiopentone; . =significance different in comparism with katemine*

It has extensive protein binding hence permitting once or at most twice daily dosing (Prescott, 2000).the binding capacity of cerftrixaxone differs somewhat between animal species (Baggot, 2001).however cerftriaxone may cause eosinophilia, hypobilirubiaemia, hypochloraemia increased bicarbonate ion concentration (Saganuwan, 2006b), hypoprorienaemia and hyperkakemia (Saganuwan, 2006c) in Nigeria local dogs. It has half-life of 0.85h and 25mg/kg body weight. cerftrixaxone is given 12-24 hourly (Prescott, 2000).however 50mg/kg bodyweight of cerftrixaxone for four days caused increased bilirudin (Saganuwan, 2006c)and hepatotoxicity in Nigeria local turkey (Saganuwan and Azubike, 2008).

Because drugs combinations are commonly used for preanaesthetic medication and general anesthesia, the potential exists for drug interaction to occur (Baggot, 2001).in view of this, the present study was designed to investigate whether sulphadimidine and cerftriaxone have ability to antagonize the anesthetics effects of thiopentone and Kate mine in Nigerian local dogs.

MATERIALS AND METHODS

Experimental Animals: Twenty- four Nigerian local dogs of either six weighing between 7 and 10 kg were used for the study. The dogs were obtained from a dog breeder who kept their mother for house security. They were fed daily with boiled rice beans meat and bone. The animals were divided into six groups A, B, C, D, E and F having four dogs per group.

Drug Administration: thiopentone sodium served as first control was intravenously administered at the dose rate of 17mg/kg body weight of into cephalic vein of four out of 24 dogs (group A). While 20 mg/kg body weight of ketamine served as second control was administered intravenous into cephalic vein of another 4 dogs (group B). Groups C and D were administered intravenous cerftriaxone and sulphadimidine at the dose rate of 23mg/kg and 100 mg/kg bodyweight respectively. Furthermore, 20 mg/kg body weight of katemine was intravenously administered in addition, to all the animals in groups C and D. However, group E and F animals were administered intravenous thiopentone sodium at the dose rate of 17 mg/kg body weight after post administration of 23mg/kg and 100mg/kg weight of cerftriaxone and sulphadimidine respectively. All the animals were observed for anaesthetic effects. Vital parameters such as duration of anesthesia, temperature, respiratory rate and heart rate were measured after 10 minutes intervals using thermometer and pericardial stethoscope for respiratory and heart rates. Duration of anesthesia and onset of anesthesia were recorded.

Statistical Analysis: Vital parameters, duration of an aesthesia and onset of anesthesia were express as means ± SD, test for significance between mean parameters in respect of control and experimental values were performed using student t-test. Bar charts were also used to present the result (Peltries and Watson, 2002).

RESULTS

The result of duration of onset of anesthesia of experimental animals from group D (9.25 ± 2.23s*) revealed significance difference in relation to the result from group B14.25 ± 0.96s) which was the control ($p < 0.05$) between the result of animals from group E (5.33 ± 0.58s*) and F (7.25 ± 4.03s*) in relation to the result from group A (17.50 ± 0.36s) (Table 1).

But the results of duration of an aesthesia of animals from Groups E (155 ± 552.90s*) and F 1664.50 ± 427.44s*) revealed significance difference ($p < 0.05$) in relation to that of animal from group a (1872.50 ± 1077.40s). Nevertheless, there was no significance difference ($p < 0.05$) between the result

of animals from groups C and Din relation to the result from group B animals. The result of onset of duration of an aesthesia of animals in the group A (17.50 ± 0.37s) in comparison to those of animals in Group B (14.25 ± 0.96s) was significantly difference ($p < 0.05$).

There was no significance difference between the temperatures values from the animals in group C and D in comparism with that of animals in group B ($p < 0.05$), more so there was no significance difference between the temperatures values of animals from group E and F in relation to that of animals from group A ($p < 0.05$). However, there was no significance different between the respiratory values of animals from group C in relation from that of group B animals as there was there lack of significant different between the values of animals from group E and A ($p > 0.05$). Although there was significant different in respiratory values of the animals of group F and A ($p < 0.05$) (Table 2).

The value of heart rate of animals from group C in comparism with that of animals from group B was significantly different ($p < 0.05$) as there was significant different ($p < 0.05$). Nonetheless, there was no significant difference in the value of heart rate between the animals of the group D and B as well as between group F and A ($p > 0.05$) (Table 2).

The duration of onset of anesthesia and duration of anesthesia were both highest in group A as duration anesthesia was lowest in group C and the onset in group of anesthesia was lowest in group E. Furthermore the duration of anesthesia was high in group B as compare in group F, then followed by group E, D and C in that order. Although the duration of onset of anesthesia was higher in group B as compare to that of group C, then followed by the Group D, F and A also in that order.

DISCUSSION

The significant difference ($p < 0.05$) between the duration of onset of anesthesia of animals from the group D (9.25 ± 2.23s*) and B (14.25 ± 0.96s) as well as group E (5.33 ± 0.58*) and F (7.25 ± 4.03s*) in relation to group A (17.50 ± 0.37s) (table1) are suggestive of the ability of sulphadimidine and ceftriaxone to interact with katemine and thiopentone, thereby decreasing the onset of duration of anesthesia of ketamine and thiopentone respectively. This agrees with the report of Saganuwan *et al* (2005) that the major processes, which determine the pharmacokinetic behaviour of a drug absorption, distribution, metabolism and excretion, are capable of being affected by co-administration of other drugs. The finding of this study is in line with earlier reports of (Gary and Tresnezsk, 1983) that the main type of interaction occurs when one drug competes with another for binding site. However, the significant difference ($p < 0.05$) in duration of anesthesia in group E (1155 ± 552.90s*) and F (1664. 50 ± 427.44s*) animals in relation to group A (1872.50 ± 1077.40s) animals is suggestive of the ability of cerftriaxone and sulphadimidine to cause decrease in duration of anesthesia (Table 1). Saganuwan *et al. (*2005) had earlier reported that thiopentone displaces sulphadimidine since the two drugs have the same binding site which is chiefly albumin. Hence, caution should be exercised when either sulphyadimidine or ceftriaxone is used pre-surgically with ketamine or thiopentone during the induction or maintenance of anesthesia in dog. Although, Saganuwan *et al.* (2005) reported that thiopentone increased the apparent volume of distribution of sulphadimidine therefore, increasing the half – life of Sulphadimidine. Nonetheless, lack of significant difference ($p>0.05$between the of anesthesia of animals in group C and D in comparism with duration of anesthesia of group B animals (Table 1) is suggestive of the inability of ceftriaxone and sulphadimidine to caused significant decreased in duration of anesthesia of ketamine. this may be attributable to the possibility of ceftriaxone and sulphadimidine having the same binding site with ketamine and so increasing ketamine excretion.

Lack of significant difference ($p > 0.05$) between the temperature value of animals in group C and D in comparism to group B animals, as well as animals from groups E and f in comparism to group A animals (table 2) was suggestive of the inability of ceftriaxone and sulphadimidine to cause significant increased in body temperature when co-administered with ketamine and thiopentone respectively.

Lack of significant difference between the respiratory value of the animals from group C and B ($p < 0.05$) and the animals from group E and A (Table 2) was suggestive of the inability of ceftriaxone to cause significant increase in temperature. This agreed with report of the Tripathy (2003) that respiration is not depressed in ketamine anesthesia even though ketamine was co-administered with ceftriaxone. The significant difference ($p < 0.05$) in respiratory value between group D and B animals as well as group F and A animals (Table 2) was suggestive of the ability of sulphadimidine to cause increased and decreased respiratory rates when used in combination with ketamine and thiopentone respectively. Ordinarily, respiratory rates are a good indicator of condition of animals and the dosage of the drugs (Booth and Mcdonald, 1992). Hence respiration should be adequately monitor in anesthesia patients by either decreasing the dosed of anaesthetic agent or by using respiratory machine.

The significant decrease ($p<0.05$) and increase in the value of heart rates of animals from group C and E in relation to the animals from group B and A respectively (Table 2)showed the ability of ceftriaxone to cause both decreased and increased heart rate. My finding agreed with the report of Tripathy (2003) and Booth McDonald (1992)that heart rates, cardiac output and blood pressure are elevated by Ketamine due to sympathetic stimulation even though ceftriaxone was co-administered with ketamine. Drugs or disease states that reduce cardiac output decrease liver blood flow and may change hepatic clearance of drug with a high

extraction ratio (E_H>0.6) (Nies *et al.*, 1973). Hence, ceftriaxone may be used to treat ketamine and thiopentone over dose and vice versa. Lack of significant difference in heart rate of group D and F animals in relation to group B and A animals showed the inability of sulphadimidine to cause increased heart rate when used in combination with either ketamine or thiopentone respectively (Table 2).

The highest duration of onset of anesthesia (1872.50 ± 1077.40s) displayed by group A animals in comparison to animals from the other groups (Table 1) agrees with the finding of Brodie *et al*. (1952) that, it is mainly redistribution of thiopentone rather than elimination by hepatic transformation that determines the duration of anesthetic effect. However, the duration of anesthesia (1440 ± 189.74s) observed from group B animals (Table 1) agrees with the finding of Baggot (2001) that the duration of anesthesia produced by a single intravenous dose of ketamine relates mainly to distribution and party depending on the size of the dose and to biotransformation. My finding is in concordance with the finding of Baggot (2001) that 5 mg/kg body weight of ketamine administered intravenously produced anesthesia of 588.0±102 seconds in dog. Since 20mg/kg body weight of ketamine administered to group B dogs produced duration of anesthesia (1440 ± 189.74s) double fold more than the duration of anesthesia (588.0 ± 102s) reported by Baggot (2001) when 5mg/kg was administered to dogs, the anaesthetic effect of ketamine may be dose dependent. Therefore, the higher the dose of the intravenous ketamine, the longer the duration of ketamine anesthesia. This relative increased dose-response phenomenon of ketamine may give ketamine superiority over thiopentone. Hence, ketamine can be used alone in contrast to thiopentone (Laurence *et al.,* 1999). To prolong anesthesia of ketamine one half of the initial dose may be administered (Hardman *et al.,* 1996). The half-life of ketamine in dog is 1 hour (Baggot, 2001). Nevertheless, the duration of onset of anesthesia and duration of anesthesia of ketamine and thiopentone were both decreased by ceftriaxone and sulphadimidine respectively in groups C, D, E and F animals in relation to groups B and A animals (Table 1).

Conclusion: Sulphadimidine and ceftriaxone caused decreased duration of both anesthesia and onset of anesthesia if either is co-administered with ketamine or thiopentone in Nigeria local dog. Sulphadimidine also caused increased respiratory rate as ceftriaxone caused decreased and increased heart rate if co-administered with ketamine and thiopentone respectively. More so, thiopentone is more potent than ketamine, but ketamine has relative dose-response higher than thiopentone.

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