

Cardiopulmonary effects of Thiopentone sodium short term anaesthesia in Diazepam premedicated donkeys (*Equus asinus L.*)

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Abstract: The current study was conducted to evaluate some of the toxic and/or adverse effects that may follow combined administration of diazepam and thiopentone sodium in donkeys. Twelve healthy male donkeys, 4-10 years of age, weighing 80-150 kg were used in this study. The donkeys were pre-medicated with diazepam (0.5 mg kg⁻¹) using intravenous (IV) route. Thiopentone sodium 5% was administered IV, 10 minutes later at two different doses i.e. 10 mg/kg or 15 mg/kg body weight. Heart and respiratory rates, rectal temperature at predetermined times, while anaesthetic parameters were monitored during anaesthesia. The first protocol resulted in the death of three animals out of six (50%), while in the second protocol, five animals out of six (83%) died due to respiratory failure. The use of thiopentone sodium in the two tested protocols was accompanied by significant increase ($P < 0.05$) in heart rate (tachycardia), while rectal temperature expressed non significant fluctuation. Animals treated with thiopentone sodium at dose rate of 10 mg/kg or 15mg/kg body weight with premedication showed significant decrease ($P < 0.05$) in respiratory rate immediately following the induction of anaesthesia. Animals received premedication with diazepam at 0.5 mg/kg and subjected to treatment with thiopentone sodium at dose level 10 mg/kg or 15 mg/kg body weight resulted in significant increase in the anaesthetic phase and non significant change in the induction time, and due to the death of the animals we could not detect the time of other phases. Both anaesthetic protocols used in this study proved to have a wide range of less to fatal detrimental effects on cardiopulmonary systems.

Keywords: Injectable anesthetics, adverse or toxic effects, equine.

Introduction

Anaesthesia and surgery in horses still carries an unacceptably high risk of death. The death rate may range from 0–63% (Mee *et al.*, 1998) to 1–5% (Young and Taylor, 1993, Johnston *et al.*, 1995). This compares unfavourably with the anaesthetic-related death rate of 0-15% in small animals (Clarke and Hall, 1990)

and 0-01% in man (Duberman and Bendixen, 1986). Thiopentone sodium anaesthesia in horses is often associated with a peculiar respiratory effect – a complete arrest of respiration for 20–30 s followed by four to eight respiratory movements. These bursts of activity followed by inactivity may persist

throughout anaesthesia (Longley, 1950; Waddington, 1950; Ford, 1951; Jones *et al.*, 1960; Tyagi *et al.* 1964). Depression of the respiratory centre was reported to There is considerable disagreement among research workers concerning the effects of thiopentone on the cardiovascular system. This may well be due to varying methods used for determinations of such things as cardiac output, differences of premedication, depth of narcosis and the degree of CO₂ retention, as well as on the speed of injection (Hall *et al.*, 2001). Ben-zodiazepines derivatives used in Veterinary medicine include diazepam, midazolam, and zolazepam. Benzo-diazepines produce hyp-notice, sedative, anxiolytic, anticonvulsant and skeletal muscle-relaxant effects by enhancing the action of neurotransmitter Gamma amino butyric acid (GABA) on its receptors (Polc, 1988). The effect of diazepam in domestic animals as premedicant is to increase the length of action of other anaesthetic agents, used as sedative and tranquilizer, and diazepam has major role in veterinary practice in control of convulsions of any origin (Hall *et al.*, 2001). Diazepam was used by many researchers to premedicate different animal species such as goats (Mouldehaur *et al.*, 1985) and Sheep (Eesa,

Materials and Methods

Site of study

This study was conducted at the premises of the Department of Clinical Studies, Faculty of Veterinary Science, University of Nyala, South Darfur State, Sudan.

be the main toxic effect of thiopentone sodium (Hall *et al.*, 2001). In goats, injection of thiopentone sodium causes tachycardia (Ghurashi *et al.*, 2008).

1994), dogs (Jani *et al.*, 1982), and horses (Muir and Masonen, 1982). When administered alone, the drug overdoses are generally limited to: coma, decreased reflexes, hypotension, respiratory depression and cardiac arrest, drowsiness, mental confusion, impaired motor functions (impaired reflexes, impaired coordination, impaired balance), and dizziness (Bendarzewska-Nawrocka *et al.*, 1980). Diazepam increases the central depressive effects of alcohol, other hypnotics/sedatives (e.g. barbiturates), narcotics, and other muscle relaxants. The euphoriant effects of opioids may be increased, leading to increased risk of psychological dependence (Holt, 1998). In Sudan, as the population of donkeys is increasing, the demand for medical care and surgical procedures may increase. Based on the growing population of donkeys and lack of sufficient or adequate reports concerning anaesthesia in this species, our objectives were to evaluate some of the cardio-respiratory parameters as well as duration of anaesthetic phases during general anesthesia in this species.

Drugs

Thiopentone sodium 5%: was used as induction agent (thiopental sodium "BP" 500mg/vial NEON Laboratories limited, India).

Diazepam: "BP" 2ml /ampoule (5mg/ml, Shanghai Pharmaceutical CO., Ltd.

Shanghai China. CMS Sudan) 0.5% was used as premedication.

Experimental animals

A total of 12 healthy male donkeys, 4-10 years old, 80-150 kg body weight, were purchased from *Local Market* (Nyala). Animals were clinically examined to eliminate diseases and received anthelmintic (Albendazole, 10mg/kg) and antibiotic (Penicillin G Procaine & Dihydrostreptomycin Sulfate Injection (Pen Strep 1ml/20kg)) as prophylactic treatment and kept for 15 days for adaptation. Animals were randomly allocated into two different protocols; they were allowed free excess to water and feed twice a day.

Experimental design

Intravenous catheter (21 G) was used for injecting the drug through the jugular vein. Animals were injected with Diazepam 0.5 mg/kg slowly intravenously, followed after 10 minutes by a rapid intravenous injection of thiopentone sodium, as follows:

Animals in treatment group one received single injection of thiopentone sodium at dose of 10 mg/kg, while animals in the second treatment group received 15 mg/kg thiopentone sodium intravenously. Anaesthetic and some physiological parameters were investigated immediately.

Each group of animals was monitored before anaesthesia, during anaesthesia and till recovery occurred.

Physiological parameters

Physiological parameters (Respiratory rate, heart rate and rectal temperature) were monitored and recorded at 10 minutes intervals using standard methods as described by Kelly (1984).

Phases of anaesthesia

Induction phase: It is the state or condition in which the animal becomes unconscious, responds negatively to painful stimuli with disappearance of selected reflexes (Jani *et al.*, 1982)

Anaesthetic phase: It was considered as the period during which the animal showed signs of unconsciousness, no reflexes, responds negatively to painful stimuli (Tamisto *et al.*, 1981).

Basal narcosis: It was assessed as the period during which the animal showed signs of unconsciousness, but responds positively to noxious or painful stimuli (Atkinson *et al.*, 1987).

Lateral recumbency: The duration at which the animal opens its eyes and reflexes were regained but it is incapable of adopting sternal position (Thurmon *et al.*, 1996).

Sternal recumbency: The period during which the animal could adopt sternal recumbency without falling to lateral recumbency and without adopting standing position (Ghurashi, 1999).

Recovery: The animal was considered to be recovered from anaesthesia when it is capable of supporting itself in standing

position and walk for ten steps without falling down (Ghurashi, 1999).

Statistical analysis

T- test was used to compare means for physiological parameters (Respiratory rate, heart rate and rectal temperature), as well as duration of the different anaesthetic phases tested using SPSS System computer package (SPSS, version 16 for Windows, SPSS Inc., Chicago, Illinois, USA) as described by (Gomez and Gomez, 1984).

Results

Anaesthetic parameters

In the first protocol (treatment group one) three animals out of six (50%) died and in the second protocol (treatment group two)

five animals out of six (83%) died due to respiratory arrest. On post mortem cyanosis in tongue and highlights cyanosis in lungs.

As shown in Table (1), increasing the dose of thiopentone sodium from 10 to 15 mg/kg body weight in Diazepam pre-medicated animals, resulted in significant prolongation of apnoea (no attempts, except physical improvement of respiration, were attempted to help animals to overcome apnoea) and anaesthetic phase, and non-significant ($P > 0.05$) decrease in induction time.

Comparison is not possible between the two groups for the other anaesthetic parameters due to death of five animals in the treatment group two (thiopentone

sodium 15 mg/kg + diazepam 0.5 mg/kg).

Physiological parameters

In Table (2) animals in the first group showed significant increase ($P < 0.05$) in heart rate (tachycardia) immediately after induction of anaesthesia and this tachycardia remained at high levels at time 5, 20, 30, 40, 50, 60, 70 and 90 minutes. Significant increase ($P < 0.05$) in heart rate was also observed only at time 5, 10 minute in animals in treatment group 2 when compared with the starting time (0 time).

As shown in Table (2) animals in the two treatment groups showed significant decrease ($P < 0.05$) in respiratory rate immediately following the induction of anaesthesia and this decrease in respiratory rate remained at significant low level at time 5 and 10 minutes after induction of anaesthesia in group 1, also significant ($P < 0.05$) decrease in respiratory rate was observed at time 5 and 10 minutes in animals in group 2 when compared with the baseline value (0 time).

As shown in Table (2) in both treatment groups, animals showed non-significant changes in rectal temperature.

Discussion

This investigation is directed towards testing the side and/or adverse effects that may follow using thiopentone sodium in combination with diazepam in donkeys, with emphasis on toxic

dynamics of tested anaesthetic protocols on cardio-respiratory parameters, together with the duration of anaesthesia and recovery as well as study of some undesirable side effects of these protocols in donkeys.

The occurrence of apnoea following induction of anaesthesia using thiopentone sodium with diazepam in both groups in this study in agreement with the findings of Karimi (1987) and Contreras and Aspe (1992), who reported the occurrence of apnoea following induction of anaesthesia with thiopentone sodium in horses and goats respectively.

Changing the dose of thiopentone sodium from 10 to 15 mg/kg in premedicated animals resulted in significant prolongation of the anaesthesia phase. This finding is supported by the general anaesthetic character of thiopentone sodium described by Hall *et al.*, (2001), who stated that the anaesthetic effect of thiopentone sodium is directly affected by the dose of the drug. Our finding is also supported by the results obtained by Rawling and Kolata (1983), although they used doses which differed from the doses used in this investigation. Premedication with diazepam 0.5 mg/kg caused the animals in group 1 to adopt either lateral or sternal recumbency. Diazepam was reported to cause lateral recumbency and difficulty in maintaining standing position as reported by Vickers *et al.* (1984) and Muir and Masonen (1982) in man and horses respectively. Comparison of the basal narcosis phase

is not possible between the two groups due to death of animals in the second group. The intravenous administration of thiopentone sodium in this study resulted in a depressive character on respiratory system and this result is in agreement with findings reported by Taylor (1990), who concluded that thiopentone sodium had a depressive character for a short time (10 minutes) on respiratory rate of non pre-medicated horses. This result is also in accordance with the findings of Ghurashi, (1999), who reported that thiopentone sodium had depressive effect on respiratory rate in goats. The significant decrease in respiratory rate following induction of anaesthesia observed in this study was in agreement with the findings of Atkinson *et al.*, (1987), Singh and Kumar, (1988b) in goats and Taylor, (1990) in ponies, Malik and Singh (2007) in horses.

According to this study heart rate showed significant increase during thiopentone sodium anaesthesia this finding is in agreement with the results obtained by Muir *et al.*, (1977) and Karimi, (1987) in horses; Rings and Muir (1982) in calves; and Rawling and Kolata (1983) and Contreras and Aspe, (1992) in goats. This study showed non-significant change in rectal temperature after induction of anaesthesia with thiopentone sodium and this finding is in agreement with findings of Kumar and Sharma, (1986), who reported non significant effect of thiopentone sodium on rectal temperature in buffaloes. Similarly, Ghurashi (1999) reported non significant

decrease in rectal temperature in goats. These results may be attributed to the fact that thiopentone sodium depresses the basal metabolism leading to lowering of body temperature (Hall *et al.*, 2001).

Conclusion and recommendations

Both anaesthetic protocols used in this study proved to have a wide range of less to fatal detrimental effects on cardio-pulmonary systems. Undesirable adverse effects associated with the use of diazepam as premedication at dose level 0.5 mg/kg such as tachycardia and apnoea may limit the usage of such drug at such dose level in surgical anaesthesia in donkeys.

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Table (1): The effect of treatment with thiopentone sodium at dose rate 10mg/kg or 15mg/kg in donkeys pre-medicated with diazepam at dose rate 0.5 mg/kg on the duration of apnoea and different anaesthetic parameters

Parameter	Apnoea (sec.)	Induction (sec.)	Anaesthesia (min.)	Sternal (min.)	Lateral (min.)	Recovery (min.)	Basal (min.)
Thio.10+DZ0.5	111.17±19.03*	25.83±3.03	41.17±8.09*	40.00±8.14	122.33±18.76	186.68±12.02	25.00±2.52
Thio.15+DZ0.5	175.00±5.00*	16.17±3.34	63.83±37.76*	ND	ND	ND	ND

Mean in the same column with asterisk are significantly different (P<0.05).

ND = not detected

Thio. = Thiopentone sodium 5%

DZ. = diazepam.

Table (2): Effect of treatment with thiopentone at 10 or 15 mg/kg in donkeys premedicated with diazepam at dose 0.5 mg/kg on respiratory rate, heart rate and rectal temperature

Time(m)	10 mg/kg			15 mg/kg		
	Resp.	Heart rate	Temp.	Resp.	Heart rate	Temp.
0	17.33±1.33*	46.67±2.62*	36.47±0.35	14.67±1.69*	44.00±1.37*	36.57±0.59
5	5.33±1.76*	104.00±12.70*	35.73±0.81	2.00±0.00*	86.33±3.95*	36.80±0.29
10	8.00±2.00*	87.33±8.67*	35.97±0.95	4.00±0.00*	62.00±9.17*	36.05±0.25
20	12.00±2.00	69.33±1.76*	35.77±0.93	ND	ND	ND
30	12.67±2.67	78.00±1.15*	35.37±1.02	ND	ND	ND
40	13.33±1.33	75.33±1.76*	35.53±1.00	ND	ND	ND
50	14.67±2.67	76.00±2.00*	35.47±1.22	ND	ND	ND
60	15.33±2.40	74.00±2.00*	35.97±1.34	ND	ND	ND
70	18.00±3.06	68.67±5.81*	35.97±1.34	ND	ND	ND
90	19.33±3.33	71.33±5.70*	36.27±1.64	ND	ND	ND

Mean in the same column with asterisk are significantly different (P<0.05).

ND = not detected

التأثيرات القلبية-الرئوية للتخدير قصير المدى المحدث بواسطة الثايوبنتون صوديوم في الحمير المعالجة تمهيدياً بالديازيبام

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المستخلص

أجريت الدراسة الحالية لتقويم بعض الجوانب السمية و/أو القاتلة التي قد تعقب الاعطاء المشترك للديازيبام و الثايوبنتون صوديوم في الحمير. اثنا عشر من الحمير الذكور، تتراوح اعمارها بين 4-10 من السنوات و اوزانها من 80-150 كجم استخدمت في هذه الدراسة. الحمير تم علاجها تمهيدياً بالديازيبام (بجرعة مقدارها 0.5 مجم/كجم) عن طريق الوريد. الثايوبنتون صوديوم 5% اعطي عن طريق الوريد، 10 دقائق بعد ذلك بجرعتين مختلفتين 10 و 15 مجم/كجم من وزن الحيوان. تم قياس ضربات القلب، معدل التنفس و درجة الحرارة من المستقيم في فترات زمنية محددة مسبقاً، بينما تم مراقبة اطوار التخدير المختلفة خلال فترة التخدير. استخدام البروتوكول الاول نتج عنه موت ثلاثة من الحيوانات (50%) بينما استخدام البروتوكول الثاني نتج عنه موت خمس من الستة حيوانات التي تم استخدامها (83%) نتيجة لفشل التنفس. حدث ارتفاع معنوي في ضربات القلب (تسارع القلب) نتيجة لاستخدام البروتوكولين أعلاه. بينما درجات الحرارة التي تم قياسها اظهرت تغيير غير معنوي. الحيوانات التي علاجها بالثايوبنتون صوديوم بالجرعتين 10 و 15 مجم/كجم مع العلاج التمهيدي اظهرت انخفاض معنوي في معدل النفس مباشرة عقب احداث التخدير. الحيوانات التي تم اعطائها الديازيبام (0.5 مجم/كجم) كعلاج تمهيدي ثم احدث التخدير فيها باعطاء الثايوبنتون صوديوم (10 أو 15 مجم/كجم) من وزن الحيوان اظهرت زيادة معنوية في زمن طور التخدير بينما لم يكن هناك اختلاف معنوي في زمن احداث التخدير و نتيجة لموت الحيوانات لم يتمكن من قياس باقي الاطوار التخديرية المختلفة. البروتوكولات التخديرية التي تم استخدامها في هذه الدراسة ثبت ان بها مدي عريض من التأثيرات الطفيفة الي القاتلة علي كل من القلب و الجهاز التنفسي.