Stability of cardiodynamic and some blood parameters in the baboon following intravenous anaesthesia with ketamine and diazepam

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ABSTRACT

The stability of cardiodynamic and some blood parameters during a slow, continuous infusion of a combination of ketamine and diazepam is reported. Contractility (dP/dt), myocardial relaxation (Tln), left ventricular end-diastolic pressure (LVEDP), left ventricular systolic pressure (LVSP), arterial blood pressure and certain blood parameters were assessed in 3 male and 3 female juvenile baboons (*Papio ursinus*). Anaesthesia was induced with 15 mg/kg ketamine IM and maintained with a continuous IV infusion (40–60 mℓ/h) of ketamine and diazepam. The mixture consisted of 2 mℓ ketamine (100 mg/mℓ), 2 mℓ diazepam (5 mg/mℓ) and 50 mℓ saline. A period of 75 ± 10 min was allowed for preparation of the animals, after which lead II of the ECG, femoral artery blood pressure and left ventricular pressure were recorded at 15-min intervals for a period of 2 h: the total duration of anaesthesia was 195 min. Arterial blood samples were analysed at 30-min intervals for blood gases, electrolytes, glucose and insulin. Left ventricular parameters were derived from the left ventricular pressure curve. Tln, LVSP and LVEDP showed small fluctuations. Contractility decreased ($p < 0.037$) at the 195-min interval. No arrhythmias or ECG changes were seen, while blood pressure decreased gradually. Serum calcium concentration decreased and blood glucose levels increased gradually over time. Anaesthesia and analgesia were sufficient and no other drugs were necessary. The animals appeared sedated and dazed 60–80 min after the procedure. A continuous infusion of a combination of ketamine and diazepam for a duration of 150 min can provide stable anaesthesia for cardiodynamic measurements.

Key words: diazepam, intravenous anaesthesia, isovolumic relaxation, ketamine, myocardial contractility.

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INTRODUCTION

In an effort to standardise anaesthesia and to ensure an undisturbed and stable cardiovascular system for data acquisition in baboons, ketamine (a dissociative anaesthetic agent), thiopentone and halothane have been compared, the latter resulting in a severe drop in blood pressure after 20 min[2]. Ketamine is used in medical and veterinary anaesthesia for induction and short-term maintenance[5], or as an adjuvant in different anaesthetic drug combinations[11,13]. In animals it is mainly given intramuscularly, although a slow intravenous infusion of ketamine alone in baboons has been reported[4]. In none of the reported studies have myocardial contractility or relaxation been measured.

Benzodiazepines like lorazepam, diazepam or midazolam have been used to alleviate the 'emergence phenomenon' of ketamine in humans[10,11].

In this paper we report the stability of cardiodynamic and relevant blood parameters during a slow, continuous infusion of a combination of a ketamine hydrochloride and diazepam to provide an undisturbed and stable cardiovascular system for data acquisition during experiments. The cardiodynamic parameters +dP/dt (the rate of rise in the pressure of the left ventricle), left ventricular isovolumic relaxation time (Tln), left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP) were used. Haemodynamic parameters included systolic, diastolic, mean arterial and pulse pressures. Relevant blood parameters were also measured.

MATERIALS AND METHODS

Animals

Three male and 3 female baboons (*Papio ursinus*) (average body weight 16.6 ± 1.46 kg; mean ± SD) from a captive colony were used in this study. The animals ($n = 6$) had *ad libitum* access to water and were fed twice a day with a maize-chow (Jabulani Foods, Springs) and supplemented with minerals and vitamins (PVM, Pretoria). The diet was supplemented with fresh fruit.

Anaesthesia

Food was withheld from the animals for 12 h before the procedure. Anaesthesia was induced with 15 mg/kg ketamine (Ketalar 100 mg/mℓ vials, Parke-Davis), given intramuscularly. When the animals were recumbent, anaesthesia was maintained with a continuous intravenous infusion of ketamine and diazepam. The mixture consisted of 2 mℓ ketamine (100 mg/mℓ), 2 mℓ diazepam (Valium 10 mg/2 mℓ vials, Roche Products) and 46 mℓ saline (0.9 % NaCl, Sabax) to obtain a final volume of 50 mℓ. The combination was infused at a rate of 40–60 mℓ/h, using an automated pump (Perfusor-Secura FT). The dose-infusion rate was determined in preliminary trials and was adjusted to eliminate clinical signs such as the toe-pinch reflex, limb movement and a palpebral reflex.

An intramuscular injection of 4 mℓ penicillin (Duplocillin, containing Procaine penicillin 150 000 IU/mℓ and Benzathine penicillin 150 000 IU/mℓ, Intervet) was given before returning the animals to their cages.

Apparatus

Recordings were made with a Hewlett Packard (HP) multichannel recording system (Model 7758) and signals stored on

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Table 1: **The effect of a continuous intravenous infusion** (40–60 mℓ/h) **of a combination of 2 mℓ ketamine** (100 mg/mℓ)**, 2 mℓ diazepam** (5 mg/mℓ) **and 46 mℓ saline on cardiodynamic parameters** (n = 6).

	Time (min)								
	75	**90**	**105**	**120**	**135**	**150**	**165**	**180**	**195**
HR (bpm)[a]	113.0	115.0	111.0	107.0	107.0	105.0	104.0	102.0	101.0
±SE	8.0	9.0	9.0	10.0	8.0	9.0	9.0	10.0	10.0
Tln (ms)	51.3	58.2	55.0	53.0	53.8	53.8	52.5	55.2	56.8
± SE	3.2	1.5	2.2	2.7	2.9	3.2	2.9	3.5	3.4
LVSP(kPa)	13.9	15.0	14.6	14.2	14.5	14.3	14.2	14.0	13.8
±SE	0.6	1.0	1.2	1.3	1.3	1.3	0.9	1.0	1.1
LVEDP (kPa)	0.6	0.8	0.9	0.7	0.9	0.8	0.8	0.8	0.6
±SE	0.2	0.1	0.8	0.1	0.1	0.2	0.2	0.2	0.3
dP/dt (kPa/s)	169.1	170.8	157.3	164.1	161.3	166.0	151.9	127.5	111.1*
±SE	14.3	6.3	8.1	19.6	19.2	18.8	16.7	15.3	19.6

*$p < 0.037$ when compared to the 75-min interval (Neuman-Keuls).
[a]Tln = left ventricular isovolumic relaxation time; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; +dP/dt = maximum rate of rise of left ventricular pressure; HR = heart rate.

Table 2: **The effect of a continuous intravenous infusion** (40–60 mℓ/h) **of a combination of 2 mℓ ketamine** (100 mg/mℓ)**, 2 mℓ diazepam** (5 mg/mℓ) **and 46 mℓ saline on blood pressure** (n = 6).

	Time (min)								
	75	**90**	**105**	**120**	**135**	**150**	**165**	**180**	**195**
SBP (mmHg)[a]	154	150	149	150	146	142	139	139	135
±SE	6	7	8	6	7	7	6	4	6
DBP (mmHg)	95	93	95	90	92	89	87	89	83
±SE	6	7	8	10	8	8	8	9	10
MAP (mmHg)	127	124	125	122	122	119	116	115	113
±SE	6	5	5	5	4	5	4	7	5

[a]SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure.

magnetic tape (HP 3968 Instrumentation Recorder) for subsequent computer analysis.

Arterial blood pressure was recorded with an HP Quarts (Model 1290A) pressure transducer and a saline filled catheter system, precalibrated in a water bath at 37 °C. Systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressure were calculated from the femoral artery pressure curve. Left ventricular pressure was measured with a calibrated, high-fidelity micro-pressure transducer (Millar 5F). A Turbo-Pascal 5-based programme (Department of Medical Physics, Medical University of Southern Africa) that uses the signal from the left ventricular pressure curve was used. The maximum rate of the rise of the left ventricular pressure curve (+dP/dt, measured in kPa/sec and used as an index of contractility), left ventricular isovolumic relaxation time (Tln), heart rate, LVEDP and LVSP were calculated from the left ventricular pressure curve.

A period of 75 ± 10 min was allowed for preparation of the animals, which included induction of anaesthesia, surgical preparation and placement of the ECG electrodes, pressure transducers, intravenous cannulas and catheters. After this 75-min period, 2 h of recording at 15-min intervals followed. The recordings at each 15-min interval lasted for 20 sec. The total duration of anaesthesia was 195 min.

Blood chemical analysis

Blood samples were collected from the femoral artery at 30-min intervals for a duration of 120 min. Samples were analysed for blood gases, serum magnesium, -calcium, -sodium and potassium, haematocrit, insulin, glucose and gamma-glutamyltransferase.

The protocol was approved by both the Research and Animal Ethics Committees of Medunsa. An independent veterinarian monitored the proceedings on random occasions.

RESULTS

Cardiodynamic parameters

The mean heart rate decreased by 12 beats/min over the 2 h recording period. This was not statistically significant. Tln, LVSP and LVEDP showed small fluctuations (Table 1). Positive dP/dt started to decrease at the 150-min recording interval and this decrease became statistically significant at the 195-min interval ($p < 0.037$) (Table 1). No arrhythmias or electrocardiographic changes were seen at any stage.

Blood pressure

Systolic pressure decreased gradually over a period of 120 min by 15 mmHg, diastolic pressure by 12 mmHg and MAP by 14 mmHg. These changes were not statistically significant (Table 2).

Anaesthesia

The drug combination produced adequate anaesthesia and analgesia and

Table 3: **The effect of a continuous intravenous infusion** (40–60 mℓ/h) **of a combination of 2 mℓ ketamine** (100 mg/mℓ), **2 mℓ diazepam** (5 mg/mℓ) **and 46 mℓ saline on arterial blood chemistry** (n = 6).

	Time (min)				
	75	**105**	**135**	**165**	**195**
pCO_2 (kPa)	5.92	6.03	6.32	6.25	6.46
±SE	0.23	0.31	0.30	0.33	0.32
pO_2 (kPa)	11.44	11.60	12.16	12.70	11.58
±SE	0.87	1.15	1.02	1.07	1.18
pH	7.34	7.33	7.32	7.32	7.30
±SE	0.03	0.02	0.02	0.02	0.03
HCO_3 (mmol/ℓ)	23.62	23.48	23.60	23.42	23.50
±SE	1.34	0.77	1.01	1.09	0.90
Glucose (mmol/ℓ)	5.45	5.78	6.56	6.80	7.23
±SE	0.52	0.30	1.17	1.29	1.44
GGT (iu/ℓ)[a]	38.75	33.25	35.50	35.00	34.50
±SE	10.28	13.20	12.49	11.04	11.77
Haematocrit (%)	38.20	39.38	39.75	39.13	40.75
±SE	3.60	1.91	2.29	2.98	2.48
Insulin (iu/ℓ)	28.33	20.76	23.08	22.30	18.05
±SE	5.32	4.65	1.88	3.44	3.66
Ca^{++} (mmol/ℓ)	1.97	1.88	1.88	1.83	1.84
±SE	0.05	0.99	0.10	0.09	0.09
Mg^{++} (mmol/ℓ)	0.67	0.63	0.63	0.62	0.62
±SE	0.05	0.06	0.06	0.06	0.06
Na^{+} (mmol/ℓ)	142.17	142.20	139.80	142.80	141.80
±SE	2.97	3.61	3.07	3.54	3.73
K^{+} (mmol/ℓ)	3.12	3.43	3.36	3.40	2.96
±SE	0.26	0.19	0.20	0.23	0.23

[a]GGT = gammaglutamyl transferase.

no additional anaesthetic drugs were necessary at any stage of the procedure. Within 20–35 min after completion of the procedure the animals responded by lifting their heads upon attempted voice arousal and within 60–80 min were able to sit but appeared sedated. No post-operative side-effects were observed.

Blood chemical analysis

The serum calcium concentration decreased gradually with time but this change was not statistically significant. Blood glucose concentration increased gradually but this increase was also not statistically significant. No changes were seen for any of the other parameters, summarised in Table 3.

DISCUSSION

We report the stability of the cardiodynamic parameters dP/dt, isovolumic relaxation time, LVEDP and LVSP for a period of 150 min of anaesthesia induced by a combination of ketamine and diazepam, However, +dP/dt did decrease (indicating negative inotropy) after 195 min ($p < 0.037$).

None of the cardiodynamic parameters recorded have been reported previously in baboons.

In an earlier study where ketamine (IM), thiopentone (infusion) or halothane (gas inhalation) were compared to assess their ability to provide stable cardiovascular parameters, halothane lowered blood pressure and heart rate more than ketamine or thiopentone. Ketamine lowered blood pressure more than thiopentone. The cardiovascular parameters were recorded for a period of 20 min only after induction[2]. In a subsequent article the duration of anaesthesia was increased to 90 min, more parameters recorded and the combination of ketamine and xylazine added for comparison[4]. More stable results were obtained with ketamine or thiopentone compared to halothane or a ketamine/xylazine combination.

We have shown that blood pressure and heart rate remained stable for 180 min with the combination that we used. A previous study reported this stability, but parameters were only recorded for a period of 20 min[10].

We have furthermore shown that continuous infusion of a combination of ketamine and diazepam for a duration of 195 min did not affect the blood parameters. This is in contrast to findings where ketamine administered to baboons caused increases in calcium, magnesium and inorganic phosphate over a 3-h period[12]. Ketamine or halothane resulted in an increase in serum potassium and sodium concentration after 90 min[12]. Our results indicate a gradual but non-significant increase in blood glucose levels during anaesthesia. In a study where glucose and insulin responses were measured after glucose loading, no effects were seen during ketamine anaesthesia[1].

It has been reported that compensated respiratory acidosis resulted after ketamine and thiopentone[4]. No changes in pO_2, pCO_2, HCO_3 and pH were seen with the anaesthesic drug combination used in our study.

It should be noted that ketamine has the ability to sensitise the myocardium to catecholamines (of which secretion is enhanced during stress such as anaesthesia) and thereby enhances the arrhythmogenicity of noradrenaline[6,8]. However no arrhythmias have been reported by other investigators[3,7]. No arrhythmias were seen in this study. It has also been reported that ketamine increased salivary and tracheobronchial mucus, necessitating the use of an anti-sialogogue[9]. No clinical signs of an increase in salivation during the procedure were observed in our study.

CONCLUSION

A combination of ketamine and diazepam used to induce anaesthesia resulted in stable cardiodynamic, haemodynamic and relevant blood parameters for a duration of 150 min with no serious side-effects.

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Book review — Boekresensie

The mammal guide of southern Africa

B Cillié

1997. Briza Publications, Arcadia, Pretoria, 223 pp., paperback. Price not stated. ISBN 1 875093 10 9.

This is an attractive, well-designed, lavishly illustrated, user-friendly field guide to virtually all of the larger mammals (down to the size of a bushbaby) that visitors to southern African conservation areas are likely to encounter. Two pages are devoted to each species. The lefthand page contains a description of the animal and a brief account of its habitat, habits, vocalisation and breeding. Relative size (compared to a human), mass, horn or tusk length (where applicable), food, life expectancy, enemies, spoor, droppings and distribution map are given in a series of boxes.

An innovation is a detailed map showing the location of 120 conservation areas in southern Africa, as well as an easy-to-use checklist of the mammals likely to be encountered in each area.

Inevitably, some errors have crept in. The eland distribution map on page 30 does not show the Drakensberg population. On page 48 the food of the grey rhebok is stated to be exclusively grass. Two definitive studies (in the Bontebok National Park and in the Free State) have shown clearly that grey rhebok feed virtually exclusively on dicotyledonous shrubs and forbs. These studies, which dispelled the myth that grey rhebok are grazers, were published in a readily accessible journal, the *South African Journal of Wildlife Research* (17: 123–127; 18: 11–14). The comparative size diagram of the hook-lipped rhinoceros (page 104) shows the silhouette of the square-lipped rhinoceros.

This is probably the best mammal field guide on the market at present, and should enjoy steady sales.

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