Cardiopulmonary Effects of a Ketamine Hydrochloride/ Acepromazine Combination in Healthy Cats

Walter Ingwersen, Dana G. Allen, Doris H. Dyson,
Peter J. Pascoe and Michael R. O'Grady*

ABSTRACT

The effect of a ketamine hydrochloride/acepromazine combination on the cardiopulmonary function of 11 healthy cats was studied. Test parameters included cardiac output, measured by thermodilution, heart rate, respiratory rate, arterial blood pressure (systolic, diastolic and mean) and arterial blood gas analysis. Values for systemic vascular resistance, cardiac index and stroke volume were calculated. The cardiac output, cardiac index, stroke volume, arterial blood pressure and arterial blood pH decreased significantly ($p < 0.006$). The arterial CO_2 increased significantly ($p < 0.006$). All changes occurred during the five to 45 minute postinduction time period. The heart rate, respiratory rate, arterial O_2 and systemic vascular resistance were not significantly altered. The anesthetic regime maintained an adequate plane of surgical anesthesia for 30-45 minutes.

RÉSUMÉ

Cette expérience consistait à étudier l'effet d'une combinaison de chlorhydrate de kétamine et d'acépromazine sur la fonction cardio-pulmonaire de 11 chats en santé. Les paramètres expérimentaux incluaient: le débit cardiaque, tel que mesuré par la thermodilution, la fréquence cardiaque, le rythme respiratoire, les pressions artérielles systolique, diastolique et moyenne, ainsi que l'analyse des gaz du sang artériel. Les auteurs calculèrent les valeurs relatives à la résistance vasculaire systémique, l'indice cardiaque et le débit systolique. Le débit et l'indice cardiaques, le débit systolique, ainsi que la pression et le pH du sang artériel, diminuèrent de façon appréciable ($p < 0,006$), alors que la teneur du sang artériel en CO_2 augmenta de façon significative ($p < 0,006$). Tous ces changements se produisirent de cinq à 45 minutes après l'induction de l'anesthésie. La fréquence cardiaque et le rythme respiratoire, l'O_2 artériel et la résistance vasculaire systémique ne subirent pas de modifications significatives. Cette approche permit d'obtenir une anesthésie adéquate pour une intervention chirurgicale d'une durée de 30 à 45 minutes.

INTRODUCTION

The use of ketamine, either alone or in combination with other pharmacological agents, has become the mainstay of feline anesthesia for many small animal practitioners. It is a versatile and easy agent to administer with relatively predictable induction and recovery times. One such combination is ketamine and acepromazine. However, with a broad range of other anesthetics available it becomes apparent that no one anesthetic agent or combination is ideal for every given situation. With this in mind, it becomes essential to develop an understanding of the potential advantages and disadvantages of any given anesthetic protocol thereby allowing its safe and judicious application.

The mechanism of action of ketamine on the central nervous system (CNS) is not well understood. It has generally been categorized as a dissociative anesthetic, a term considered vague at best by some investigators (1-3). The term cataleptic anesthesia has been suggested as being more accurate (2). The debate centers on the net effect of ketamine on the CNS (i.e. stimulation vs depression) and on the level within the CNS that this takes place (1-4). Recent evidence suggests that at dosages required for anesthesia, neural information may reach the cortical level but fail to be perceived due to a depression or a functional disorganization of the cortical association areas (1,4). Anesthesia and analgesia are the final result. Further evidence implicates ketamine as producing opiate mediated analgesia (5).

Ketamine causes a direct depression of myocardial contractility that is independent of heart rate (HR) (6-9). Its net effect, *in vivo*, is one of cardiovascular stimulation, an indirect result of its sympathomimetic effect and possible vagolytic action (2,4,10). The result is an increase in HR and an increase in cardiac output (CO) with stroke volume (SV) remaining unchanged (2,4,10). Arterial blood pressure (ABP) is elevated secondary to the increase in CO as systemic vascular resistance (SVR) remains unchanged (2,4,10). Central venous pressure (CVP) tends to rise (4,10). Ketamine's vasopressor activity is abolished with CNS depressants (2) as well as alpha adrenergic blocking agents (7,11). Due to the lack of profound cardiovascular depression

*Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario N1G 2W1.

Reprint requests to Dr. D.G. Allen.

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ketamine has been advocated for use during anesthesia of the high risk cardiac patient (12,13). However, attendant upon the cardiovascular stimulation is an increase in myocardial work and as such myocardial oxygen demands (14,15). This may be detrimental to patients with valvular or ischemic heart disease (16).

Ketamine is known to increase cerebral blood flow and intracranial pressure and as such is not recommended for use in patients with cranial trauma or intracranial masses (4,17). As well, its epileptogenic nature precludes usage in known epileptics (4). Ketamine is considered to cause a dose dependent respiratory depression evidenced by a slight increase in arterial CO_2 ($PaCO_2$) (4). Respiration is characterized as apneustic, shallow and irregular (4,18).

Laryngeal and pharyngeal reflexes are often considered functional, although weak. Intubation is therefore recommended (2,4). The hyperptyalism induced by ketamine is responsive to the administration of an anticholinergic (2,4).

Ketamine, when used alone, tends to cause a hypertonic or cataleptic state characterized by muscle rigidity that makes patient manipulation difficult. Thus the use of ketamine in combination with other tranquilizer/sedatives has been advocated. Common combinations evaluated in the cat have been ketamine/xylazine (19,20-23) and ketamine/acepromazine (7,19,20-22).

Acepromazine (ACP) is an ataractic drug of the phenothiazine group. The major cortical effect is tranquilization with variable sedation exerted primarily at sub-cortical levels by reduction of the brain stem arousal mechanism (reticular activating system) (24). Although ACP does not have any analgesic activity, it lowers alertness making pain more tolerable (24). The major side effect of ACP is arterial hypotension caused mainly by an alpha-sympathetic blockade (24-26). Hypotension may also be mediated through central vasomotor depression, a spasmolytic effect on vascular smooth muscle, ganglionic blockade and direct depression of the myocardium (24). At clinical doses, (0.1 to 0.2 mg/kg) (24-26), ACP has little effect on respiration. Although respiratory rate (RR) may be decreased, the minute volume remains unchanged (22). It produces good tranquilization for 4-6 h following an intramuscular injection (24).

Investigations to date have concentrated on ABP, HR, RR, CVP and blood gas analysis as indicators of cardiopulmonary function. Although inferences regarding cardiac performance can be made from these parameters, knowledge of the CO is required to make a definitive statement and allow for the calculation of important physiological cardiovascular indices such as SVR, cardiac index (CI) and SV. The purpose of this project was to study the effect of a ketamine/acepromazine combination on the cardiopulmonary function of healthy cats.

MATERIALS AND METHODS

Eleven mature cats of either sex and mixed breed were used. They had a mean weight of 3 kg (± 1.1 SD) and were judged healthy on the basis of history, physical examination, chest radiographs and an electrocardiogram (ECG). The cats were brought into the hospital facility and allowed a 24 h acclimatization period. Anesthesia was induced with 5% halothane (Somnothane, Hoechst, Montreal) in oxygen at a flow rate of 5 L/min administered to the cats in a 22 L (5 gallon) aquarium or cat box. Following induction the cats were retrieved from the cat box, intubated and maintained on the least inspired concentration of halothane allowing surgical cut down and exposure of the left jugular vein and carotid artery. This allowed placement of the thermodilution (Edwards Laboratories, Santa Ana, California), injectate (Edwards Laboratories, Santa Ana, California) and arterial catheters in the pulmonary artery, right atrium and left carotid artery respectively. The technique of catheter insertion and location verification has been described in previous reports (23,27).

Following a minimal 24 h recovery period, the ketamine (Ketaset, rogar/STB, Montreal)/ACP (Atravet, Hoechst, Montreal) combination was administered intramuscularly, in the same syringe, at a dose of 20 mg/kg and 0.11 mg/kg respectively. The 24 h recovery time following catheter implantation prior to the experiment was deemed adequate on the basis of a pilot study in which a small group of cats was tested 24 and 144 h following catheter implantation in regards to their CO, HR, SV, ABP and RR. No statistical difference between results was obtained and this protocol has been used in previous experimentation (19-23). The CO, HR, ABP, RR and arterial blood gas values were recorded immediately prior to anesthesia and at 5, 10, 15, 30, 45, 60, 90 and 120 min postinduction. To measure CO, the thermodilution catheter was connected to a cardiac output computer (Edwards Laboratories, Santa Ana, California) and 2 mL of 5% dextrose at room temperature was used as the thermodilution test solution injected into the right atrium via the injectate catheter. The CO was displayed by digital readout. A VR-6 Simultrace Recorder (Electronics for Medicine, White Plains, New York) was used to follow ABP (systolic, diastolic and mean) was well as displaying a continual ECG to monitor HR and rhythm. Respiratory rate was monitored visually. The SV (^{CO}/HR), CI (^{CO}/kg) and SVR[$^{mean\ APB}_{x80}$/CO)](28) were calculated from the above data. The results were statistically analyzed using a paired t-test allowing each animal to act as its own control. To protect against a type I error the predetermined alpha value of 0.05 was divided by the number of paired comparisons setting the level of significance at $p < 0.006$. During the data collection body temperature was monitored via the thermodilution catheter and all cats were maintained at normothermia (37.5-38.5° C) with a water heating pad.

RESULTS

The ketamine/ACP combination produced a good plane of surgical anesthesia that lasted approximately 30-45 min. This was judged by the lack of response (i.e. gross motor movement, changes in HR, rhythm and ABP) to toe pinches using a hemostat.

The CO (mL/min), CI (mL/min/kg) and SV (mL/beat) demonstrated similar responses (Table I). Maximal

TABLE I. Results of Cardiac Output, Cardiac Index, Stroke Volume and Heart Rate in 11 Cats Under Ketamine/ACP Anesthesia

Time (min)	Cardiac Output (L/min)		Cardiac Index (mL/min/kg)		Stroke Volume (mL/beat)		Heart Rate (beats/min)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Pretest	0.67	0.037	197.31	15.60	3.31	0.37	191	6.93
5	0.52	0.028	157.01	9.83	2.45	0.29	214	13.72
10	0.51	0.029	154.08	9.60	2.58	0.23	203	12.42
15	0.52	0.033	154.55	10.90	2.64	0.33	194	12.50
30	0.49	0.027	140.71	7.93	2.43	0.35	206	17.85
45	0.51	0.037	152.85	10.13	2.57	0.34	204	14.71
60	0.53	0.042	163.89	11.00	2.71	0.43	207	11.18
90	0.55	0.039	158.91	10.03	2.71	0.25	207	13.98
120	0.61	0.057	179.01	19.36	2.83	0.18	203	11.56

depression was evident 30 min postinduction, being 73%, 71% and 73% of baseline values respectively. The depression was significant for CO from 5-45 min, and CI and SV were significantly depressed at 30 min. These indices attained near pretest levels 120 min following induction.

Systolic, diastolic and mean ABP also decreased over time with a maximal depression 10 min into the anesthetic regime, that corresponded to an approximate 35% decrease from pretest values (Table II). These changes were significant from the 5-45 min readings. Heart rate, on the other hand, did not change significantly from pretest values (Table I).

$PaCO_2$ and pH demonstrated statistically significant alterations from pretest values from the 5 to 30 min measurements (Table III). This corresponded with the time of maximal decrease in RR from 5 to 30 min (Table III) although the decline in RR was not deemed statistically significant. Systemic vascular resistance was not significantly changed nor was PaO_2 (Table II and III respectively).

DISCUSSION

The use of thermodilution has improved the measurement of CO in small animal patients such as the feline, comparing favorably with indicator dye dilution, the Fick method and the electromagnetic flowmeter technique (23,27,29,30).

Ketamine has been advocated for use in high risk cardiac patients due to its lack of cardiovascular depression, a function of its sympathomimetic properties (12,13). However, when used in combination with ACP, a significant depression of cardiopulmonary function occurred. Ketamine's ability to raise CO is secondary to its positive chronotropic effect as SV remains unchanged (2,4,8-10). Cardiac output is defined by the formula HR x SV (28). When ketamine was combined with ACP, the resultant drop in CO was secondary to the fall in SV as HR remained unchanged. Cardiac output is passive and, HR aside, is controlled by those factors influencing SV. Stroke volume is determined by preload (CVP), afterload (SVR), myocardial contractility and cardiac rhythm (10,28). Although CVP was not measured in this project, both ketamine and ACP have been shown to increase preload (4,10,26). It would therefore follow that when ketamine and ACP are used together, preload would again tend to rise and this has been demonstrated with other ketamine/sympatholytic (23) as well as ketamine/specific alpha-antagonistic combinations (11). Only depressions of CVP would be limiting to SV as elevations would favour an increase in SV and CO via stimulation of the Frank-Starling mechanism (28). Results for SVR remained unchanged throughout the study and cardiac rhythm remained normal. The conclusion was that a depression of myocardial contractility, caused by the ketamine/ACP combination, was the cause of the depressed SV and subsequent CO decline. Ketamine alone and in combination with ACP has been shown to depress myocardial function in the cat (6,7). Acepromazine is an alpha-antagonist and although it would, as such, tend to have more of an effect on peripheral vessels and ABP, it may be implicated in exacerbating the ketamine induced decline in myocardial contractility as alpha-receptors have recently been theorized to exist in the myocardium and to subserve a positive inotropic function (31).

The drop in CO was preceded by a fall in ABP. Ketamine has been stated to have both a peripheral beta and alpha adrenergic effect as SVR does not change appreciably when ketamine is used alone (11). The marked hypotension produced by the ketamine/ACP combination was therefore probably a combination of antagonism of alpha-mediated vasoconstriction (a function of ACP alpha blockade) as well as beta 2 mediated vasodilation (a ketamine related property). Arterial blood pressure is a function of blood volume, blood flow (CO) and the resistance (SVR) which it meets. As blood volume and SVR remained unchanged, the decline in CO was also implicated in the hypotensive state. Although ACP undoubtably induced the early hypotension, this was most likely exacerbated by the CO decline. A compensatory rise in HR, which would have

TABLE II. Results of Arterial Blood Pressure (Systolic, Diastolic and Mean) and Systemic Vascular Resistance in 11 Cats Under Ketamine/ACP Anesthesia

Time (min)	Systolic BP (mm Hg)		Diastolic BP (mm Hg)		Mean BP (mm Hg)		Systemic Vascular Resistance (dynes sec cm^{-5})	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Pretest	119.8	12.03	87.1	7.11	103.4	9.63	12802.44	1288.06
5	82.5	8.46	60.3	5.78	70.4	6.57	11073.20	940.80
10	76.2	7.09	53.9	3.49	63.6	4.25	9896.40	718.70
15	82.0	6.53	57.6	4.61	69.4	4.86	10270.50	537.28
30	80.7	7.60	58.1	5.28	68.5	6.36	11247.56	656.07
45	79.6	7.94	56.8	6.17	67.0	6.77	10344.80	702.85
60	88.8	8.73	63.8	7.64	75.2	7.81	10277.38	860.21
90	94.0	6.91	72.1	5.82	82.3	6.12	11437.78	696.09
120	87.7	10.20	71.0	9.67	79.0	9.83	11078.67	1325.66

TABLE III. Results of Respiratory Rate and Arterial Blood Gas Analysis in 11 Cats Under Ketamine/ACP Anesthesia

Time (min)	PaO_2 (mm Hg)		$PaCO_2$ (mm Hg)		pH		Respiratory Rate (breaths/min)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Pretest	108.9	8.29	25.9	0.94	7.41	0.037	36	5.38
5	101.1	2.76	28.4	1.16	7.36	0.012	25	4.16
10	104.2	2.89	30.6	0.89	7.35	0.009	20	2.02
15	102.6	4.70	31.2	0.68	7.36	0.008	21	2.10
30	105.9	3.29	29.7	1.13	7.37	0.010	24	2.65
45	110.9	5.85	29.1	1.23	7.38	0.010	28	3.10
60	114.8	4.65	27.8	1.02	7.39	0.008	31	3.84
90	113.4	2.98	25.5	1.46	7.40	0.015	42	4.50
120	110.4	9.51	25.3	2.01	7.40	0.012	38	4.20

maintained or elevated CO and subsequently ABP, was absent.

At clinical doses, ACP has very little effect on respiration (24,26). However, it has been shown to act synergistically with other known respiratory depressive agents (24). The statistically significant alterations in pH and $PaCO_2$ can be attributed to the respiratory depressant properties of ketamine magnified by its combination with ACP. These results coincide with observations made by other authors (19-22).

As stated earlier, ketamine has been advocated for use in high risk cardiac patients (12,13). This may not be appropriate in valvular and ischemic heart disease due to an increase in myocardial oxygen consumption (16). When used in combination with ACP, a significant state of cardiovascular depression occurred. The apparent sparing effect of ketamine on the cardiovascular system, secondary to its sympathomimetic activity, was negated by ACP's sympatholytic properties. Another disadvantage of this combination is that it is an injectable regime. Although this allows for an easy induction, it does not lend itself to rapid reversal. It also tempts one to take airway patency for granted, and as such, these patients are often not intubated, which is of some concern since pharyngeal reflexes are weak and the combination does cause respiratory depression.

Therefore, the above changes in cardiopulmonary function may result in cardiovascular embarrassment when this combination is used in cats with known cardiovascular disease or hypovolemic conditions and should not be used in those patients. It remains a good anesthetic regime, when used judiciously, in the healthy cat.

REFERENCES

1. **MORI K, KAWAINATA M, MITANI H, YAMAZAKI M, FUJITA M.** A neurophysiologic study of ketamine anesthesia in the cat. Anesthesiology 1971; 35: 373-382.
2. **McCARTHY TC.** The phencyclidine anesthetics: Their effects on central nervous, cardiovascular and respiratory function. Vet Anesth 1976; 3: 49-52.
3. **KAYAMA Y.** Stimulant and depressant effects of ketamine on neocortical activity in cats. Br J Anaesth 1983; 55: 655-660.
4. **WRIGHT M.** Pharmacologic effects of ketamine and its use in veterinary medicine. J Am Vet Med Assoc 1982; 180: 1462-1471.
5. **FINCK AD, NGAI SH.** Ketamine interacts with opiate receptors in vivo. Anesthesiology 1981; 55: A241.
6. **BECKER M, BELINGER R.** Ketamine and myocardial contractility in the cat. Proc Assoc Vet Anaesth Great Britain and Ireland 1982; 10: 232-238.
7. **BECKER M, BELINGER R.** Effects of ketamine and its combination with acepromazine on the cardiovascular system of the cat. Proc Assoc Vet Anaesth Great Britain and Ireland 1982; 10: 277-279.
8. **VALICENTI JF, NEWMAN WH, BAGWELL EE,** *et al.* Myocardial contractility during induction and steady state ketamine anesthesia. Anesth Analg 1973; 52: 190-194.
9. **DIAZ FA, BIANCO JA, BELLO A,** *et al.* Effects of ketamine on canine cardiovascular function. Br J Anaesth 1976; 48: 941-945.
10. **MUIR WW.** Anesthesia and the heart. J Am Vet Med Assoc 1977; 171: 92-97.
11. **TRABER DL, WILSON RD, PRIANO LL.** The effect of alpha-adrenergic blockade on the cardiopulmonary response to ketamine. Anesth Analg 1971; 50: 737-742.
12. **NETTLES DC, HERRON TJ, MULLEN JF.** Ketamine induction in poor risk patients. Anesth Analg 1973; 52: 59-64.
13. **CORSSEN G, ALLARDE R, BROCH F,** *et al.* Ketamine as sole anesthetic in open heart surgery. A preliminary report. Anesth Analg 1970; 491: 1025-1031.
14. **TWEED WA, MINUCK M, MYMIN D.** Circulatory responses to ketamine anesthesia. Anesthesiology 1972; 37: 613-619.
15. **SMITH G, THORBURN J, VANCE JP, BROWN DM.** The effects of ketamine on the canine coronary circulation. Anesthesia 1979; 34: 555-561.
16. **SPOTOFF H, KORSHIN JD, SORENSEN MB, SKOVSTED P.** The cardiovascular effects of ketamine used for induction of anesthesia in patients with valvular heart disease. Can Anaesth Soc J 1979; 26: 463-467.
17. **LUMB WV.** Anesthesia for the traumatized patient. Arch: Offic J Am Coll Vet Surg 1974; 3: 49-50.
18. **JASPAR N, MAZZARELLI M, TESSIER C, MILIC-EMILI J.** Effect of ketamine on control of breathing in cats. J Appl Physiol 1983; 55: 851-859.
19. **SANFORD BS, COLBY ED.** Feline anesthesia induced by ketamine/acepromazine and ketamine/xylazine. Feline Pract 1982; 12(3): 16-24.
20. **COLBY ED, SANFORD BS.** Feline anesthesia with mixed solution of ketamine/xylazine and ketamine/acepromazine. Feline Pract 1982; 12(2): 14-24.
21. **COLBY ED, SANFORD BS.** Feline blood gas values during anesthesia induced by ketamine/acepromazine and ketamine/xylazine. Feline Pract 1982; 12(1): 23-26.
22. **COLBY ED, SANFORD BS.** Blood pressure and heart and respiratory rates of cats under ketamine/xylazine, ketamine/acepromazine anesthesia. Feline Pract 1981; 11(5): 19-24.
23. **ALLEN DG, DYSON DH, PASCOE PJ, O'GRADY MR.** Evaluation of a xylazine-ketamine hydrochloride combination in the cat. Can J Vet Res 1986; 50: 23-26.
24. **HALL LW, CLARKE KW.** Phenothiazine tranquilizers. In: Hall LW, Clarke KW, eds. Veterinary Anaesthesia. London: Baillière Tindall, 1983: 52-54.
25. **TURNER DM, ILKIW JE, ROSE RJ, WARREN JM.** Respiratory and cardiovascular effects of five drugs used as sedatives in the dog. Aust Vet J 1974; 50: 260-265.
26. **POPOVICH NA, MULLANE JF, YHAP EO.** Effects of acetylpromazine maleate on certain cardiorespiratory responses in dogs. Am J Vet Res 1972; 33: 1819-1824.
27. **ALLEN DG, NYMEYER DH.** A preliminary investigation on the use of thermodilution and echocardiography as an assessment of cardiac function in the cat. Can J Comp Med 1983; 47: 112-117.
28. **DODGE HT, KENNEDY JW.** Cardiac output, cardiac performance, hypertrophy, dilatation, valvular diseases, ischemic heart disease and pericardial disease. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: W.B. Saunders, 1985: 292-331.
29. **DYSON DH, McDONELL WN, HORNE JA.** Accuracy of thermodilution measurement of cardiac output in low flows applicable to feline and small canine patients. Can J Comp Med 1984; 48: 425-427.
30. **DYSON DH, ALLEN DG, McDONELL WN.** Comparison of three methods for cardiac output determination in cats. Am J Vet Res 1985; 46: 2546-2552.
31. **ADAMS HR.** New perspectives in cardiopulmonary therapeutics: receptor selective adrenergic drugs. J Am Vet Med Assoc 1984; 185: 966-973.