Med. J. Cairo Univ., Vol. 62, No. 3, September (Suppl.): 247 - 258, 1994.

Experimental Study of the Antiarrhythmic Activity of Midazolam, Clonidine and their Combination Against Epinephrine Induced Arrhythmia

SOHEIR ABOU EL AZM, Ph.D.; HANAA ABOU EL NOUR, M.D.;
FATMA A. EL BATRAWY, Ph.D. and
EMAN A. ABD EL RASHID, M.D.

The Departments of Pharmacology and Anaesthesiology, Faculty of Medicine, Cairo University.

Abstract

The present study was performed to demonstrate the antiarrythmic and haemodynamic effects of midazolam and clonidine and their combination together on epinephrine induced arrhythmia in anaesthetized cats. Furthermore, the nature of interaction between them was investigated by using the selective benzodiazepine antagonist flumazenil. The arrhythmogenic dose of epinephrine (ADE_1) was determined prior to drug infusion, 2 hours after the start of infusion of the drug (ADE_2) and following i.v. administration of 1mg/kg flumazenil (ADE_3). The results showed that ADE increased from baseline values of 30 ± 5 to 90 ± 8 μg/kg following midazolam infusion (40 μg/kg/min) and returned to 30 ± 5 μg/kg following flumazenil administration (1mg/kg). Midazolam produced a reduction of systolic & diastolic blood pressure by 15.4% & 10% respectively with no change in the heart rate. Meanwhile, clonidine infusion (0.5 μg/kg/min) increased ADE from 30 ± 7 to 150 ± 6 μg/kg & was not affected by flumazenil injection. It also produced significant bradycardia only. As regards the combination of midazolam & clonidine, the ADE increased from 30 ± 5 to 160 ± 5 μg/kg & also was not affected by flumazenil injection. The haemodynamic parameters showed significant increase in both systolic & diastolic blood pressure and significant bradycardia. In conclusion, it was found that midazolam & clonidine have antiarrythmic activity against epinephrine induced arrhythmia by different mechanisms. The pharmacological antagonism of midazolam by flumazenil could suggest that at least part of its antiarrhythmic effect is mediated via benzodiazepine receptors. The combination of both drugs did not show any difference in antiarrhythmic activity of clonidine alone an effect which should be further investigated. The hypertension occurring from the combination should also be explained or investigated.

Introduction

BENZODIAZEPINES are frequently used as preoperative medication because of their sedative, anxiolytic and antigrade amnesic properties [1]. These drugs act at receptor sites located on α-aminobutyric acid (GABA)-ergic neurons [2]. Midazolam is being selected increasingly for use in patients with cardiovascular compromise. Although clinical doses of midazolam have minimal effects on cardiac function, the influence of midazolam (and other benzodiazepine sedatives) on cardiac arrhythmogenesis has yet to be elucidated fully [3]. Muir et al [4] demonstrated decrease in the frequency of ventricular ectopic beats after diazepam administration in conscious dogs following coronary artery occlusion. This apparent antiarrhythmic effect was attributed to anxiolysis and associated reduction in endogenous catecholamine secretion [5,6].

In contrast, it has been suggested that midazolam may have arrhythmogenic properties [7].

Clonidine is a centrally acting α_2 selective agonist with an $\alpha_2 : \alpha_1$ selectivity ratio of approximately 200 : 1 [8]. It has been introduced recently for preanaesthetic medication, because of its analgesic [9, 10], anxiolytic and sedative effect [8, 11, 12]. Clonidine has proven to be effective in reducing neuroendocrine responses to stressful stimuli preoperatively [13, 14], as well as haemodynamic variability during surgery [11, 15].

Lechat and Schmidt [16] and Thomas and Tripathi [17] reported that clonided accorded significant protection against arrythmogenic effects of oubain. The reduction of sympathetic tone and the inhibition of the release of neurotransmitters may be the contributing factor for the antiarrythmic activity of clonidine [17].

Recently, Segal et al. [11] demonstrated an enhanced sedative response in humans receiving a combination of an α_2 agonists and benzodiazepine. Also, Salonen et al. [12] demonstrated a pharmacodynamic mechanism for the synergistic interaction between the α_2 adrenergic agonist dexmedetomidine and midazolam in rats, which mechanistically, is excreted at either a pre-or-post receptor locus.

The purpose of this study was firstly, to determine the antiarrhythmic activity of midazolam and clonidine against epinephrine arrhythmogenicity. Secondly, it is a trial to find a mechanism for this antiarrhythmic activity by evaluation of the effect after the specific benzodiazepine antagonist flumazenil.

Material and Methods

Drugs used:

Midazolam (Hoffman, La Roche, Nuttey) supplied as ampoule 15 mg in 3ml solution Clonidine hydrochloride (Cipia) Flumazenil (La Roche); epinephrine hydrochloride (Misr, A. R E.).

Animals:

Adult cats of either sex weighing about 2-4 kg were used, anaesthesia was induced by ether and maintained by alpha chloralose (80mg/kg). The trachea was intubated to allow artificial ventilation by an animal respirator at a rate of 20 breats/min and the femoral vein was cannulated for drug and fluid administration and the carotid artery cannulated for arterial pressure monitoring. Lead II ECG was recorded. Following instrumentation and 1.5 hour after induction of anaesthesia, the arrhythmogenic dose of epinephrine (ADE) was determined using the method described by Manille et al. [18]. The I.V. injection of epinephrine was started at the minimum dose of 5 μ/kg and the dose was doubled every 15min until four premature ventricular contractions were recorded within 15 sec. After determination of baseline ADE_1 in first group (Gp I), a loading infusion of midazolam to a total dose of 1.5 mg/kg was administered over 5 min followed by maintenance infusion of midazolam at a rate of 40 mg/kg/min. The arrhythmogenic ADE_2 was determined 2 hours after, and again 15 min after a slow (over 5 min) I.V. bolus of flumazenil (1mg/kg) ADE_3. In second group (Gp II) ADE_2 was determined after 2 hours from clonidine infusion in a dose of 0.5/μg/kg/min [17]. ADE_3 was determined also 15' after flumazenil administration (1mg/kg). In the third group (Gp III) ADE_2 was determined 2 hours after I. V. infusion of midazolam and clonidine in the same previous doses. ADE_3 was determined 15' after flumazenil. In the fourth group, (Gp IV) ADE_2 was determined 15 min after I.V. administration of flumazenil at a bolus of 1mg/kg. Haemodynamic parameters (heart rate, systolic and diastolic arterial pressures) were recorded at the time the ADE was achieved under the different treatment conditions. The results were assessed by Student "t" test, $p < 0.05$ was considered statistically significant.

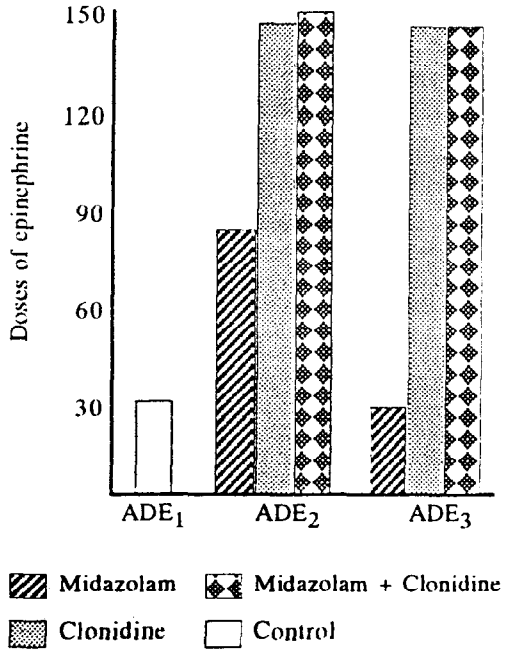
Results

I- Effect of midazolam, clonidine & flumazenil on epinephrine induced arrhythmia:

I.V. infusion of midazolam (40 μg/kg/min) and clonidine (0.5 μg/kg/min) produced a significant increase in ADE_2 from mean baseline value of 30 ± 5 to 90 ± 8 μg/kg respectively. The subsequent administration of flumazenil (1 mg/kg) reversed the antiarrthythmic effect of midazolam only as shown by a return to baseline values [Table (1) Barchart (1)].

This I.V. infusion of combination of midazolam and clonidine in the same previous doses produced a significant increase in the ADE_2 from 30 ± 5 to 160 ± 5 μg/kg.

The subsequent I.V. injection of flumazenil (1mg/kg) had no effect on the antiarrhythmic action of both drugs combined together (Table, I Barchart 1).



Bar Chart 1: Effect of midazolam, Clonidine and flumazenil on arrhythmogenic does of epinephrine.

Flumazenil (1mg/kg I.V.) did not change the ADE_1, showing no-anti-arrhythmic action, Table (I).

II- Haemodynamic effect of midazolam, clonidine & flumazenil before arrhythmia:

The changes from baseline values of initial haemodynamic parameters heart rate, systolic & diastolic blood pressure measured immediately prior to epinephrine injection for ADE determination were represented in Table (II). Midazolam I.V. infusion (40 µg/kg/min) produced a 10% decrease in the diastolic blood pressure & a 15.4% decrease in systolic blood & no change in the heart rate (Fig. 1). Clonidine I.V. infusion (0.5 µg/kg/min) produced insignificant effects on the arterial blood pressure while it produced significant bradycardia where the heart rate decreased form 150 ± 5 to 100 ± 4 (-33%) (Fig. 2).

The I.V. infusion of combination of midazolam & clonidine produced 33% & 30% increase in systolic & diastolic blood pressure respectively. The heart rate was significantly reduced from 150 ± 5 to 107 ± 8 (-28%) (Fig. 3). Flumazenil I.V. had no effect on arterial blood pressure and heart rate (Fig. 4).

III- Haemodynamic effect of midazolam, clonidine & flumazenil during arrhythmia:

The haemodynamic parameters (heart rate, systolic & diastolic blood pressure) measured at the time when the arrhythmic activity was achieved, were represented in Table (III).

As regards the effect on heart rate, no change was observed during determination of ADE_1, ADE_2 & ADE_3, but compared to the control rate, there was bradycardia which was more significant in clonidine and combination of clonidine & midazolam groups, Table (III).

There was, insignificant increase in SAP (+3.4%) and (+4.5%) increase -

Table (I): Effect of Midazolam, Clonidine and Flumazenil on Arrhytmogenic Dose of Epinephrine.

	ADE_1 µg/kg	ADE_2 µg/kg	ADE_3 µg/kg
Midazolam 40 µg/kg min	30 ± 5	90 ± 8**	30 ± 6
Clonidine 0.5 µg/kg min	30 ± 7	150 ± 6**	150 ± 5
Midazolam + clonidine 40 ug/kg min 0.5 µg/kg min	30 ± 5	160 ± 5**	150 ± 7
Flumazenil 1mg/kg.	30 ± 5	30 ± 5	

Values are expressed as mean ± S E M.

* $p < 0.05$ Compared with control value.

** $p < 0.01$ Compared with control value.

Table (II): Hemodynamic Parameters Measured Before Initiation of Epinephrine Dose for Determination of the Arrhythmogenic Dose.

Infusate	Measurements	S A P (mm Hg)	% change	D A P (mm Hg)	% change	H R (beats/min)	% change
Midazolam 40 µg/kg min	Baseline	130 ± 7		100 ± 2		150 ± 6	
	+ 2 h infusion	110 ± 6	(- 15.4)	90 ± 3	(- 10)	150 ± 8	(- - -)
Clonidine 0.5 µg/kg min	Baseline	120 ± 5		100 ± 4		150 ± 5	
	+ 2 h infusion	110 ± 6	(- 8.3)	100 ± 2	(- - - -)	100 ± 4	(- 33 %)
Midazolam + Clonidine	Baseline	120 ± 5		100 ± 4		150 ± 5	
	+ 2 h infusion	160 ± 7	(+ 33)	130 ± 2	(+ 30)	107 ± 8	(+ 28)
Flumazenil 1 mg kg	Baseline	120 ± 6		100 ± 3		150 ± 6	
	+ 2 h infusion	120 ± 8	(- - -)	100 ± 2	(- - -)	150 ± 4	(- - - -)

Data are expressed as mean ± S E M. Percent changes (%) are expressed as percentage change of mean values from baseline mean values.

S A P = systolic arterial pressure. D A P= diastolic arterial pressure.

HR = heart rate.

Table (III): Hemodynamic Parameters Measured During Determination of the Arrhythmogenic Dose of Epinephrine.

Infusate	Measurements	S A P (mm Hg)	% change	D A P (mm Hg)	% change	H R (beats/min)	% change
Midazolam	Baseline	280 ± 10	----	110 ± 6	----	base line H.R. 150	
40 ug/kg min	+ 2 h infusion	290 ± 12	(+ 3.4)	115 ± 9	(+ 4.5)	136	
	+ Flumazenil	290 ± 13	(+ 3.4)	115 ± 7	(+ 4.5)	136	
Clonidine	Baseline	280 ± 8	----	100 ± 6	----	136	
0.5 ug/kg min	+ 2 h infusion	250 ± 10	(- 10.7)	100 ± 8	(0)	136	
	+ Flumazenil	260 ± 9	(- 7)	100 ± 6	(0)	136	
Midazolam +	Baseline	250 ± 10	----	100 ± 9	----	136	
Clonidine	+ 2 h infusion	260 ± 9	(- 7)	100 ± 8	(+ 30)	136	
	Flumazenil	260 ± 12	(- 7)	130 ± 6	(+ 30)	136	
Flumazenil	Baseline	280 ± 11	----	100 ± 6	----	136	
1 mg kg	after Flumazenil	270 ± 12	(- 3.5)	110 ± 5	(+ 10)	136	

Data are expressed as mean ± S E M. (%) change = change of mean from baseline mean values.
S A P = systolic arterial pressure. D A P= diastolic arterial pressure.
HR = heart rate.

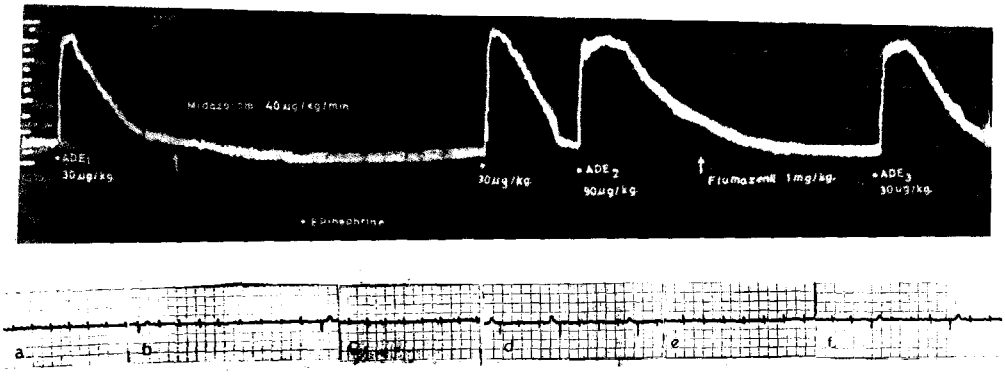


Fig. (1): Hemodynamic parameters measured before and during determination of the arrthythmogenic dose of epinephrine.
A: Effect on arterial blood pressure.
B: ECG Tracing shows: a) Normal HR, b) HR during determination of ADE_1, c) HR during midazolam infusion, d) HR during determination of ADE_2, e) HR after Jinjection of flumazenil, f) HR during determination of ADE_3.

DAP following midazolam infusion (Fig. 1) Table (III), and insignificant decrease in SAP and increase - DAP, following flumazenil administration, Table (III). Meanwhile, following clonidine infusion SAP decreased by 10.4%, which remained decreased by 7% after flumazenil administration (Fig. 2) combination of midazolam and clonidine produced - 7% decrease - SAP and 30% increase in DAP which was unchanged after flumazenil administration (Table III) (Fig. 3).

Discussion

This study has demonstrated that I.V. infusion of midazolam (40 µg/kg/min) produced a significant increase of ADE and that effect was antagonized by flumazenil administration. Flumazenil itself had no effect on epinephrine induced arrhythmia.

Court et al. [3] demonstrated that midazolam infusion results in either no effect (with low dose infusion 10 µg/kg/min) or flumazenil reversible suppression of epinephrine arrhythmogenesis with high dose infusion (40µg/kg/min) in halothane anesthetized dogs.

Benzodiazepine sedatives have been shown to depress basal and stress induced increases in plasma catecholamines [6,19]. It is difficult to speculate the exact mechanism responsible for increase in the arrhythmogenic threshold following midazolam infusion. One possible contributing factor is the arterial hypotension observed following midazolam administration - 10% reduction in diastolic and -15.4% in systolic arterial blood pressure (Table II), as arterial pressure is an important determination of the epinphrine arrhythmia threshold. This hypotension is presumably due to venodilation of the splanchnic vasculature [20, 21]. However, Court et al. found that ADE was unchanged following low dose of midazolam infusion (10µg/kg/min) with associated similar, mild reduction in diastolic pressure, suggesting that other mechanisms, either distinct form or in addition to systemic hypotension, may be responsible or the observed alteration in arrhythmia threshold.

The pharmacological antagonism by flumazenil, a specific benzodiazepine antagonist, observed in this study could suggest that the antiarrhythmic effect of midazolam is at least in part mediated via benzodiazepine receptor interaction. A large proportion of the effect of benzodiazepines is exerted by binding to specific receptor sites and enhancing the actions of gamma- aminobuyric acid (GABA), a major inhibitory neuro-transmitter within the central nervous system [22]. Recent studies suggest that GABA-ergic neurons exert atonic inhibitory influence over central autonomic nervous system outflow [23]. Blockade of GABA-ergic inhibition at different levels of neuraxis modulates parasympathetic & sympathetic outflow to the cardiaovascular system [24]. Di Micco

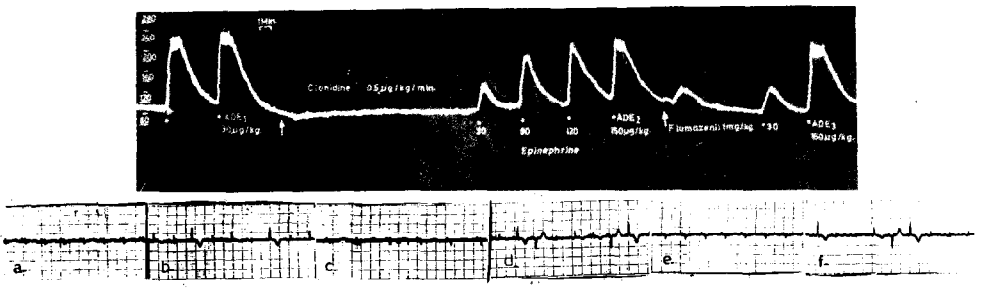


Fig. (2): Hemodynamic parameters measured before and during determination of the arrthythmogenic dose of epinephrine.
A: Effect on arterial blood pressure.
B: ECG Tracing shows: a) Normal HR, b) during ADE_1, d)during clonidine infusion, d) during ADE_2, e) effect of lumazenil on H R, f) during ADE_3.

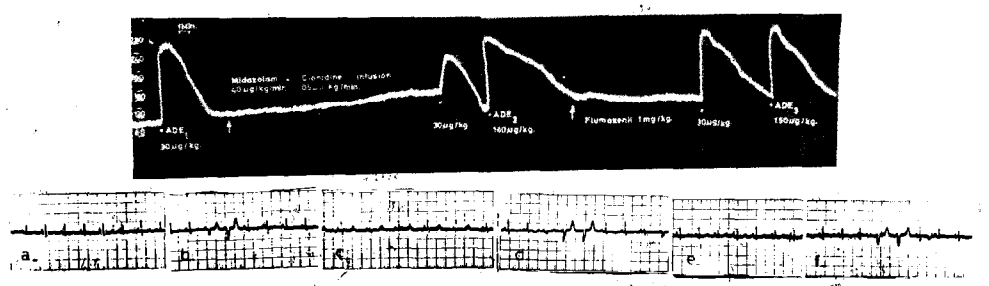


Fig. (3): Hemodynamic parameters measured before and during determination of the arrthythmogenic dose of epinephrine.
A: Effect on arterial blood pressure.
B: ECG Tracing shows: a) Normal HR, b) during ADE_1, d)during clonidine infusion, d) during ADE_2, e) effect of flumazenil on H R, f) during ADE_3.

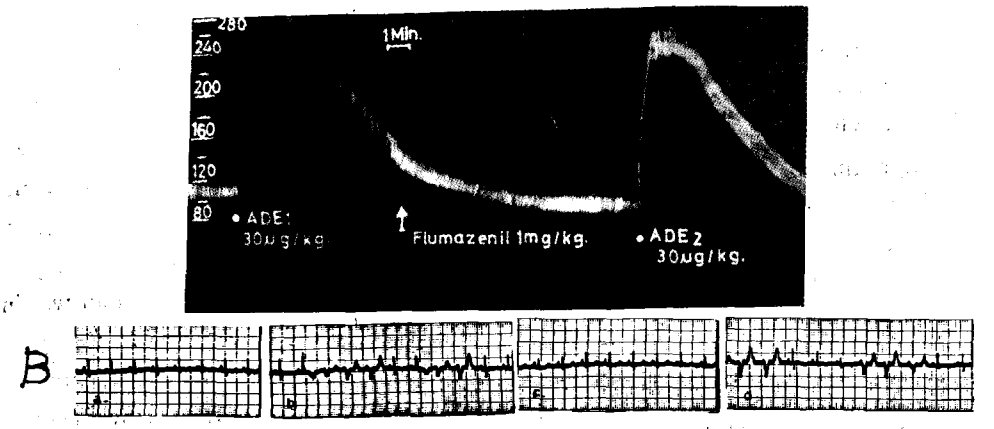


Fig. (4): Hemodynamic parameters measured before and during determination of the arrthythmogenic dose of epinephrine.
A: Effect on arterial blood pressure.
B: ECG Tracing shows: a) Normal HR, b) during ADE_1, d)during clonidine infusion, d) during ADE_2, e) effect of flumazenil on H R, f) during ADE_3.

[25] reported that, benzodiazepines, including midazolam, have a primarily parasympatholytic effect in rats. In other species, the autonomic effects of benzodiazepines is predominantly sympatholytic. Benzodiazepines have been shown to antagonize the hypertension, tachycardia and arrhythmias associated with toxic doses of local anesthetics in dog [26] presumably by enhancement of sympathetic nervous system inhibition.

Midazolam has been reported to decrease central sympathetic outflow, to lower circulating concentrations of catecholamines, and to decrease transiently baroceptor activity that controled heart rate. Vagal mechanisms could also be involved in maintenance of unchanged heart rate [6]. This could explain the finding in this study that the lowering in arterial blood pressure with heart rate not differing from the baseline level. Thereby the increase in epinephrine arrhythmia threshold observed in this study may be attributed to a decrease in sympathetic nervous system outflow.

The current study demonstrated that clonidine (a selective α_2 agonist) infusion of 0.5 μg/kg/min, inhibits the arrhythmogenic effect of 30 ± 5 to 150 ± 6 mg/kg this response was not blocked after flumazenil administration.

Hayashi et al. [27] demonstrated that dexmedetomidine, a selective α_2 agonist in a dose 0.5 μg/kg/min. produced three fold increase in both the arrthythmogenic dose of epinephrine & the plasma epinephrine concentration in anesthetized dogs. Other α_2 adrenergic agonist have been shown to exert an antiarrhythmic action in other arrhythmia models [17, 28]. The precise mechanisms involved in the antiarrhythmic action of α_2 agonists are not clear. If α_2 adrenoceptors were to exist in the heart, the stimulation of these receptors may be expected to produce identical second messenger effects as is seen with B-antagonists, which are also blockers of epinephrine - induced arrhythmia [29]. However, until now there have been no data to support the existence of postsynaptic α_2 adrenoceptors in the mammalian heart [30, 31].

Another indirect mechanism by which α_2 adrenoceptors agonists may ameliorate epinephrine-induced arrhythmias, may be attributed to bradycardia produced [32]. The α_2 agonist inhibits neuronal firing rate from locus ceruleus, leading to a decrease in sympathetic outflow. This action may decrease the release of norepinephrine at the cardiac neuro-effect junction, mimicking the action of a class II antiarrhythmic drug [30]. The reduction of sympathetic transmitter release was accompanied by small decreases or no change in blood pressure & decrease in heart rate, both a centrally mediated vagomimetic effect & a sympatholytic action are possible causes of the bradycardia [33]. This is in accordance with the present study where neither the

centrally mediated hypotensive effect nor the peripherally mediated hypertensive effect was seen during clonidine infusion but significant bradycardia was demonstrated.

Another possible mechanism is that α_2 agonist exerts its antiarrhythmic effect via stimulation of central α_2 adrenoceptors and that effect is independent on changes in hemodynamic parameters. Hayashi et. al [27] found that only the centrally active α_2 antagonist (Atipamezole) that crosses the blood-brain barrier, blocked the antiarrhythmic action of dexedetomidine. In agreement with that, the results of this study which showed that flumazenil could not block or reverse the antiarrhythmic effect of clonidine.

Moreover, in the present work, the I.V. infusion of the combination of midazolam & clonidine did not show any potentiation of antiarrhythmic activity. The observed rise in the arterial blood pressure may be one of the possible reasons for this effect, as the arterial blood pressure has been suggested to be an important factor in the genesis of epinephrine arrhythmias [34]. This rise in arterial blood pressure may be due to pripheral action of clonidine in peripheral vasculature or may be attributed to mixed agonist antagonist effect of clonidine at α_2 receptor or to an α_2 -agonits effect [35]. However, such a response to clonidine might be expected to potentiate arrhythmias, which is opposite to what was found in the present study.

The results of the present work were able to assess the role of blood pressure response to epinephrine in causing the observed difference between midazolam, clonidine & their combination of arrhythmogenic threshold to epinephrine. Neither hyper-nor hypotension appear to contribute to the inter-group differences in arrhythmogenic thresholds, reinforcing the conclusion of Atlee and Malkinson [36] that the systolic blood pressure response to epinephrine does not explain the increase in arrhythmogenicity after clonidine.

Studies of the antiarrhythmic action of the combination of midazolam & clonidine should be further investigated.

References

1. KANTO J.: Br. J. Anaesth., 53: 179-187, 1965.
2. SQUIRES RF andBRAESTRUP C.: Nature, 266: 732-734, 1978.
3. COURT, M., DODMAN, N., GREENBIA D., AGARWA R. and KUMAR A.: Anesthesiology, 76: 155-162, 1993.
4. MUIR W W, WERNER L L and HAMLIN R L.: Am. J. Vet. Res., 36 1203-1266, 1975.
5. DRISCOL, EJ, SMITACK, ZH, and LIGHTBODY P. M.: J. Oral Surg., 30: 332-343, 1972.
6. MARTY J., GAUZIT R, LEFEVRE P., and HENZEL C.: Anesth. Analg., 65: 113-9, 1982.

7. ARCOS, G.J.: Anesthesiology, 67 612, 1987.

8. MAZE, M. and TRANQUILLI, W.: Anesthesiology, 74: 581-605, 1991.

9. BERNARD J. M. HAMMERMILL J L, PASSUTI N, PINAUD M.: Anesthesiology, 75: 577-82, 1991.

10. FILOS, K., PATZONI O, GOUDAS I.C, BOSAS O, KASSARAS A, and GARTAGANIS.: Anesthesiology, 77: 267-74, 1992.

11. SEGAL IS, JARVIS D J, DUNCAN S R, WHITE P F, and MAZE, M: Anesthesiology, 74: 220-225, 1991.

12. SALONEN M., REID K. and MAZE M.: Anesthesiology, 76: 1004-1011, 1991.

13. ENGELMAN E, LIPSZYC M, GILBART E.: Anesth. Analg., 71: 178-87. 1991.

14. QUINTIN L, ROUDOT R, ROUX C. et al.: Br. J. Anaesth., 66 108-15, 1991.

15. GHIGNONE M, CALVILLA O. and QUINTIN L.: Anesthesiology, 67: 3-10, 1987.

16. LECHAT, P. and SCHMITT, H.: Eur. J. Pharmac., 78: 21-32, 1982.

17. THOMAS G P, and TRIPATHI RM.: Br.. Pharmacol., 89: 385-388, 1986.

18. MANILLE B, B, SCHMIDT H< HEYMOL G, GAILER E.: Europ J. Pharmacol., 35: 235, 1976.

19. GAUINANN, D M, YOKSH T L, TYCE G M.: Anesthesiology, 73: 425-432, 1990.

20. GELMAN S, REVES J G and HARRIS D.:Anesth. Analg., 62 : 135-139, 1993.

21. RAYNOLD AK.: Can J. Physiol. Pharmaol., 62: 183-198, 1984.

22. GUIDOTTI.: Neuropharmacology, 22: 1471-1479, 1982.

23. WIBLE J L, LUFT, F C and DIMICCO J.A.: Am. J. Physiol., 254: R 680- R687, 1988.

24. WILLETTE R N. BARCAS, P. P., KRIEER J. and SAPZU H.: J. Pharmacol. Exp. Ther., 230: 34-39, 1983.

25. DI MICCO, J A.: Neuropharmacology, 26: 553-559, 1987.

26. De'JONG RH and HEAVNER JE.: Anesthesiology, 39: 633-638, 1973.

27. HAYASHI, Y., SUMIKAWA, K. MAZE, M., YAMATODAN A., T., KURO, M. and YOSHIYA, I.: Amesthesiology, 75: 113-117, 1991.

28. HARRON DWG, BREZINA M, LILLIE C, KOBINGER W.: Eur. J. Pharmacol., 110: 301-308, 1986.

29. GRAHAM R M and LANIER S M.: The heart and Cardiovascular sysem. Edited by Fozzard H. A, haber E, Katz A M Morgan HE. New York, Raven Press, pp. 1059-1095, 1986.

30. WILLIANS, E M V.: Am. J. Cardiol., 64: 51-91, 1989.

31. HOUSMANS P R.: Anesthesiology, 73: 919-922, 1990.

32. ZINK J, SASYNIUK BL., DRESSEL PE.: Anesthesiology, 43: 548-555, 1975.

33. AANTAA R., KANTO J., SCHEININ M. and SCHEINIA H.: Anesth. Analg., 70: 407-13, 1990.

34. HAYASHI Y., SUMIKAWA K., TASHIRO G., YOSHIYA I. FUKUMITSU K., YOSHIYAL: Anesthesiology, 68: 902-907, 1988.

35. LARACH, DR, SCHULTER H G, DERR J A, LARACH M G, HENSLEY H A, SELIS R.: Anesthesiology, 66: 781-792., 1987.

36. ATLEE JL and MALKINSON CE: Anesthesiology, 57: 282-288, 1982.