J. Pharm. Pharmacol. 1981, 33: 194
Communicated September 30, 1980

0022-3573/81/030194-01 $2.50/0

LETTERS TO THE EDITOR

Influence of some psychotropic agents on $CaCl_2$-induced arrhythmias in the rat

G. GRIMALDI, C. A. MAGGI*, A. MELI, *Pharmacology Department Research Laboratories, A. Menarini Pharmaceuticals, 50131 Florence, Italy*

Ventricular arrhythmias may occur as the result of a 3–4 fold increase in serum Ca^{2+} concentration and can be produced in animals by the intravenous injection of high doses of $CaCl_2$ (see Szekeres & Papp 1975). $CaCl_2$ induces arrhythmias by a direct action on the myocardium and possibly also by an indirect action mediated through the autonomic nervous system. Malinow et al (1953) showed that $CaCl_2$-induced arrhythmias could be partially prevented by surgical destruction of certain areas of the c.n.s. We have determined the potential anti-arrhythmic properties of some psychotropic agents on $CaCl_2$-induced arrhythmias in the rat.

Male albino rats, Wistar–Morini strain, 350–400 g, were anaesthetized with intraperitoneal urethane (1 g kg^{-1}). Lead II e.c.g. was recorded and visualized on a Hewlett-Packard oscilloscope. $CaCl_2$ and test compounds were injected into the left femoral vein.

Arrhythmias were induced by a bolus injection of 1 ml kg^{-1} of 14% $CaCl_2$. The aqueous vehicle or test compounds were administered to groups of 6 animals each 2 min before $CaCl_2$. E.c.g. tracings were scored according to a modification of Malinow et al (1953), i.e. 0 = no sign of arrhythmia, 1 = single extrasystoles, atrial or ventricular, 2 = coupled extrasystoles, ventricular rhythm, ventricular tachycardia, 3 = short runs (no more than 3 seconds) of ventricular fibrillation, 4 = long runs (over 3 seconds) of ventricular fibrillation.

Protection is expressed as % reduction of arrhythmic score of treated compared with control animals.

Percent protection values were plotted against the log-dose and the linear regression calculated according to the method of minimum squares.

ED50 values and their 95% confidence limits were calculated according to Litchfield & Wilcoxon (1949).

With the exception of diazepam and sulpiride, all the drugs tested antagonized to varying degrees $CaCl_2$-induced arrhythmias in the rat (Table 1). The anti-arrhythmic effects of various psychotropics, particularly those possessing 'quinidine-like' properties have been attributed to their peripheral rather than central effects (Fekete & Borsy 1964; Alexander 1968; Baum et al 1971; Wang & James 1979). Since central as well as peripheral mechanisms play a role in the genesis of $CaCl_2$-induced arrhythmias in the rat (Malinow et al 1953; Szekeres & Papp 1975; Cuparencu et al 1978), it is possible that clozapine and haloperidol, which do not possess 'quinidine-like' properties, antagonize $CaCl_2$-induced arrhythmias, by interfering with the c.n.s.-mediated component of this phenomenon.

Table 1. Effect of some psychotropic drugs on $CaCl_2$-induced arrhythmias in the rat.

Treatment	Dose (mg kg^{-1})	% Protection	ED50 (mg kg^{-1}) and 95% confidence limits
Oxazepam	10	0	25·6 (13·3–49·0)
	25	42	
	50	92	
Chlordiazepoxide	10	17	14·9 (14·4–15·4)
	15	50	
	20	75	
Clozapine	5	17	11·2 (9·5–13·3)
	10	44	
	20	75	
Diazepam	Inactive up to 20 mg kg^{-1}†		
Sulpiride	Inactive up to 60 mg kg^{-1}		
Haloperidol	1	12	2·8 (2·5–3·0)
	2	37	
	4	64	
Chlorpromazine	5	20	7·3 (5·6–9·6)
	7·5	50	
	10	81	
Imipramine	2·5	31	3·1 (3·1–3·1)
	3·75	67	
	5	92	
Clomipramine	1·25	25	2·3 (1·4–3·7)
	2·5	50	
	5	87	

All results are the means of six experiments.
† Upper limit of solubility in aqueous vehicle.

* Correspondence.

REFERENCES

Alexander, C. S. (1968) Circulation 38: 1014–1022

Baum, T., Eckfeld, D. K., Shropshire, A. T., Rowles, G., Varner, L. L. (1971) Arch. Int. Pharmacodyn. 193: 149–170

Cuparencu, B., Ticsa, I., Csutak, V., Sandor, V. I., Barzu, T., Safta, L. Do Trung, Dam. (1978) Agressologie 19: 367–378

Fekete, M., Borsy, J. (1964) Med. Exp. 10: 93–103

Litchfield, J. T., Wilcoxon, F. (1949) J. Pharmacol. Exp. Ther. 96: 99–113

Malinow, M. R., Battle, F. F., Malamud, B. (1953) Circ. Res. 1: 554– 559

Szekeres, L., Papp, J. Gy. (1975) Handbook Exp. Pharmacol. 16: 131–182

Wang, C. M., James, C. A. (1979) Life Sci. 24: 1357–1366