J. Pharm. Pharmacol. 1990, 42: 360–362
Communicated October 30, 1989

Suppression of ventricular arrhythmias resulting from acute coronary artery ligation in rat by imipramine

SAMIHA A. M. EL-MAHDY, A. A. ALHAIDER, AFAF A. MAHGOUB, ABDULWAHAB M. BASHANDY, *Department of Medical Pharmacology, College of Medicine, King Saud University, Riyadh 11495, Saudi Arabia, P.O. Box 22452*

Abstract—The potential antiarrhythmic activity of imipramine against ventricular arrhythmias induced by coronary artery ligation in rats has been investigated and compared with procainamide. Imipramide (1 and 5 mg kg^{-1}) or procainamide (5 and 10 mg kg^{-1}) or solvent were injected intravenously 30 min before ligation. Imipramine reduced the total number of ventricular ectopic beats as well as the incidence and duration of ventricular tachycardia and ventricular fibrillation. The drug did not significantly affect the blood pressure but reduced the heart rate. The antiarrhythmic activity of imipramine is postulated to be due to a quinidine-like effect and/or α-adrenergic blocking activity. The study confirms the potential utility of imipramine as an antiarrhythmic drug.

Tricyclic antidepressants have been implicated in the precipitation of cardiac arrhythmia (Moorehead & Knox 1965; Kantor et al 1975; Ramanathan & Davidson 1975) as well as being demonstrated to be effective against cardiac arrhythmias (Bigger et al 1977; Kantor et al 1978; Giardina et al 1979). Wilkerson (1978) found that imipramine was effective against ouabain-induced ventricular arrhythmias in dogs, and later demonstrated that amitriptyline and nortriptyline decreased ventricular ectopic activity and induced sinus rhythm in conscious dogs 24 h after coronary occlusion (Wilkerson & Henderson 1980).

The present study was conducted to evaluate the prophylactic antiarrhythmic activity of imipramine against ventricular arrhythmias induced by acute coronary artery ligation in rats.

Materials and methods

Male Wistar rats (300–400 g) were anaesthetized with pentobarbitone sodium (60 mg kg^{-1}, i.p.) and ether anaesthesia. The left carotid artery was cannulated for blood pressure recording and a femoral vein for drug administration. The electrocardiogram was recorded by a standard lead I. The chest was opened by a midsternal incision and the left coronary artery was ligated according to the method described by Kane et al (1979). The test drugs or equivalent volumes of saline were given 30 min before ligation. Imipramine was given in doses of 1 and 5 mg kg^{-1}; procainamide in doses of 5 and 10 mg kg^{-1}. The severity of arrhythmias was assessed during the early 30 min post-ligation period by counting the number of ventricular extrasystoles and measuring the duration of ventricular tachycardia (VT) and ventricular fibrillation (VF) as described by Kane et al (1979). The results were expressed as mean ± standard error of the mean. The difference between means was examined statistically by Student's *t*-test.

Results

Acute coronary artery ligation in control rats resulted in pronounced ventricular arrhythmia during the 30 min post-ligation period, with many ventricular ectopic beats and high incidence (100 and 71%) of prolonged attacks of VT and VF (Table 1, Fig. 1). Pretreatment with imipramine (1 mg kg^{-1}) significantly reduced the total number of ventricular ectopic beats ($P < 0.05$), the duration of VT ($P < 0.001$), as well as the incidence (44%) and duration of VF ($P < 0.05$) (Table 1, Fig. 2). Increasing the dose of imipramine to 5 mg kg^{-1} resulted in further reduction of the number of ventricular ectopic beats ($P < 0.02$) and incidence of VT (44%), but the duration of VT and VF as well as the incidence of VF were not reduced more than the value obtained by 1 mg doses (Table 1). The prophylactic effect of imipramine (1–5 mg kg^{-1}) was more or less comparable with procainamide (5–10 mg kg^{-1}), the effects of which are shown in Table 1 and Fig. 3 for comparison.

Discussion

In this study, we found that imipramine (1–5 mg kg^{-1}) reduced the incidence and severity of ventricular arrhythmias induced by acute coronary artery ligation in rats. The antiarrhythmic activity of imipramine was comparable with that of procainamide (5–10 mg kg^{-1}). Our results are in agreement with previous studies that pointed to the antiarrhythmic activity of imipramine in patients with atrial and ventricular arrhythmias (Bigger et al 1977; Kantor et al 1978; Giardina et al 1979) and in reducing premature ventricular contractions when used in patients for the

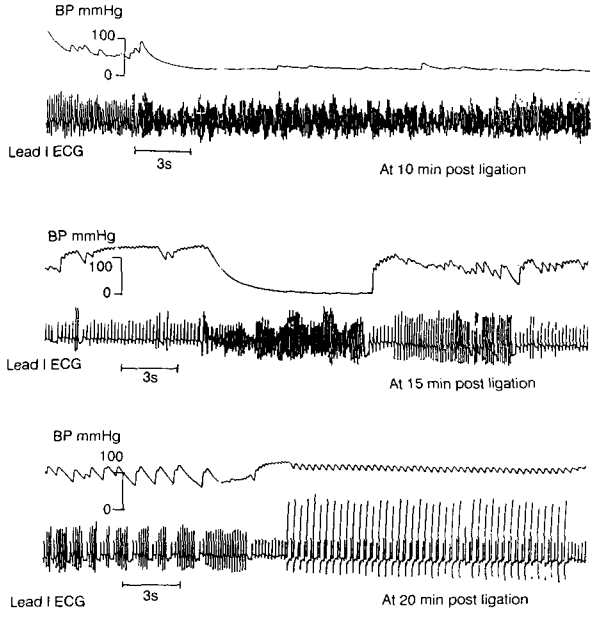

FIG. 1. Ventricular arrhythmia induced by acute coronary artery ligation in anaesthetized rats.

Correspondence to: S. A. M. El-Mahdy, Department of Medical Pharmacology, College of Medicine, King Saud University, Riyadh 11495, P.O. Box 22452, Saudi Arabia.

Table 1. The effect of imipramine and procainamide on ventricular arrhythmias resulting from acute coronary artery ligation in rat.

Drug	n	Dose (mg kg^{-1})	Ventricular ectopic beats	Ventricular tachycardia Duration (s)	Ventricular tachycardia Incidence (%)	Ventricular fibrillation Duration (s)	Ventricular fibrillation Incidence (%)	Survival (%)
Control	7		1836±383	178±16	100	44±15	71	100
Imipramine	9	1	774±162*	29±15****	100	1·1±0·7*	44	100
	8	5	543±143**	29±16****	44	1·2±0·69*	42	100
Procainamide	5	5	890±111***	125±18*	100	3·54±0·95*	80	100
	5	10	410±189**	17±10*	60	5·8±5·8*	20	100

Values are mean±s.e.m. *$P<0.05$, **$P<0.02$, ***$P<0.01$, ****$P<0.001$.

treatment of depression following myocardial infarction or coronary artery bypass-graft (Raskind et al 1982).

This beneficial effect of imipramine in ventricular arrhythmias induced by myocardial ischaemia is probably attributable to the quinidine-like membrane stabilizing effect of the drug. Imipramine was found to possess a more potent local anaesthetic activity than lignocaine in desheathed frog nerves (Guerrero & Molgo 1974) and therapeutic plasma levels were associated with quinidine-like electrophysiological effects including increased PR, QRS and QT intervals (Bigger et al 1977; Kantor et al 1978; Giardina et al 1979). Imipramine is also known to possess an α-adrenoceptor blocking activity (Baldessarini 1985) which might contribute to its antiarrhythmic effect (Stephenson et al 1960; Corbalan et al 1976).

Although imipramine blocks reuptake of catecholamines and thus may potentially possess an arrhythmogenic effect, in this study, it was not arrhythmogenic in doses less than 10 mg kg^{-1}. This is in accordance with clinical studies, where no serious dysrhythmias were observed following chronic treatment with therapeutic doses of imipramine (Burckhardt et al 1978; Giardina et al 1979), whereas lethal cardiac arrhythmias have been reported after overdoses (Biggs et al 1977). In the present study imipramine did not significantly affect the systemic arterial blood pressure. Some authors have reported that patients under chronic treatment with imipramine commonly developed orthostatic hypotension due to its α-blocking action (Glassman et al 1979; Thayssen et al 1981; Raskind et al 1982; Baldessarini 1985) whereas, other investigators found no orthostatic hypotension after 3 weeks of treatment with imipramine and other tricyclic antidepressants (Burckhardt et al 1978). Furthermore, imipramine was found to produce bradycardia, despite its well documented anti-cholinergic properties. This observation is in agreement with that of Alhaider (1985) who found that imipramine (1 and 5 mg kg^{-1}) decreased the heart rate in anaesthetized rabbits. This effect is probably due to a direct quinidine-like effect on the heart, since it was also found that procainamide produced a similar reduction in the heart rate.

In conclusion, pretreatment of rats with imipramine before

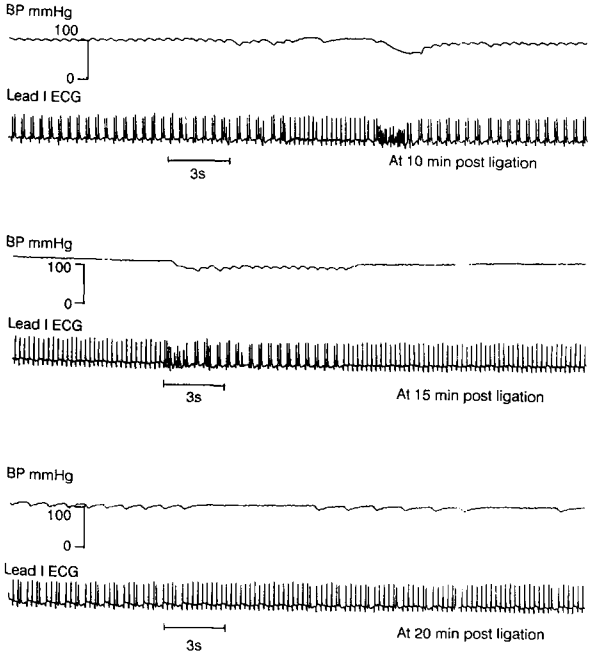

FIG. 2. Ventricular arrhythmia induced by acute coronary artery ligation in anaesthetized rats pretreated with imipramine (1 mg kg^{-1}, i.v.) 30 min before ligation.

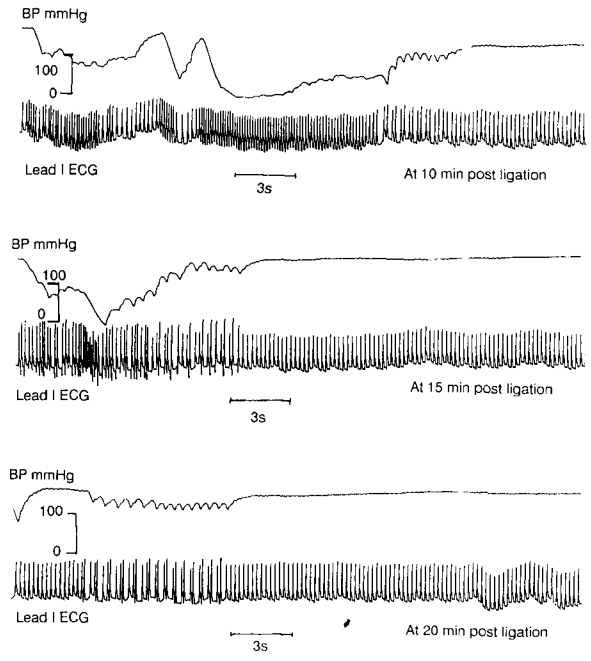

FIG. 3. Ventricular arrhythmia induced by acute coronary artery ligation in anaesthetized rats pretreated with procainamide (5 mg kg^{-1}, i.v.) 30 min before ligation.

coronary artery ligation has been found to exert a prophylactic effect against ventricular arrhythmias induced by acute coronary artery ligation. This antiarrhythmic activity is most likely attributed to a quinidine-like membrane stabilizing effect with a possible contribution of α-adrenoceptor blocking activity. The study confirms the potential utility of imipramine as an antiarrhythmic agent.

References

Alhaider, A. A. (1985) Antihistamine, anticholinergic and cardiovascular effects of 2-substituted-4-phenyl-quinoline derivatives. Life Sci. 38: 601–608

Baldessarini, R. J. (1985) Drugs and the treatment of psychiatric disorders. In: Goodman, L. S., Gilman, A. (eds) The Pharmacological Basis of Therapeutics. 7th edn, Macmillan, New York, pp 387–445

Bigger, J. T., Jr., Giardina, E. G. V., Perel, J. M., Kantor, S. J., Glassman, A. H. (1977) Cardiac anti-arrhythmic effect of imipramine hydrochloride. N. Engl. J. Med. 296: 206–208

Biggs, J. T., Spiker, D. G., Petit, J. M., Ziegler, V. E. (1977) Tricyclic antidepressant overdose: incidence of symptoms. J. Am. Med. Ass. 238: 135

Burckhardt, D., Raeder, E., Muller, V., Imhof, P., Neubauer, H. (1978) Cardiovascular effects of tricyclic and tetracyclic antidepressants. Ibid. 239: 213–216

Corbalan, R., Verrier, R. L., Lown, B. (1976) Differing mechanisms for ventricular vulnerability during coronary artery occlusion and release. Am. Heart J. 92: 223–230

Giardina, E. G. V., Bigger, J. T., Jr., Glassman, A. H., Perel, J. M., Kantor, S. J. (1979) The electrocardiographic and antiarrhythmic effects of imipramine hydrochloride at therapeutic plasma concentrations. Circulation 60: 1045–1052

Glassman, A. H., Bigger, J. T., Jr., Giardina, E. V., Kantor, S. J., Perel, J. M. (1979) Clinical characteristics of imipramine-induced orthostatic hypotension. Lancet i: 468–472

Guerrero, J., Molgo, J. (1974) Effects of imipramine upon frog nerve excitability and conduction. Arch. Int. Pharmacodyn. 209: 26–37

Kane, J. A., McDonald, F. M., Parratt, J. R. (1979) Coronary artery ligation in anaesthetized rats as a model for assessment of antidysrhythmic activity; the effects of lignocaine, propranolol and ORG 6001. Br. J. Pharmacol. 66: 463–464

Kantor, S. J., Bigger, J. T., Jr., Glassman, A. H., Macken, D. L., Perel, J. M. (1975) Imipramine-induced heart block: a longitudinal case study. J. Am. Med. Assoc. 231: 1364–1366

Kantor, S. J., Glassman, A. H., Bigger, J. T., Jr., Perel, J. M., Giardina, E. V. (1978) The cardiac effects of therapeutic plasma concentrations of imipramine. Am. J. Psychiatry 135: 534–536

Moorehead, C. N., Knox, S. J. (1965) Imipramine-induced auricular fibrillation. Ibid. 122: 216–218

Ramanathan, K. B., Davidson, C. (1975) Cardiac arrhythmia and imipramine therapy. Br. Med. J. 1: 661–662

Raskind, M., Veith, R., Barness, R., Gumbrecht, G. (1982) Cardiovascular and antidepressant effects of imipramine in the treatment of secondary depression in patients with ischaemic heart disease. Am. J. Psychiatry 139: 1114–1117

Stephenson, S. E., Cole, R. K., Parrish, T. F., et al (1960) Ventricular fibrillation during and after coronary artery occlusion. Incidence and protection afforded by various drugs. Am. J. Cardiol. 5: 77–87

Thayssen, P., Bjerre, M., Kragh-Sorensen, P. (1981) Cardiovascular effects of imipramine and nortriptyline in elderly patients. Psychopharmacology 74: 360–364

Wilkerson, R. D. (1978) Antiarrhythmic effects of tricyclic antidepressant drugs in ouabain-induced arrhythmias in the dog. J. Pharmacol. Exp. Ther. 205: 666–669

Wilkerson, R. D., Henderson, J. D. (1980) Antiarrhythmic activity of amitriptyline analogues in conscious dogs after myocardial infarction: cyproheptadinium methiodide. J. Med. Chem. 23: 1255–1258

J. Pharm. Pharmacol. 1990, 42: 362–363
Communicated November 6, 1989

In-vivo and in-vitro hepatoprotective effect of 4-thia-prostaglandin E_1 and 7-fluoroprostacyclin in rats

TAMOTSU KOYAMA, HIROSHI UNO, SHIGEYUKI ISHII, KIYOSHI BANNAI, ATSUO HASATO, TOKUTARO MAKITA, *Institute for Second Biomedical Research, Teijin Ltd, 4-3-2 Asahigaoka, Hino, Tokyo 191, Japan*

Abstract—4-Thia-prostaglandin E_1 and to a lesser extent 7-fluoroprostacyclin showed a potent protective effect against carbon tetrachloride-induced liver injury in-vivo and in-vitro in rat.

The cytoprotective action of prostaglandins has been intensively studied in gastric mucosa damaged by aspirin, ethanol, and taurocholate (Robert et al 1979; Teramoto et al 1987). Stachura et al (1981) showed protection by prostaglandins in the liver in which acute damage induced by carbon tetrachloride was reduced by 16,16-dimethyl prostaglandin E_2. Several other prostaglandins have a hepatoprotective effect (Arai et al 1986) and we now report studies of two prostaglandin derivatives, 4-thia-prostaglandin E_1 (4-thia-PGE_1) and 7-fluoroprostacyclin (7-fluoro-PGI_2) given orally and examined in-vitro.

Correspondence to: T. Koyama, Institute for Second Bio-medical Research, Teijin Ltd, 4-3-2 Asahigaoka, Hino, Tokyo 191, Japan.

Methods

In-vitro experiment. Male Sprague–Dawley rats (158–192 g, Shizuoka Laboratory Animal Corp., Hamamatsu, Japan) were given sodium phenobarbitone 80 mg kg^{-1} d^{-1} i.p. for 3 days and then fasted overnight before use. Isolated hepatocytes were prepared by collagenase perfusion (Nakamura et al 1981). The hepatocytes were plated in a 9 cm^2 plastic dish (Corning) at a density of 1×10^5 cells cm^{-2} in William's E medium (Flow Laboratories) containing 10% foetal calf serum heat-inactivated at 56°C for 10 min (Flow Laboratories), 100 μg mL^{-1} benzylpenicillin potassium (Meiji, Tokyo, Japan), 100 μg mL^{-1} streptomycin sulphate (Meiji, Tokyo, Japan), and 0·25 μg mL^{-1} amphotericin B (Flow Laboratories). After incubation at 37°C in a humidified atmosphere of air/CO_2 (95:5) for 3 h to allow the cells to attach, the cultures were rinsed with Hanks BSS and incubated for 1 h in complete Williams E medium with 0·08% ethanol (vehicle), 4-thia-PGE_1 or 7-fluoro-PGI_2 at final concen-