J. Pharm. Pharmac., 1973, **25**, 700–704 *Received May* 14, 1973

Further observations on the experimental antidysrhythmic activity of indoramin hydrochloride

S. RASHID AND B. J. ALPS

Wyeth Institute of Medical Research, Huntercombe Lane South, Taplow, Maidenhead, Berkshire, U.K.

Indoramin showed potent activity in reversing severe myocardial conduction disorders and ventricular fibrillation induced by hypothermia, and protected against the precipitation of electrically-induced ventricular fibrillation at low doses in pentobarbitone-anaesthetized cats. It would appear that the α-adrenoceptor blocking and local anaesthetic membrane stabilizing properties of indoramin are responsible for the mechanisms by which these dysrhythmias are reversed as they are with those induced by ouabain and adrenaline, previously described.

Indoramin has been shown, in animal experiments, to be a potent hypotensive drug possessing α-adrenoceptor blocking and myocardial inhibitory properties (Alps, Hill & others, 1972; Alps, Borrows, & others, 1972). Whilst indoramin does not depress the myocardium by β-adrenoceptor blockade it does possess local anaesthetic activity, and in an attempt to examine this property further the drug was examined for antidysrhythmic activity against adrenaline and ouabain-induced irregularities. As a result, indoramin was found to possess potent antidysrhythmic properties (Alps, Hill & others, 1971).

The antidysrhythmic actions of indoramin have now been further investigated using dysrhythmias induced by hypothermia and electrically-induced ventricular fibrillation (Szekeres & Papp, 1971) in anaesthetized cats.

METHODS

Dysrhythmias induced by hypothermia

Three cats of either sex, 1·6 to 2·0 kg, were anaesthetized with pentobarbitone-sodium (30 mg kg^{-1}, intrathoracically). The trachea was cannulated and the animals were ventilated artificially by a Palmer respirator. The cephalic vein and carotid artery were prepared for injection of test compounds and for recording left ventricular blood pressure respectively. The left femoral artery was divided and cannulated at two points. The cannula from the upper abdominal end was connected via a Watson-Marlow peristaltic pump, through fine bore tubing to a glass coil connected to the cannula inserted into the peripheral femoral artery. The glass coil was immersed in ice and ice bags were placed around the animals to lower body temperature. The blood was circulated through the cooling system and reintroduced into the peripheral cut end of the femoral artery. Rectal temperature was monitored by means of a glass thermometer.

Electrically-induced ventricular fibrillation

Five cats, 1·6 to 2·0 kg, of either sex, were anaesthetized with pentobarbitone-sodium (30 mg kg^{-1} intrathoracically) and prepared for a general haemodynamic study (Alps & others, 1972). Fine insulated copper wire (S.W.G. 40, 0·75 ohm resistance) was coiled around the catheter to the left ventricle. The wire (cathode) was fixed at the catheter tip at which point the wire was cleaned of its insulation. A hypodermic needle was positioned subcutaneously over the region of the left ventricle on the left side of the chest and served as the anode.

Before the electrical stimulation commenced the following parameters were recorded on a Grass Model 7 polygraph:— ecg Lead II; respiration; left intraventricular pressure (generally) and its first derivative (peak positive dp/dt); aortic blood pressure; and heart rate. Animals were artificially ventilated throughout the experiment once the basic cardiovascular data had been recorded. The parameters of stimulation (Scientific Research Instruments stimulator) necessary to precipitate ventricular fibrillation before antidysrhythmic drug administration were established. The voltage necessary to induce fibrillation was variable between animals, ranging from 10 to 30 V. Frequency also varied between 20–30 Hz for 1·0 ms duration for a period of 8 s. The "control" fibrillation was induced 2 to 3 times in each animal. The test compound was then injected in doses of 0·25, 0·5, 1, 5 mg kg^{-1} (i.v., cumulatively). In one experiment a single dose of 5 mg kg^{-1} was injected. Ten min after the administration of each dose of test compound all the haemodynamic parameters were recorded at a fast paper speed (100 mm s^{-1}) and the threshold electrical fibrillation stimulus was again applied. If no fibrillation occurred the voltage was increased until the condition appeared. The process was repeated for all doses of the compound in every experiment.

RESULTS

Dysrhythmias induced by hypothermia

Hypothermia caused the blood pressure to fall and the heart rate to slow significantly. Various types of dysrhythmias were produced, ranging from progressive atrioventricular conduction disturbance and heart block to multiventricular extrasystoles and ventricular fibrillation. The hypothermic temperature at which any dysrhythmia occurred was variable (15–28°) but there were obvious progressive changes in the nature of the QRS T waveform in the ecg leading up to a dysrhythmia. It is possible that the rate of cooling (which was not controlled in these experiments) influenced both the type of irregularity seen and the temperature at which it occurred.

In one out of three experiments, ventricular fibrillation was produced at 22° and this was partially converted by 0·5 mg kg^{-1} indoramin i.v. to a more co-ordinated ventricular rhythm (Fig. 1D). Increasing the dose to cumulative 2 mg kg^{-1} restored sinus rhythm and a further increase to 7 mg kg^{-1} partially restored the configuration and polarity of the T wave to normality. In another experiment almost total heart block was produced at 19° but slow sinus rhythm was restored by indoramin (1 mg kg^{-1}, i.v.) (Fig. 2C). In the third experiment a severe conduction disturbance involving both the atria and ventricles was produced by hypothermia. Episodes of atrial flutter, interrupted by QRS T complexes (of normal appearance) were observed which were interrupted by periods of complete electrical silence. Cumulative doses of indoramin (5 mg kg^{-1}) restored sinus rhythm.

Electrically-induced ventricular fibrillation

The range of voltages required to produce "control" fibrillation in all the five experiments made was 10–30 V. In two experiments, indoramin (0·25 mg kg^{-1}) was effective in protecting against the electrical induction of ventricular fibrillation, an increase in voltage of 100% being necessary in both cases before fibrillation could again be precipitated. Increasing the dose of indoramin in both experiments produced additional protection. In two other experiments, a single dose of indoramin (1

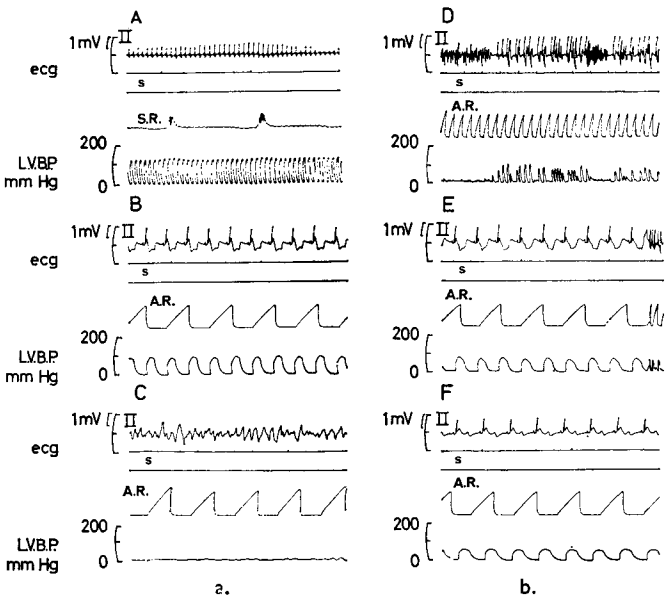

FIG. 1a. Traces of Lead II of the ecg, respiration and left intraventricular pressure (L.V.B.P.) recorded from a pentobarbitone anaesthetized cat under conditions of hypothermia. Panel A: Control records before the hypothermic procedure commenced (spontaneous respiration S.R.). Body temperature 36°. Panel B: Bradycardia and inversion of the T wave occurred at 25° (artificial respiration A.R.). Panel C: Ventricular fibrillation occurred at 22° (artificial respiration A.R.).

b. The influence of indoramin on ventricular fibrillation induced by hypothermia in a pentobarbitone anaesthetized cat. Panel D: Within about 10 s of the injection of indoramin 0·5 mg kg^{-1}, i.v. there was partial stabilization of the ventricular complex and as can be seen by the return of pressure beats, improved mechanical efficiency of the heart. Panel E: Sinus rhythm was restored at a cumulative dose of indoramin 2·0 mg kg^{-1}, i.v. Note in comparison with panel B, Fig. 1a, that the T wave is still inverted. Panel F: At cumulative indoramin 7 mg kg^{-1}, i.v. the configuration and polarity of the T wave was partially restored to normality.

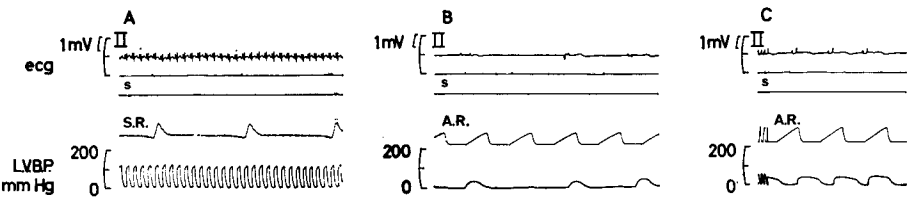

FIG. 2. Traces of Lead II of the ecg, respiration and left intraventricular pressure (L.V.B.P.) recorded from a pentobarbitone anaesthetized cat under conditions of hypothermia. Panel A: Control records before the hypothermic procedure commenced (spontaneous respiration S.R.). Body temperature 36°. Panel B: At 19° almost complete heart block occurred (artificial respiration A.R.). Panel C: Within about 15 s of the injection of indoramin 1 mg kg^{-1} there was a return of slow sinus rhythm.

mg kg^{-1}) gave protection of 100 and 150% respectively and in a fifth experiment, a dose of indoramin (5 mg kg^{-1}) gave protection of 400% against ventricular fibrillation.

DISCUSSION

Indoramin showed potent activity in reversing severe dysrhythmias induced by hypothermia and afforded protection against electrically induced ventricular fibrillation in anaesthetized cats. The degree of antidysrhythmic activity observed in these experiments was analagous to that previously demonstrated for indoramin against adrenaline and ouabain-induced disorders in this species (Alps & others, 1971).

It has been shown by other workers that α-adrenoceptor blocking agents effectively inhibit cardiac dysrhythmias induced by adrenergic stimuli (Acheson, Farah & French, 1949; Nickerson & Nomaguchi, 1951), and interest in this area is being renewed (Brkic & Stern, 1965; Garvey, 1969). Garvey (1969) and Nickerson & Hollenburg (1968) have provided evidence that the cardiac adrenoceptors responsible for these dysrhythmias are α-adrenoceptors that are selectively blocked by α-adrenoceptor blocking drugs. It seems probable that at least part of the antidysrhythmic action of indoramin is due to its potent α-blocking action ($pA_2 = 7{\cdot}4$; Alps & others, 1972) on the α-adrenoceptors in the myocardium.

The fact that dysrhythmias induced by hypothermia can be mediated through the sympathetic innervation to the heart has been shown by Shumacker, Riberi & others (1956). They found that cardiac sympathectomy and sympatholytic drugs afforded protection against hypothermic ventricular fibrillation. It is also known that the susceptibility of the heart to fibrillation in moderate hypothermia is due to an increased excitatory state of the central autonomic centre (hypothalamus) responsible for the nervous control of the heart. On this basis agents which inhibit the autonomic nervous system at different levels may protect against dysrhythmias induced by hypothermia. Cookson, Neptune & Bailey (1952) found that piperoxan was such an agent, effective in protecting against hypothermic fibrillation. This drug is an α-adrenoceptor blocker which depresses the myocardium but causes direct vasoconstriction of the coronary and peripheral blood vessels (Goodman & Gilman, 1971). In contrast, dihydroergotoxine which is also an α-adrenoceptor blocker has hardly any direct influence on the control of the sympathetic nervous system.

Another possible explanation for the antidysrhythmic activity of indoramin against hypothermically-induced irregularities of cardiac rhythm could be its local anaesthetic activity. In hypothermia there is prolongation of conduction time in the myocardium, accompanied by a reduction in the effective refractory period. Local anaesthetic drugs, with membrane-stabilizing properties, decrease the rate of depolarization, reduce conduction velocity and increase the length of the effective refractory period.

In electrically-induced ventricular fibrillation, Wiggers (1940) found that large areas of myocardium continued to contract in unison for a few seconds after the onset of the condition. The electrocardiogram in this case is characterized by large waves which become progressively smaller. The maximal diastolic potential diminishes, the refractory period shortens and conduction becomes slower. All these changes in the heart can be reversed by local anaesthetic drugs and it appears that this may be the mechanism by which indoramin protects against electrically-induced fibrillation.

It seems likely, therefore, that the α-adrenoceptor blocking and local anaesthetic membrane stabilizing properties of indoramin are also responsible for the mechanism

by which the two additional experimental arrhythmogenic test situations, reported here, are antagonized.

Acknowledgement

The authors wish to thank Mr. R. Bridle for technical assistance.

REFERENCES

ACHESON, G. H., FARAH, A. & FRENCH, G. N. (1949). *J. Pharmac. exp. Ther.*, **97**, 455–465.

ALPS, B. J., BORROWS, E. T., JOHNSON, E. S., STANIFORTH, M. W. & WILSON, A. B. (1972). *Cardiovascular Res.*, **6**, 226–234.

ALPS, B. J., HILL, M., FIDLER, K., JOHNSON, E. S. & WILSON, A. B. (1971). *J. Pharm. Pharmac.*, **23**, 678–686.

ALPS, B. J., HILL, M., JOHNSON, E. S. & WILSON, A. B. (1972). *Br. J. Pharmac.*, **44**, 52–62.

BRKIC, S. & STERN, P. (1965). *Acta Pharm. jugosl.*, **15**, 147–151.

COOKSON, B. A., NEPTUNE, W. C. & BAILEY, C. D. (1952). *Dis. Chest*, **22**, 245–260.

GARVEY, H. L. (1969). *Archs int. Pharmacodyn. Thér.*, **182**, 376–390.

GOODMAN, L. S. & GILMAN, A. (1971). *The Pharmacological Basis of Therapeutics.* 4th edn. London: Macmillan.

NICKERSON, M. & HOLLENBURG, N. K. (1968). *Physiological Pharmacology*, **4**, 243. New York and London: Academic Press.

NICKERSON, M. & NOMAGUCHI, G. M. (1951). *J. Pharmac. exp. Ther.*, **101**, 379–396.

SHUMACKER, H. B. JR., RIBERI, A., BOONE, R. D. & KAJIKURI, H. (1956). *Ann. surg.*, **143**, 223–229.

SZEKERES, L. & PAPP, GY. J. (1971). Experimental cardiacarrhythmias and antiarrhythmic drugs. Budapest: Akadémiai kiadö.

WIGGERS, C. J. (1940). *Am. Heart J.*, **20**, 399–412.