J. Pharm. Pharmacol. 1986, 38: 772–773
Communicated February 20, 1986

Antiarrhythmic effect of acute and chronic amiodarone treatment in conscious rats

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The effect of amiodarone after acute and chronic pretreatment was studied in the early phase of arrhythmias induced by coronary artery ligation in conscious rats. Both acute and chronic amiodarone pretreatments improved survival during the first 20 min after coronary ligation. Only chronic amiodarone pretreatment reduced significantly the incidence of ventricular fibrillation. It was concluded that chronic amiodarone pretreatment seemed to be more effective than the acute one.

Long term oral amiodarone treatment supresses both supraventricular and ventricular arrhythmias and this is believed to be related to drug-induced prolongation of refractoriness (Zipes et al 1984). On the basis of its unique pharmacological properties, including an extremely long half-life of about 30–45 days, Waxman (1985) suggested that there was little role for the intravenous form of amiodarone. Recently studies have demonstrated acute electrophysiological effects following amiodarone given intravenously which are still a matter of controversy (Bertholet et al 1983; Ikeda et al 1984; Mason et al 1984; Wellens et al 1984).

Other reports have suggested that intravenous amiodarone may be effective in terminating supraventricular and ventricular tachyarrhythmias (Patterson et al 1983; Mostow et al 1984). The present experiments were undertaken to compare the prophylactic antiarrhythmic efficacy of acute and chronic amiodarone pretreatment against the early phase of arrhythmias induced by coronary ligation in conscious rats.

Method

The method of Leprán et al (1983) was used. Young male rats, 200–250 g, were anaesthetized by ether inhalation.

After thoracotomy, a loose loop of thread was placed around the descending branch of the left coronary artery. The end of the loop was exteriorized through a polyethylene tube. Thereafter, the chest was closed. Artificial ventilation was not needed during the entire surgical maneouvre. The ends of the thread were hidden subcutaneously. Seven to ten days after that operation, the thread was exteriorized under light anaesthesia and the loop tightened, thereby producing acute myocardial ischaemia. ECG recordings were taken by a bipolar thoracic lead both before and continuously for 20 min after ligation (Medicor ER 362). The occurrence of several types of arrhythmias and the survival ratio were determined.

The post-ligation arrhythmias were categorized as ventricular extrasystole (single, double or triple premature beats), bradycardia (heart rate lower than 200 beats min^{-1}, typical signs of A-V block), ventricular fibrillation (very high frequency potentials with irregular amplitudes) as was suggested by Leprán et al (1983).

The hearts of animals which survived the first 24 h were stained by nitro-tetrazolium blue solution according to Leprán et al (1983). Thereby, we were able to demonstrate the infarction that developed. The cases (n = 5) where infarction did not appear were excluded from the evaluation as unsuccessful surgeries. Animals were given amiodarone HCl (Cordarone inj. Labaz) 50 mg kg^{-1} i.p. 30 min before the ligation in a volume of 1 ml kg^{-1} in the acute experiments and 50 mg kg^{-1} daily for 21 days by gavage in a volume of 1 ml kg^{-1} in chronic experiments. Control rats received physiological saline solution intraperitoneally. Statistical analysis of the results were with the χ^2 and Student's non-paired *t*-test.

Results

The results are summarized in Table 1. Both acute and chronic amiodarone pretreatment improved the survival during the early phase of arrhythmias. Between the second and 16th hour after the ligation 1 animal died in the control, two in the acute and one in the chronic amiodarone-pretreated group, due to late ventricular fibrillation (not shown in Table 1). Fatal bradyarrhythmia due to complete A-V block caused the death of 5 animals in the control group, 5 in the acute amiodarone-pretreated group and 6 in the chronic amiodarone-pretreated group. Arrhythmias developed in all animals within the first 20 min after the ligation. There was no significant difference in the occurrence of the less severe types of arrhythmia such as extrasystoles and ventricular tachycardia between the control and the acute and chronic amiodarone-pretreated groups. However, the incidence of the ventricular fibrillation was less in the acute and significantly less in the chronic amiodarone-pretreated groups than in the control group. It is worthwhile mentioning that after both types of amiodarone pretreatment the chance of survival from ventricular fibrillation improved compared with control animals.

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Table 1. Effect of acute and chronic amiodarone treatment in the early phase of arrhythmias induced by coronary ligation in conscious rats.

Groups	Number of animals	Survival (%)	Occurence of arrhythmias: Fatal bradycardia (%)	ES (%)	VT (%)	VF (%)	Survival rate of VF attacks (%)
Control	30	3/30 (10·0)	5/30 (16·7)	24/30 (80·0)	18/30 (60·0)	23/30 (76·7)	1/23 (4·3)
Acute amiodarone treatment 50 mg kg^{-1} i.p.	33	14/33* (42·7)	5/33 (15·1)	26/33 (78·6)	19/33 (57·6)	19/33 (57·6)	5/19 (26·3)
Chronic amiodarone treatment 50 mg kg^{-1} day^{-1} for 21 days orally	29	16/29* (55·2)	6/29 (20·7)	22/29 (75·9)	19/29 (65·5)	10/29* (34·5)	3/10 (30·0)

Key; ES, extrasystole; VT, ventricular tachycardia; VF, ventricular fibrillation.
* Asterisks denote statistically significant ($P < 0{\cdot}01$) differences from the control group, calculated by the χ^2 test.

Discussion

As shown in these experiments, both acute and chronic amiodarone pretreatments inhibited acute phase arrhythmias caused by coronary ligation in conscious rats. In our study the antiarrhythmic efficacy of amiodarone was comparable to that reported with lignocaine and pindolol in the same experimental procedure (Leprán et al 1983). As we have found, Patterson et al (1983) also found chronic amiodarone pretreatment more effective than acute amiodarone pretreatment in preventing sudden death caused by ventricular fibrillation in conscious dogs. The antiarrythmic action of amiodarone may be linked to its ability to prolong refractoriness after long term administration (Zipes et al 1984). The effect of acute amiodarone application on the refractoriness is still a matter of controversy (Mason et al 1984; Patterson et al 1983). Acute exposure of amiodarone causes use-dependent $\dot{V}_{max}$ depression, even after relatively low therapeutic concentrations, in guinea-pig papillary muscle and dog Purkinje fibres (Mason et al 1984; Varró et al 1985).

We used the commercial Cordarone injection which contained polysorbate (Tween) 80 solution in our experiment. Because it has been reported to increase the effective refractory period in in-vitro (Northover 1984) and in-vivo (Torres-Arraut et al 1984) experiments, but further studies are needed to evaluate the possible contribution of the solvent to the antiarrhythmic effect of the Cordarone injection.

Patterson et al (1983) found similar amiodarone concentrations in the plasma and in the right ventricular wall after acute and chronic pretreatment. However, the main metabolite, desethylamiodarone, was detected in plasma and in tissues only after long term amiodarone pretreatment. Recently, desethylamiodarone was reported to produce significant cardiac electrophysiological changes in rats (Nattel 1985). It is possible that desethylamiodarone is responsible for the augmented antiarrhythmic effect of chronic amiodarone pretreatment but other factors acting after long term amiodarone administration cannot be ruled out.

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