Effects of NS-2, a New Class 1 Antiarrhythmic Agent, and AFD-19, Its Active Metabolite, on Ventricular Arrhythmias Induced by Coronary Artery Occlusion and Reperfusion in Anesthetized Rats: Comparison with Disopyramide and Mexiletine

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ABSTRACT—We studied the antiarrhythmic effects of NS-2 (4-diisobutylamino-1,1-diphenyl-l-butanol maleate) and AFD-19 (active metabolite of NS-2) on early stage ventricular arrhythmias induced by coronary artery occlusion and reperfusion in anesthetized male rats. These effects were compared with those of disopyramide and mexiletine. Drugs were intravenously administered either before or after coronary occlusion. When administered 5 min before occlusion, 3 mg/kg of NS-2 and AFD-19 exhibited equivalent antiarrhythmic activity to that of 5 mg/kg of disopyramide and mexiletine, as assessed by reductions in the number of premature ventricular complexes and in the incidences of ventricular tachycardia and ventricular fibrillation. In a dose of 5 mg/kg, the antiarrhythmic effects of NS-2 and AFD-19 were more pronounced. When administered 5 min after coronary artery occlusion, only NS-2 and AFD-19 (in doses of 5 mg/kg) had significant antiarrhythmic effects. None of the drugs influenced the severe ventricular arrhythmias induced by reperfusion when administered 1 min before reperfusion. In conclusion, NS-2 might be effective in reducing the severity of the life-threatening ventricular arrhythmias that occur during acute myocardial infarction.

Keywords: Arrhythmia (ischemia-induced, reperfusion-induced), NS-2, AFD-19, Antiarrhythmic drug (class 1)

NS-2 (4-diisobutylamino-1,1-diphenyl-1-butanol maleate) is a novel class 1 antiarrhythmic agent and AFD-19 (4-isobutylamino-1,1-diphenyl-1-butanol maleate) is an active metabolite of NS-2. Although there seems little doubt that class 1 antiarrhythmic agents are effective against ectopic ventricular beats occurring several hours after onset of myocardial infarction in animal experiments (1), there is some controversy concerning their efficacy during the early phase of ventricular arrhythmias; i.e., those occurring during the first 30 min following coronary occlusion (2-8). This may reflect differences in underlying electrophysiological changes occurring at different stages of ischemia. The time of administration appears to be also important. In this study, the antiarrhythmic effects of NS-2 and AFD-19 were evaluated on the early stage ventricular arrhythmia induced by coronary artery occlusion and reperfusion in anesthetized rats, and their activity was compared with those of established class 1 drugs, disopyramide and mexiletine. We also evaluated the difference in the efficacy of each drug when administered either before or after the onset of ischemia and also on reperfusion arrhythmias when administered just prior to reperfusion.

MATERIALS AND METHODS

Male Sprague-Dawley rats (200-300 g) were anesthetized with 60 mg/kg sodium pentobarbitone administered intraperitoneally. The femoral vein was cannulated for drug administration, and the trachea was cannulated for artificial respiration. Systemic blood pressure was continuously monitored via a catheter inserted into the carotid artery. A standard limb lead I was continuously recorded, together with systemic blood pressure, on a Grass Model 7D recorder (Grass Instrument Co., Quincy, MA, USA). The chest was opened by a left thoracotomy, followed by
sectioning of the 4th and 5th ribs, approximately 2 mm to the left of the sternum (9). Artificial respiration was started immediately with room air, using a volume of 2 ml/100 g and a rate of 54 strokes/min in order to maintain arterial blood gases and pH within the normal range. After incising the pericardium, the heart was exteriorized using gentle pressure on the rib cage. A 6/0 braided silk suture attached to a 10-mm micropoint reverse cutting needle was placed under the coronary artery. The heart was replaced in the chest, and the rat was allowed to recover for 15 min. Rats that had arrhythmias during the recovery time and/or had a mean arterial blood pressure of less than 70 mmHg were discarded.

All experiments were performed in accordance with the Guidelines for Animal Experiments in Yamanashi Medical University.

**Studies to determine the effects of disopyramide, mexiletine, NS-2 and AFD-19 on occlusion-induced arrhythmias when administered before coronary occlusion**

Seventy-eight rats were used in this protocol. Rats were divided into 8 groups with 9–10 rats in each group. The rats received, by intravenous administration, either saline (n = 10, the vehicle for mexiletine), polyethylene glycol 200 (n = 9; the vehicle for disopyramide, NS-2 and AFD-19), disopyramide (5 mg/kg, n = 9), mexiletine (5 mg/kg, n = 10), NS-2 (either 3 or 5 mg/kg, n = 10 and 10) or AFD-19 (3 or 5 mg/kg, n = 10 and 10). The injection volume of each agent was adjusted to 0.5 ml with saline. Coronary ligation was commenced 5 min after drug administration, and the electrocardiogram and systemic arterial blood pressure were continuously recorded for 30 min after coronary ligation. Blood pressure and sinus rate were measured before injection; at 1 min, 3 min, 5 min after injection; and at 1 min, 5 min, 10 min, 15 min and 30 min after coronary artery occlusion.

**Studies to determine the effects of disopyramide, mexiletine, NS-2 and AFD-19 on occlusion-induced arrhythmias when administered after coronary occlusion**

Eighty-two rats were used in this protocol. Drugs and the doses were the same as above. The number of rats in each group was 10, except for group 1 (saline control) where 12 rats were used. Each drug was administered 5 min after coronary occlusion. The electrocardiogram and systemic arterial blood pressure were continuously recorded for 30 min after coronary occlusion. Blood pressure and sinus rate were estimated before occlusion and at 1 min and 5 min after occlusion (before injection), 6 min after occlusion (1 min after injection), 8 min after occlusion (3 min after injection), 10 min after occlusion (5 min after injection), 15 min after occlusion (10 min after injection) and 30 min after occlusion (25 min after injection).

**Studies to determine the effects of disopyramide, mexiletine, NS-2 and AFD-19 on reperfusion arrhythmia**

Both ends of the ligature placed under the left coronary artery were passed through a small plastic tube. Regional myocardial ischemia could be induced by pulling the suture and pressing the tube against the surface of the myocardium. The ischemia could be maintained for any desired period by clamping the tube and the suture. Reperfusion could be initiated by declamping and removing the tube.

We first evaluated the relationship between occlusion time (i.e., the duration of ischemia) and the severity of the arrhythmias resulting from reperfusion, and we ultimately used 6 min of occlusion time to determine the effects of each drug on reperfusion-induced arrhythmias. The doses of drugs were the same as above. Each drug was administered at 5 min after coronary occlusion (1 min before reperfusion). The electrocardiogram and systemic arterial blood pressure were recorded continuously for 20 min after reperfusion.

**Assessment of arrhythmias**

The total number of premature ventricular complexes (PVC), incidence of ventricular tachycardia (VT), incidence of ventricular fibrillation (VF) and mortality rate during 30 min after coronary occlusion in occlusion arrhythmias and during 20 min after reperfusion in reperfusion arrhythmias were assessed in comparison with a control group. VF is not necessarily a terminal event in this model.

The values are expressed as the mean ± standard error. Changes within each group were compared by the paired Student’s t-test, whereas differences between groups were assessed by the Mann-Whitney U-test. Changes in incidences of events were analyzed by Fisher’s exact probability test. Differences were regarded as significant if the P-values were less than 0.05.

All drugs were kindly supplied by Nippon Shinyaku Co., Ltd. (Kyoto).

**RESULTS**

**The effects of disopyramide, mexiletine, NS-2 and AFD-19 on occlusion arrhythmias when administered before coronary artery occlusion**

In this model, premature ventricular activity commences at 4 min after the onset of ischemia, with pronounced activity over the next 10 min (mainly as VT), and this is then followed by a period of arrhythmic silence with only a few ventricular complexes (Fig. 1). Effects of class 1 antiarrhythmic drugs on the ischemia-induced arrhythmias are summarized in Fig. 2. There were no significant differences between the arrhythmias in the saline...
control group and polyethylene glycol #200 (PEG #200) vehicle control group with respect to the total number of PVC, incidences of VT, incidences of Vf or in mortality rate (10% in the saline group, 33% in the polyethylene glycol group). The total numbers of PVC in the control groups were 1185 ± 158 beats (saline) and 1160 ± 163 beats (PEG #200). Although disopyramide and mexiletine decreased the total numbers of PVC to 632 ± 204 beats and 696 ± 226 beats, respectively, these differences were not significant. Even 3 mg/kg of NS-2 and AFD-19 significantly decreased the total numbers of PVC. A 5 mg/kg dose of NS-2 and AFD-19 was more effective. The total numbers of PVC were 682 ± 121 beats (NS-2, 3 mg/kg, P < 0.05 vs. control), 480 ± 164 beats (NS-2, 5 mg/kg, P < 0.01 vs. control), 503 ± 135 beats (AFD-19, 3 mg/kg, P < 0.01 vs. control) and 429 ± 111 beats (AFD-19, 5 mg/kg, P < 0.01 vs. control), respectively. VT was significantly suppressed by only 5 mg/kg of AFD-19 (40%, P < 0.01 vs. control 100%). Incidences of Vf were

**Fig. 1.** Distribution of ventricular arrhythmias following acute coronary occlusion in anesthetized rats. Note that arrhythmic activity commences between 4 min and 15 min after occlusion and that there is very little ectopic activity between 15 min and 30 min. Hatched bars indicate the number of PVC occurring as VT.

**Fig. 2.** The effects of disopyramide (DSP, 5 mg/kg), mexiletine (MXT, 5 mg/kg), NS-2 (3 and 5 mg/kg) and AFD-19 (3 and 5 mg/kg) on ventricular arrhythmias (number of premature ventricular complexes, incidences of VT (open bar) and Vf (closed bar)) when given 5 min prior to coronary artery occlusion in anesthetized rats. Polyethylene glycol #200 (PEG #200) was used as the vehicle for DSP, NS-2 and AFD-19. NS-2 and AFD-19 significantly decreased the number of PVC. Only AFD-19 significantly suppressed the occurrence of VT and Vf. NS-2 and AFD-19 are particularly effective in reducing ischemia-induced arrhythmias. The results are given as means ± standard error. *P < 0.05, **P < 0.01 vs. vehicle control.
60%, 56%, 10% (P < 0.05 vs. control), 10% (P < 0.05 vs. control), 10% (P < 0.05 vs. control), 20%, 0% (P < 0.01 vs. control) and 0% (P < 0.01 vs. control), respectively. AFD-19 was rather more effective than NS-2. Arrhythmic death was completely abolished by an antiarrhythmic drug.

Effects of disopyramide, mexiletine, NS-2 and AFD-19 on occlusion arrhythmias when administered after coronary occlusion

Figure 3 shows the effects of drugs administered after occlusion. In contrast to the pretreatment, antiarrhythmic effects were attenuated when drugs were administered after occlusion. Only 5 mg/kg of NS-2 and AFD-19 significantly decreased the total numbers of PVC. None of the drugs reduced the incidence of the more serious ventricular arrhythmias (VT, Vf) or mortality (mortality in the mexiletine group, 20% vs. saline control 20%; mortality in the disopyramide, NS-2 and AFD-19 group, 10–20% vs. PEG #200 control, 10%).

Hemodynamic effects of disopyramide, mexiletine, NS-2 and AFD-19 when administered before and after coronary artery occlusion

The results are summarized in Figs. 4 and 5. The vehicles slightly decreased the heart rate and increased the mean arterial blood pressure. When administered before coronary occlusion, disopyramide decreased the heart rate from $423 \pm 23$ to $334 \pm 15$ beats/min (P < 0.01) and increased the mean arterial blood pressure from $81 \pm 3$ to $105 \pm 7$ mmHg (P < 0.01), whereas mexiletine decreased the heart rate from $447 \pm 10$ to $365 \pm 14$ beats/min (P < 0.01), but did not affect the arterial blood pressure. NS-2 significantly decreased both the heart rate and the blood pressure in a dose-dependent manner, whereas AFD-19 decreased the heart rate from $467 \pm 14$ to $376 \pm 11$ beats/min (P < 0.01) at the dose of 3 mg/kg and from $433 \pm 16$ to $357 \pm 17$ beats/min (P < 0.01) at the dose of 5 mg/kg, but did not influence the blood pressure. The hemodynamic changes induced by coronary artery occlusion were similar in all groups; there was a slight increase in the heart rate and a significant decrease in the blood pressure with some recovery over the 30-min occlusion period.

The hemodynamic effects of drugs administered after coronary artery occlusion are summarized in Fig. 5. Disopyramide significantly reduced the heart rate from $443 \pm 23$ to $343 \pm 17$ beats/min (P < 0.01), but did not affect the mean blood pressure. Mexiletine significantly reduced both the heart rate from $461 \pm 23$ to $359 \pm 23$ beats/min (P < 0.01) and the mean blood pressure from $78 \pm 6$ to $62 \pm 4$ mmHg (P < 0.01). NS-2 and AFD-19
decreased the sinus rate and the mean blood pressure in a
dose-response manner. Compared with the hemodynamic
effects of drugs administered before occlusion, mexiletine
and AFD-19 decreased the mean blood pressure, and the
increase in blood pressure by disopyramide was attenuat-
ed, but decreases in the heart rate were accentuated.

Fig. 4. The effects of disopyramide (DSP, 5 mg/kg), mexiletine (MXT, 5 mg/kg), NS-2 (3 and 5 mg/kg) and AFD-19 (3 and 5
mg/kg) on heart rate (○) and mean arterial blood pressure (▲) when given 5 min prior to coronary artery occlusion. The effects
of the vehicles (saline and polyethylene glycol #200 (PEG #200)) are also given. The results are given as means±standard error.
*P<0.05, **P<0.01 vs. values of zero min.

Effects of disopyramide, mexiletine, NS-2 and AFD-19 on
reperfusion arrhythmias when administered 1 min prior
to the onset of reperfusion

The severity of reperfusion arrhythmias depends on the
duration of the preceding ischemic period (10, 11). Few ar-
rhythmias occur following periods of 1 or 3 min of ische-
mia, but there is pronounced ectopic activity with a high
incidence of Vf, most of it might be terminal, when the myocardium is reperfused following the 5-min occlusion periods (Table 1). The severity of arrhythmias following 6-min occlusion was similar.

None of the drugs significantly influenced the severity of reperfusion arrhythmias when administered 1 min prior to the onset of reperfusion (Table 2).

DISCUSSION

The results of the present study indicate that NS-2 and AFD-19 are rather more effective than the standard antiarrhythmic agents, disopyramide and mexiletine in suppressing ischemia-induced arrhythmia in anesthetized rats, particularly when they are administered before occlusion. All of drugs evaluated were much less effective if given after
Table 1. Reperfusion arrhythmias in anesthetized rats following occlusion times of 1, 3, 5 and 6 min

| Occlusion | No of PVC (beats) | Incidence of VT (%) | Incidence of Vf (%) | Mortality (%) |
|-----------|-------------------|---------------------|---------------------|--------------|
| 1 min (n=8) | 1 ± 1             | 0                   | 0                   | 0            |
| 3 min (n=17) | 10± 7             | 0                   | 0                   | 0            |
| 5 min (n=24) | 306±145           | 83                  | 71                  | 58           |
| 6 min (n=10) | 208± 50           | 100                 | 70                  | 50           |

Only following 5 and 6 min occlusion periods, reperfusion arrhythmias are severe. PVC: premature ventricular complex, VT: ventricular tachycardia, Vf: ventricular fibrillation.

Table 2. Reperfusion arrhythmias following 6 min coronary artery occlusion period in anesthetized rats

| n | Duration of VT/Vf (sec) | Incidence of Vf (%) | Mortality (%) |
|---|-------------------------|---------------------|--------------|
| Saline | 10 | 208±50 | 70 | 50 |
| PEG #200 | 8 | 234±41 | 75 | 63 |
| DSP | 5 mg/kg | 10 | 180±26 | 90 | 40 |
| MXT | 5 mg/kg | 9 | 163±27 | 100 | 10 |
| NS-2 | 3 mg/kg | 9 | 203±31 | 56 | 89 |
| NS-2 | 5 mg/kg | 8 | 144±33 | 63 | 88 |
| 5AFD-19 | 3 mg/kg | 8 | 159±28 | 100 | 75 |
| AFD-19 | 5 mg/kg | 7 | 125±22 | 100 | 71 |

Drugs and vehicles were administered 1 min prior to reperfusion (i.e., 5 min after onset of occlusion). There were no significant effects on reperfusion-induced arrhythmias. Abbreviations are the same as Table 1.

NS-2 and AFD-19 on Ventricular Arrhythmias

Table 1. Reperfusion arrhythmias in anesthetized rats following occlusion times of 1, 3, 5 and 6 min

Table 2. Reperfusion arrhythmias following 6 min coronary artery occlusion period in anesthetized rats

The onset of occlusion. Marshall et al. (8) reviewed the antiarrhythmic effects of sodium channel blocking agents on early phase arrhythmias induced by coronary artery occlusion in anesthetized rats and concluded that most sodium channel blocking agents, when administered prior to occlusion, suppress the number of PVC and reduce the incidences of VT. Winslow et al. (12) also reported that disopyramide administered 15 min prior to the onset of coronary occlusion suppressed the early phase arrhythmias induced by coronary artery occlusion in rats.

Antiarrhythmic agents effective under the ischemic condition are thought to act by altering the duration of the refractoriness, by modifying the conduction velocity and the degree of the inhomogeneity (13). From the experiments using normal guinea pig papillary muscles, Kojima and Ban (14) demonstrated that there are two phases in the recovery process of \( V_{\text{max}} \), the early recovery phase having a time constant of 10–30 msec and the late recovery phase with a time constant of 2–3 sec. The recovery time constants (2–3 sec) for AFD-19 and NS-2 were similar to that of procainamide (class 1a), greater than those of lidocaine and mexiletine (class 1b) and smaller than that of flecainide (class 1c). NS-2 is reported to have a high affinity for inactivated channels with an intermediate recovery time constant, whereas AFD-19 is suggested to have a higher affinity for open channels and an intermediate recovery time constant. When NS-2 is administered systemically, it would be expected to have a unique profile of antiarrhythmic activity with a combined effect on inactivated sodium channels (the parent compound) and on open sodium channels (the active metabolite). In spite of these apparent differences, the effects of NS-2, AFD-19, disopyramide and mexiletine on coronary artery occlusion-induced arrhythmias were almost the same. A decrease in conduction velocity may play the most important role in suppressing coronary occlusion-induced arrhythmias in rats. Early stage ventricular arrhythmia induced by myocardial ischemia is reported to be related to the extracellular potassium concentration (15), cyclic AMP (16) and prostaglandins (17). Mapping studies reveal that ischemia-induced arrhythmia in dogs might be induced by reentrant mechanisms and that the impulse travels through the ischemic area surrounding the infarcted area (13). The reentrant mechanism needs a dual pathway, unidirectional block, and conduction delay. Almost all class 1 antiarrhythmic agents decrease the conduction velocity and some of them have effects to elongate the action potential duration. So these agents might block one reentrant circuit, but might set up another reentrant circuit. When drugs are administered before occlusion, the distribution of drugs would be uniform. However, the tissue concentration of drugs administered after occlusion must be lower in the hypoperfused ischemic area than in normoperfusion area, especially in a species such as the rat which has a very poor coronary collateral circulation. This imbalance in the tissue distribution might intensify the electrical inhomogeneity that results from myocardial ischemia, and this may be the main reason why when the drugs are administered after occlusion, they are not effective against early ischemic arrhythmias; and, indeed, some aggravate them. Moreover, the administration of drugs after coronary occlusion usually lowers blood pressure, and hence presumably decreases coronary perfusion.

In the clinical situation, there are few opportunities to administer antiarrhythmic agents before the onset of myocardial infarction, although it has been recommended that lidocaine should be given as soon as a ventricular arrhythmia is documented after myocardial infarction (18). Many studies have confirmed the effectiveness of drugs in the treatment of arrhythmias in the coronary care unit; i.e., on the later stages of acute myocardial infarction, but there are few studies in the very early stages of acute myocardial infarction. There are several reasons for this.
The first reason is a high mortality rate in the first two hours after the onset of an acute coronary attack. The rate of mortality rapidly declines after then. The second reason is that acute myocardial infarction occurs in the large majority of patients outside of hospitals. Pantridge (19) reported that only 16% of patients reach the hospital within 4 hr of the onset of symptoms, a figure that has not been greatly improved upon over the succeeding 20 years.

Our results indicate that class I antiarrhythmic agents administered after coronary occlusion are less effective against early stage arrhythmias of myocardial infarction than those administered prior to occlusion in anesthetized rats. Moreover, the administration of drugs after occlusion lowered the blood pressure, which might result in a decrease in myocardial perfusion. They did not modify reperfusion-induced arrhythmias if given just prior to the onset of reperfusion. However, as described before, AFD-19 is an active metabolite of NS-2 and has different sodium channel blocking properties from those of NS-2. Therefore, NS-2 given orally before the onset of acute myocardial infarction is expected to be more effective. The combination therapy of different types of class I antiarrhythmic agents has already been reported to have a beneficial effect in a clinical study (20).

REFERENCES

1. Lazzara R, El-Sherif N, Hope RR and Scherlag BJ: Ventricular arrhythmias and electrophysiological consequences of myocardial ischemia and infarction. Circ Res 42, 740–749 (1978)
2. Han J, Goel BD, Yoon MS and Rodgers R: Effects of propranolol and lidocaine on ventricular automaticity and re-entry during acute coronary occlusion. Am J Cardiol 34, 171–178 (1974)
3. Allen JD, James RGG, Kelly JG, Shanks RG and Zaidi SA: Comparison of the effects of lignocaine and mexiletine on experimental ventricular arrhythmia. Postgrad Med J 53, 35–45 (1977)
4. Corr PB, Helke CJ and Gillies RA: Exacerbation of coronary occlusion-induced ventricular arrhythmias by the vagolytic effect of propranolol. Cardiovasc Res 8, 486–492 (1978)
5. Marshall RJ and Parratt JR: Prophylactic lignocaine and early post-coronary artery occlusion dysrrhythmias in anaesthetized greyhounds. Br J Pharmacol 71, 597–600 (1980)
6. Kane KA and Winslow E: Antidysrrhythmic and electrophysiological effects of a new antianginal agent, bepridil. J Cardiovasc Pharmacol 2, 193–203 (1980)
7. Marshall RJ, Muir AW and Winslow E: A comparison of the intensity and duration of the antidysrhythmic effect of mexiletine and Org 6001 in anesthetised rats. Br J Pharmacol 74, 381–388 (1981)
8. Marshall RJ and Winslow E: The effects of sodium channel inhibitors on early arrhythmias associated with acute myocardial ischaemia. In Early Arrhythmias Resulting from Myocardial Ischaemia, Edited by Parratt JR, pp 251–294, Macmillan, London (1982)
9. Clark C, Foreman MJ, Kane KA, McDonald FM and Parratt JR: Coronary artery ligation in anaesthetized rats as a method for the production of experimental dysrrhythmias and for the determination of infarct size. J Pharmacol Methods 3, 357–368 (1980)
10. Kane KA, Parratt JR and Williams FM: An investigation into the characteristics of reperfusion-induced arrhythmia in the anaesthetised rat and their susceptibility to drugs. Br J Pharmacol 82, 349–357 (1984)
11. Manning RJ and Hearse DJ: Reperfusion-induced arrhythmias: mechanisms and prevention. J Mol Cell Cardiol 16, 497–518 (1984)
12. Winslow E, Marshall RJ, Campbell JK and Muir AW: Effects of diet-induced hypokalaemia on the efficacy of antiarrhythmic drugs against ventricular arrhythmias evoked by coronary artery ligation in the anaesthetised rat. J Cardiovasc Pharmacol 9, 257–266 (1987)
13. Janse MJ, Capelle FJL, van Morsink H, Kleber AG, Wilms-Schopman F, Cardial R, Naumann d’Alvoncourt C and Durrer D: Flow of injury current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischaemia in isolated porcine and canine hearts. Circ Res 47, 151–165 (1980)
14. Kojima M and Ban T: Effects of AFD-21, a novel class I antiarrhythmic agent, and AFD-19, its active metabolite, on the maximum rate of rise of action potentials in guinea pig papillary muscles: Dependence on time, resting potential, and action potential duration. J Cardiovasc Pharmacol 13, 483–493 (1989)
15. Hirsch HJ, Franz CH, Bos L, Bissig R, Lang R and Schramm M: Myocardial extracellular K+ and H+ increase and noradrenaline release as a possible cause of early arrhythmias following acute coronary occlusion in pigs. J Mol Cell Cardiol 12, 579–593 (1980)
16. Podzuweit T, Els DJ and McCarthy J: Cyclic AMP mediated arrhythmias induced in the ischaemic pig heart. Basic Res Cardiol 76, 443–448 (1981)
17. Mest HJ, Blass KE and Forster W: Effects of arachidonic, linolenic and oleic acid on experimental arrhythmias in cats, rabbits and guinea pigs. Prostaglandins 14, 163–172 (1978)
18. Harrison DC: Should lidocaine be administered routinely to all patients after acute myocardial infarction. Circulation 58, 581–584 (1978)
19. Pantridge JF: Mobile coronary care. Chest 58, 229–234 (1970)
20. Duff JJ, Roden D, Primm PK, Oates JA and Wooley RL: Mexiletine in the treatment of resistant ventricular arrhythmias: Enhancement of efficacy and reduction of dose-related side effects by combination with quinidine. Circulation 67, 1124–1128 (1983)