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# SUPPRESSION BY ORALLY-ADMINISTERED NIFEDIPINE, NISOLDIPINE AND NILUDIPINE OF EARLY, LIFE-THREATENING VENTRICULAR ARRHYTHMIAS RESULTING FROM ACUTE MYOCARDIAL ISCHAEMIA

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The oral administration to rats of the calcium antagonists nifedipine, nisoldipine and niludipine (3 mg/kg, 1–1.25 h before acute coronary ligation) greatly reduced the duration of ventricular tachycardia and fibrillation (VF) occurring in the first 30 min post-ligation period. The duration of VF was especially reduced (by 74–92%). None of the animals so treated died compared with a 40% mortality in the controls.

**Introduction** There have been few published studies in which the possible antiarrhythmic effects of the so-called 'calcium antagonists' (calcium slow channel blocking drugs) have been examined early in myocardial ischaemia. Indeed, only the effects of verapamil have been examined against the early, potentially life-threatening, ventricular arrhythmias that result from acute coronary artery ligation. In the original study in dogs anaesthetized with pentobarbitone, Kaumann & Aramendia (1968) demonstrated that verapamil reduced the incidence of ventricular fibrillation from 10/11 in the controls to 1/10. Similar protection has also been observed in a more recent study by Elharrer, Gaum & Zipes (1977). We have recently described (Kane, McDonald & Parratt, 1981) the effectiveness of intravenous low-dose nifedipine against early postinfarction ventricular arrhythmias in anaesthetized rats; the present paper demonstrates that considerable protection is also observed when nifedipine or its structural analogues, niludipine (Kodama, Hirata, Toyama & Yamada, 1980) or nisoldipine (Kazda, Garthoff, Meyer, Schlossman, Stoepel, Towart, Vater & Wehinger, 1980) are administered orally 1–1.25 h before acute coronary artery ligation.

**Methods** Male Sprague-Dawley rats (250–350 g) were anaesthetized with pentobarbitone sodium (6 mg/100 g, intraperitoneally), catheters placed in the carotid artery (for pressure measurement) and in a femoral vein, and the electrocardiogram recorded by means of standard limb leads. The rats were subjected to coronary artery ligation as described in detail by Clark, Foreman, Kane, McDonald & Parratt (1980) and the early post-ligation arrhythmias assessed by counting the number of ventricular ectopic beats during the initial 30 min post-ligation period and by measuring the incidence and duration of both ventricular tachycardia (VT) and ventricular fibrillation (VF) as previously described (Clark *et al.*, 1980). Spontaneous defibrillation is common in this species during this early phase and there are very few arrhythmias between 30 min and 2 h post-ligation; late (post 2 h) arrhythmias were not assessed.

Nifedipine, niludipine and nisoldipine (generously provided by Dr S. Kazda, Bayer AG, Wuppertal) were dissolved in a mixture of ethanol (30%), polyethylene glycol 300 (5%), glycerol (5%) and distilled water; solutions were freshly prepared in the dark each day and kept protected from light. The drugs were administered in a dose of 3 mg/kg 1–1.25 h before ligation (i.e. 30–45 min before induction of anaesthesia) by means of a stomach tube; controls received an equivalent volume of the solvent.

**Results** There was a high incidence of ventricular ectopic beats in the solvent control group (Table 1), especially in the period between 11 and 25 min after coronary artery ligation. There were also prolonged periods of both VT and VF (Table 1) and a high mortality (40%). Ventricular fibrillation was the cause of death in all the animals that died during this early period. The animals pretreated with the calcium antagonists had a slightly reduced number of ventricular ectopic beats (Table 1) although this was only statistically significant with niludipine. The most marked reduction occurred in the 16–20 min post-ligation period. For example, there were $575 \pm 179$ ventricular ectopic beats in the control group during this period but only $58 \pm 3$, $70 \pm 42$ and $62 \pm 30$ ectopic beats in the same period in those rats pretreated with nifedipine, niludipine and nisoldipine, respectively. There was an even more marked suppression in the 20–30 min post-ligation period ($709 \pm 175$ ectopic beats in the controls but only $2 \pm 1$, $14 \pm 7$ and

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**Table 1** The effect of orally administered nifedipine, niludipine and nisoldipine on early ventricular arrhythmias resulting from acute coronary artery ligation in anaesthetized rats

| Group | Total ventricular ectopic beats | Duration(s) of Ventricular tachycardia | Duration(s) of Ventricular fibrillation | Incidence of VF (%) | Mortality (%) |
|---|---|---|---|---|---|
| Control (solvent) | 2883 ± 529 | 137 ± 27 | 82 ± 22 | 40 | 40 |
| Nifedipine | 1100 ± 344 | 57 ± 3* | 9 ± 5* | 25 | 0 |
| Niludipine | 888 ± 196* | 37 ± 13* | 6 ± 3* | 30 | 0 |
| Nisoldipine | 1762 ± 316 | 90 ± 30 | 21 ± 7* | 40 | 0 |

Values are mean ± s.e.mean. $n = 8-10$. *$P < 0.05$

16 ± 4 ectopic beats in the three treated groups: $P < 0.01$). There was no arrhythmias at all in the 26–30 min period in any of the treated groups compared to 260 ± 84 ectopic beats in the controls.

However, the most pronounced effect of the three compounds was suppression of the early and life-threatening ventricular arrhythmias (Table 1) and especially in duration of VF. Although VF still occurred in these animals, it lasted only a few seconds and rapidly reverted spontaneously to sinus rhythm. None of the animals treated with these compounds died, compared to a 40% mortality in the controls.

With the exception of nisoldipine, there were minimal effects on systemic arterial blood pressure (116 ± 9 mmHg systolic and 88 ± 9 mmHg diastolic in the controls and 100 ± 2 mmHg and 67 ± 5 mmHg in the nisoldipine group) and only nisoldipine significantly changed heart rate (442 ± 28 beats/min in the controls and 410 ± 23 beats/min after nisoldipine; $P < 0.05$). Both nifedipine and niludipine *increased* heart rate (to 526 ± 7 and 505 ± 7 beats/min respectively).

**Discussion** These results demonstrate, for the first time and in one species, the marked ability of three structurally related calcium slow-channel blocking drugs, when given by the oral route, to suppress the early and life-threatening ventricular arrhythmias that result from experimental acute myocardial ischaemia. The precise mechanism of this protective action is unclear but there appear to be two main and related possibilities: (i) Nifedipine abolishes abnormal automaticity in Purkinje fibres obtained from canine subendocardium 24 h after acute coronary artery ligation, as well as that induced in normal Purkinje fibres following exposure to barium chloride (Dangman & Hoffman, 1980). (ii) Nifedipine reduces the conduction delay which occurs within 5–10 min of the onset of acute myocardial ischaemia in dogs (Nakaya, Hattori & Kanno, 1980). This could result from a diminished degree of ischaemic injury as a result of increased blood flow, a 'sparing' effect on endogenous energy resources and/or a reduced intracellular sequestration of the metabolic byproducts of ischaemia.

These findings may have significant clinical consequences. One of the three agents (nifedipine) has been used for many years in the treatment of angina pectoris and has also been shown to reduce the severity of ischaemic changes following experimental myocardial infarction. The present studies suggest that this compound (as well as nisoldipine and especially niludipine) might have the additional pharmacological property of reducing the severity of the early life-threatening ventricular arrhythmias which might result from myocardial infarction. These studies suggest that such compounds might merit clinical trial, to investigate whether, if given to patients after a first myocardial infarction, they might reduce the likelihood of sudden cardiac death occurring after a subsequent infarction.

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