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Reduction of mortality by sulphinpyrazone after experimental myocardial infarction in the rat

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In the Anturan Reinfarction Trial (ART 1978), reinfarctions and, expecially, sudden cardiac deaths were less frequent among patients treated with sulphinpyrazone than among those receiving placebo medication. There is wide, general interest in elucidating the mechanism by which sulphinpyrazone brings about these protective effects. Although they are presumed to be in some way related to its platelet-stabilizing action, conclusive evidence is lacking and exactly how the two phenomena are linked is still very much a matter of conjecture. Various research groups have therefore investigated the effects of sulphinpyrazone on the course of events following acute experimental myocardial infarction in animals. In their initial studies, Kelliher et al and Povalski et al (in press) and Moschos et al (1979) found that the early arrhythmias (ventricular fibrillation, ventricular tachycardia and ventricular extrasystoles) occurring subsequent to coronary occlusions in cats and dogs were less frequent if the animals had been pretreated with sulphinpyrazone. We have studied the effects of the drug on mortality after ligation of the left anterior descending coronary artery (LAD) in the rat.

The operation was performed according to Selye et al (1960) in male rats (Tierfarm Sisseln), 222 ± 2 g, anaesthetized with ether. Essentially, this technique consists in ligating the LAD between the left auricle and the pulmonary cone. If the operation is completed within 30 s, spontaneous respiration recommences after air has been expelled from the thorax by gentle lateral pressure and the wound closed.

A few animals died as a result of haemorrhage during or shortly after the operation. In the present series of experiments, there were four deaths in the sulphinpyrazone group and two among the controls. These animals were not included in the evaluation of the results.

Sulphinpyrazone was administered for three days in a dose of 30 mg kg^{-1} s.c. twice daily, mornings and evenings. The controls received 0·9% NaCl (saline). LAD ligature was performed on the second day of treatment, that is between 1–6 h after the third sulphinpyrazone dose. No attempt was made to relate subsequent mortality with the exact time, after the last dose, of coronary artery ligation. After surgery, i.e. excluding the animals that died during the operation, the sulphinpyrazone group numbered 91 rats and the control group 103. These were composed of 12 separate control and sulphinpyrazone-treated groups with 5–11 rats in each.

The post operative mortality was followed up in both groups over a period of 21 days. In computing the mortality rates, a distinction was drawn between deaths within 30 min of the operation and later deaths. This was done because, according to previous findings (Kane et al 1979; Kenedi & Losonci 1973), deaths occurring in the first half hour are predominantly due to arrhythmias, whereas, in our own experience, the main causes of subsequent deaths are pulmonary oedema, hydrothorax or massive infarctions with dilatation of the heart. During the observation period, mortalities were recorded daily; autopsies were performed on the animals that died later than 30 min after operation.

The surviving animals were killed on the 21st day. The hearts were removed, the atria and the right ventricles dissected at the septal junction, and the creatinine phosphokinase (CPK) contents of the left ventricles determined according to Kjekshus & Sobel (1970). The magnitude of the infarcts was estimated from the amounts of CPK released. Allowance for changes in enzyme content due to the surgical trauma were made on the basis of the contents found in the left ventricles of 24 sham-operated rats (exposure of the heart without LAD ligation). In addition, 22 large large infarcts were excised and the CPK contents of this tissue determined.

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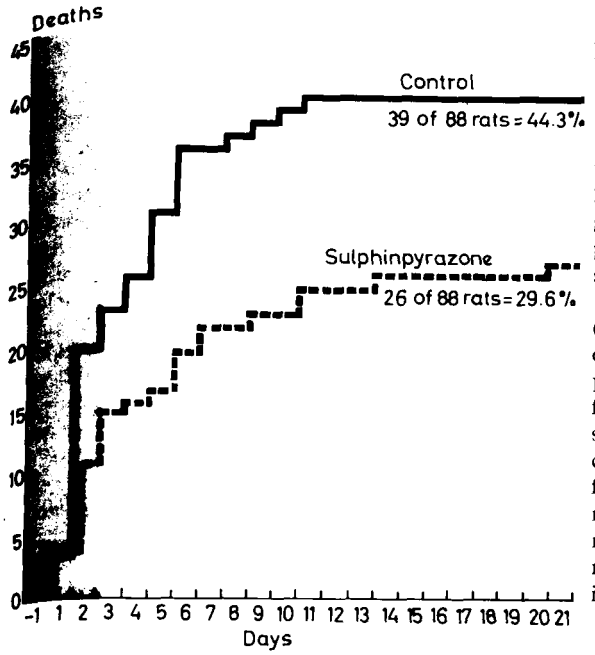

FIG. 1. Mortality rate in rats 30 min to 21 days after ligation of the LAD. Sulphinpyrazone was given for three days at a dose level of 30 mg kg^{-1} s.c. twice daily (shaded area).

The data were analysed statistically on a Hewlett-Packard Model 2100-B desk calculator. Significances were tested by the one-tailed CHI^2-test of Student's *t*-test.

During the first 30 min after LAD ligation, 15 of 103 (14·6%) rats in the control group and 3 of 91 (3·3%) in the sulphinpyrazone group died. The difference was statistically significant ($P < 0.01$).

The mortality rates recorded between 30 min and 21 days after the operation are shown in Fig. 1. Of the 88 animals in each group that had survived the first half hour, 39 controls (44·3%) and 26 in the sulphinpyrazone group (29·6%) died during this period ($P < 0.05$). Up to the sixth day after LAD ligation, or for about five days after the withdrawal of treatment, distinctly fewer deaths occurred in the sulphinpyrazone group than among the controls. From then on until the 21st day, mortality was low in both groups, and there was no statistically significant difference between them.

The mean magnitude of the infarct estimated from the amount of CPK release corresponded to 49·3 ± 2·0% of the mass of the left ventricle in the control group (n = 49) and to 45·2 ± 2·0% in the sulphinpyrazone group (n = 62). The difference was not statistically significant.

In keeping with the findings made in cats and dogs (Kelliher et al; Povalski et al in the press; Moschos et al 1979), the lower early mortality rate after sulphinparazone treatment was presumably due to the less frequent occurrence of ventricular fibrillation, though special ECG studies would have to be performed to confirm this assumption. No explanation can be given for the lower subsequent mortality. It was certainly not due to less extensive damage to the contractile myocardial tissue, and the overall effects have certain resemblances to the effects of sulphinpyrazone observed in the ART study in post-infarction patients.

We thank Mr. W. Vesely for his skilled technical assistance.

February 15, 1980

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