EFFECT OF BENZIODARONE ON MYOCARDIAL BLOOD FLOW IN RABBIT

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In the search for an effective coronary vasodilator a benzofuran derivative has been favourably reported on by Charlier (1961). This drug, benziodarone (2-ethyl-3-(4-hydroxy-3:5-di-iodobenzoyl)coumarone); "cardivix," "amplivix"), has been studied in the isolated heart preparation and in the intact dog. Charlier reported that the drug produced an increased coronary blood flow without a change in systemic blood-pressure and so appeared to act specifically on the coronary vessels. It was also shown that benziodarone could, in the dog, cause a regression of the E.C.G. changes following anoxia and could also favourably influence the E.C.G. after acute coronary occlusion. Clinical reports of the effectiveness of benziodarone have also been favourable (Gillot, 1959; Bekaert and Aubert, 1961). The drug has not yet been assessed in this country, however, and we now report the effect of benziodarone on myocardial blood flow in the normal rabbit and also in rabbits with experimental atheroma.

Methods

Rabbits of about 2.5 kg. were anaesthetized with 25% urethane (5 ml. intravenously) and pentobarbitone sodium (as required). Myocardial blood flow was measured by the technique of internal calorimetry (Grayson and Mendel, 1961), and is similar to that used in the myocardium by Lange (1959). Internal calorimetry depends upon the principle that if heat is supplied to a tissue from an external source the resulting temperature of the tissue will depend upon its blood flow. Thus if the blood flow is large the heat will be conducted away rapidly and the rise in tissue temperature will be small; if the blood flow is small a greater rise in tissue temperature will result. In internal calorimetry a combined heater and thermocouple (0.5 mm. wide by 10 mm. long) is embedded in the myocardium. Current is supplied to the heating element in a cyclic fashion as follows: 0.200 amp² for 24 seconds (lower equilibrium); 0.600 amp² for 17 seconds; 0.315 amp² for 24 seconds (upper equilibrium); no current for 17 seconds. This cycle, lasting 82 seconds, is continuously repeated.

The resulting temperature of the myocardium, in relation to a reference "cold junction" in the aorta, is recorded on a Cambridge four-channel recorder. The difference in temperature between the upper and lower equilibria forms the basis of measurement and can be made at intervals of 82 seconds. If the difference between the lower and upper equilibria increases, a drop in flow has resulted, and if it decreases a rise in flow has resulted. Since the measurement is essentially that of thermal conductivity, changes in flow are expressed as thermal conductivity ($\delta k \times 10^{-4}$) in relation to that of tissue with no blood flow. Blood-pressure was measured from a femoral artery by means of a capacitance manometer and recorded on the Cambridge four-channel recorder. Electrocardiograms were recorded on an Ediswan pen oscillograph, using lead II. Injections were given into a femoral vein. Experimental atheroma was produced by adding cholesterol (2 g. daily) to the normal diet of young rabbits for six months.

Results in Normal Rabbits

Effect of a Single Injection of Benziodarone.—A typical result (Fig. 1A) shows the effect of a single intravenous injection of benziodarone (5 mg./kg.) on myocardial blood

flow and mean systemic blood-pressure. Resistance to flow (R) is derived from the expression $R = B.P. / \delta k$ (pressure/flow). It can be seen that there was a rapid and marked increase in flow followed by a slow decline to initial levels within 10 minutes. Blood-pressure showed a small increase but resistance to flow showed a sharp fall. Similar increases of blood flow and falls in calculated resistance were obtained in six experiments. In all experiments the main increase in myocardial flow lasted from 5 to 30

FIG. 1.—Effect on myocardial blood-flow, blood-pressure, and resistance of: A, Single injection of benziodarone. B, Infusion of glyceryl trinitrate.

minutes (average 20), but in some experiments a small increase over the initial flow persisted for much longer (up to 90 minutes). Mean systemic blood-pressure was not changed by more than 10 mm. Hg, and calculations of coronary resistance always showed a decrease. The heart rate was not affected.

This response is contrasted (Fig. 1B) with that due to an infusion of glyceryl trinitrate (15 μ g./kg./m.) in the same animal. At first there was a small rise in flow which decreased during the period of infusion to the pre-infusion level, the blood-pressure showed a marked fall, and there was a fall in resistance which returned to initial levels by the end of the infusion.

Effect of Acute Coronary Ligation.—In the artificially ventilated rabbit with open chest and heart freed from the pericardium it was not found possible to obtain a consistent E.C.G. pattern. After ligation of the left anterior descending coronary artery the extent of S-T deflection from isoelectric levels again varied with respiration. The E.C.G. pattern, moreover, could in different animals be similar to that seen in either posterior or anterior infarction, a difference that can be explained by the position of the heart in this preparation. When benziodarone was given at intervals after coronary occlusion, there was no clear difference in the time taken for the S-T deflection to return to near isoelectric levels from controls.

Results of Experiments on Atherosclerotic Animals

The effect of a single injection of benziodarone (5 mg./kg.) was investigated in six animals with experimental

atheroma. The blood cholesterol of the animals used was in the region of 500 mg./100 ml., compared with control levels of 80–120 mg./100 ml. Results were considered only in those animals which showed obvious macroscopic atherosclerosis in the aorta. A typical result is shown in Fig. 2. It can be seen that in spite of marked atherosclerosis the response to a single injection of benziodarone was similar to that obtained in normal animals, an increase in blood flow with a decrease in resistance and little change in blood-pressure being recorded in all six experiments.

FIG. 2.—Effect of single injection of benziodarone on myocardial blood-flow, blood-pressure, and resistance in a rabbit with experimental atheroma.

Discussion

Benziodarone has been shown to increase blood flow in the myocardium of the intact rabbit. The major increase in flow took place within 10 minutes, but slight increases above basal flow were noted in some animals for as long as 90 minutes. The systemic blood-pressure, by contrast with glyceryl trinitrate, showed only small changes, which suggests that the drug exerts a specific coronary vasodilator action in the doses used (5 mg./kg intravenously). The reason for such specificity is not clear, but it is not due to increased tissue oxidation in the myocardium (Charlier, 1961). We were unable to confirm in the rabbit the observations of Charlier that benziodarone favourably affects the E.C.G. changes after coronary artery ligation.

Many drugs which dilate coronary vessels have proved disappointing in clinical practice. One of the reasons may be that most drugs are examined on "normal" coronary vessels. In the present work we have used animals known to have atherosclerosis involving the coronary vessels and it was clear that benziodarone produced an increase in myocardial blood flow similar to that in normal rabbits. The correlation between animals with induced atherosclerosis and human disease must be viewed with care. There is certainly a difference in both the composition and the quantity of lipids in the plasma of normal humans and normal rabbits, but the plasma lipid pattern in atherosclerotic rabbits tends to become more like that found in human disease (Gofman *et al.*, 1950). There are also differences in extent and distribution of the pathological changes, for in the rabbit the atherosclerosis is more widespread.

Since the drug appears to have a specific dilator effect on the coronary vessels, and is able to induce coronary dilata-

tion in rabbits with experimental atherosclerosis, the results of clinical trials in this country should be of interest.

Summary

The effect of benziodarone on myocardial blood flow has been investigated, by means of a heated thermocouple technique, in normal rabbits and in rabbits with experimental atheroma. Intravenous benziodarone increased myocardial blood flow in both groups, without an effect on blood-pressure or heart rate. The main increase in myocardial blood flow lasted about 20 minutes, but smaller increases were found for longer periods. Benziodarone did not affect the E.C.G. pattern after ligation of a coronary artery.

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DOUBLE-BLIND TRIAL OF BENZIODARONE IN ANGINA PECTORIS

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Ideally any vasodilator drug used in the treatment of angina pectoris should have a powerful specific dilator action on the coronary arteries and should not increase the work of the myocardium disproportionately to the increase in coronary flow.

Of a series of more than 300 benzofuran derivatives tested on dogs and rabbits by Charlier and his associates (Deltour *et al.*, 1961), benziodarone (2-ethyl-3-(4-hydroxy-3:5-di-iodo-benzoyl)coumarone; "cardivix"; "amplivix") was found to be the most active coronary vasodilator. It fulfilled the above desiderata for such a drug and therefore has been studied in angina pectoris. The main work has been that of Gillot (1959), who observed a good effect in 77% of 180 subjects treated with benziodarone in an average dose of 300 to 400 mg. daily. Similar very favourable results have been reported by Dailheu-Geoffroy and Nataf (1961). Five double-blind trials have been published (Bekaert and Aubert, 1961; Vastesaeger, Rochet, and Leloup, 1961; Bredmose, 1962; Johnsen, 1962; Kloster, 1962), but with varying results.

In view of these findings we now report a double-blind trial of benziodarone against an inert control substance.