Pharmacology of Anti-Anginal Agents

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For me, 1967 is a double centennial year; it commemorates both the year of Canadian Federation and the first use of nitrites for angina pectoris. It was in 1867 that Lauder Brunton published his paper in the Lancet on the use of “Nitrite of Amyl for Angina Pectoris” (Brunton, 1867). For me, 1967 is a double centennial year; it commemorates both the year of Canadian Federation and the first use of nitrites for angina pectoris. It was in 1867 that Lauder Brunton published his paper in the Lancet on the use of “Nitrite of Amyl for Angina Pectoris” (Brunton, 1867). It is sad to reflect that apart from this one lucky break this is really the only significant progress we have made in the medical treatment of angina pectoris in the last hundred years. The reason for this lack of progress is that we did not understand why nitrites were so beneficial and, consequently, we supplied explanations which were incorrect. Having done that, we subsequently have tried to produce better drugs with the same presumed action. When Brunton wrote his paper he deduced that the pain of angina was related to an elevation of blood pressure. He knew that nitrite of amyl could produce prostration and a thin thready pulse, and he thought it probably worked by lowering the blood pressure. For some time thereafter other drugs that were supposed to lower blood pressure were given therapeutic trial. Then, it was discovered that injection of nitrates into the coronary artery of an animal caused an increase in coronary flow. From this time on it was assumed that nitrates relieved angina pectoris by increasing coronary flow. It is for this reason that, if you want to look up anti-anginal drugs in any contemporary textbook, you must look them up under the title of “Coronary Vasodilator Drugs.”

For the last 40 years or so manufacturers have continued to produce more potent vasodilator drugs as judged by their ability to increase coronary flow in the normal heart. Unfortunately none of them has worked. The drug that drew my attention to this dilemma is one of the most potent of these preparations, dipyridamole (Persantine). While nitroglycerin produces only a small increase in coronary flow, lasting from 30 seconds to 1 minute, dipyridamole, given in a reasonable dose intravenously or by mouth, may double coronary flow for 20 to 30 minutes. It will do this without increasing myocardial oxygen consumption, so that the whole myocardium and the coronary sinus blood oxygen content increase proportionately. This ought to be beneficial if increasing coronary flow is going to relieve angina, and for this reason we carried out a careful clinical trial of this agent (Kinsella, Troup, and McGregor, 1962). We could find no therapeutic effect at all. Following this experience we decided to pause and try to review the pathophysiology of angina and to consider in what ways it might theoretically be influenced by therapy.

Pathologic Physiology of Angina Pectoris

Firstly, we now know that angina pectoris is not just a sensation of pain and discomfort. It is a syndrome which includes not only pain, but also electrocardiographic changes, a shift to anaerobic me-
TABOLISM WITH PRODUCTION OF LACTATE AND ACUTE LEFT VENTRICULAR FAILURE, WHEN THE INVOLVED MUSCLE MASS IS LARGE ENOUGH. WE ALSO KNOW THAT THIS SYNDROME OCCURS WHENEVER THERE IS A DISCREPANCY BETWEEN THE DEMAND FOR MYOCARDIAL OXYGEN AND ITS SUPPLY. THIS DISCREPANCY MAY, THEREFORE, BE CORRECTABLE BY REDUCING OXYGEN CONSUMPTION OR BY INCREASING OXYGEN SUPPLY.

NORMAL OXYGEN SUPPLY DEMANDS FULLY OXYGENATED BLOOD AND NORMAL HEMOGLOBIN. WHEN THE ANGINAL PATIENT SUDDENLY GETS WORSE IT MUST NOT NECESSARILY BE CONCLUDED THAT ONE OF HIS CORONARY ARTERIES HAS BECOME OCCLUDED, THOUGH THIS MAY OF COURSE BE OCCURRING. IT COULD WELL BE THAT HIS HEMOGLOBIN HAS DROPPED DUE, E.G., TO BLEEDING PILES OR A PEPTIC ULCER. ALTERNATIVELY HE MAY HAVE BECOME ANOXEMIC DUE TO PULMONARY EMBOLISM OR PNEUMONIA; OR HE MAY HAVE INACTIVATED UP TO 20% OF HIS HEMOGLOBIN BY SMOKING EXCESSIVELY. LIKewise, HIS CORONARY FLOW MAY BE VERY DEPENDENT ON AN ADEQUATE ARTERIAL PRESSURE. Thus angina may be precipitated in the hypertensive patient with coronary disease by the successful treatment of hypertension. Whenever angina becomes exacerbated, these possibilities should be considered first.

The discrepancy between oxygen supply and demand can also be influenced, of course, by changes in myocardial oxygen consumption. Dr. Richardson (Dr. David W., an earlier speaker at the symposium) has been telling us that the amount of tension developed by the muscle fiber and the rate with which it is developed are the two critical determinants of oxygen consumption. However, the tension developed is influenced by two major variables. One is the amount of pressure developed in the ventricular chamber, and the other is the ventricular volume. According to the relationship between tension, pressure, and radius described by Laplace, the tension necessary for each fiber to develop a certain pressure will increase with the radius of curvature of the ventricle. A small ventricle can thus produce the same pressure with a smaller wall tension. It is more efficient. All other things being equal then, one might expect angina to be exacerbated by ventricular enlargement and improved by reduction in ventricular size. Fear or emotion causing increased sympatho-adrenal activity will increase both the force of contraction, the rate of development of tension, and the heart rate. These are good reasons why the blocking agent Propranolol, referred to earlier in this symposium, ought to raise the anginal threshold. The disappointing thing is how relatively poorly does work, and I think, used at random in an anginal population, this drug is probably going to have more dangers than benefits. There are people, however, such as the thyrotoxic and the patient who gets pain associated with emotion, in whom I suspect this drug will prove to be extremely beneficial.

Mechanism of Action of Nitrites

Let us now consider the possible mechanism of action of the nitrite drugs, because these are the only really useful group of drugs available to us. First of all, it is clear that they do not just act by relieving pain. They are capable of lowering ventricular end-diastolic pressure, of abolishing the lactate production in the myocardium, and of abolishing the electrocardiographic changes of angina. The question is how they achieve this effect. Theoretically, they might either decrease myocardial oxygen consumption, or increase oxygen supply, or do both at once.

The prime effect of the nitrites is on vascular smooth muscle, and they cause an increase in large vessel diameter with veno-dilatation. When administered to a resting subject or to an anesthetized animal there is a fall in venous pressure, venous return to the heart, ventricular volume, cardiac output, and blood pressure. As we have seen, these effects should reduce myocardial oxygen consumption and may well explain the relief obtained by this drug in the resting subject. However, nitroglycerin will also produce relief in the exercising subject, and it is unlikely that the same mechanisms operate. For example, we have found that when patients are cycling on an ergometer a nitroglycerin tablet may actually increase the cardiac output, and the hypotensive effect of the drug is almost completely abolished (Hoeschen et al., 1966). Thus we have turned again to the possibility that nitrites may indeed exert their effect by changing coronary flow.

Now I would like to distinguish carefully between increasing coronary flow in a normal heart and redistributing flow to the most ischemic areas of a chronically diseased heart. On consideration it would seem that the very last drug that you would choose to relieve angina pectoris is one which increases coronary flow in the normal heart. There is already present an extraordinarily effective mechanism which will increase or reduce coronary flow according to the local metabolic need, and as far as we can see it is geared very closely to oxygen tension. Any substance which increases coronary flow in the normal heart must do so by interfering with this autoregulatory mechanism, and it has been shown that this mechanism is completely paralyzed following a dose of a potent vasodilator drug such as dipyridamole (Fam and McGregor, 1967). This cannot be beneficial if local hypoxia is already causing maximum flow to the most ischemic areas of heart muscle. Indeed, in the presence of coronary narrowing it might even have an adverse effect by increasing flow to non-ischemic areas of heart muscle.

In atherosclerotic coronary disease it is the large coronary vessels
which are narrowed. Studies which Dr. W. Fam and I are carrying out at present indicate that these vessels take no part in autoregulation. Thus to increase flow through them it is necessary to use a vasodilator substance which will act at this site in the coronary tree. It may well be that the diseased vessels themselves are incapable of vasodilatation, but as you well know the ischemic areas of muscle may be partly or wholly supplied by collateral vessels arising from healthy neighbouring coronary arteries. A drug which acts on these arteries may be expected to increase flow into the ischemic areas of the heart through collateral channels. It is probably significant that this is precisely the site of action of nitroglycerin.

Angiographic observation tells us that a nitroglycerin tablet will increase the size of all the larger coronary arteries for several minutes, and we have found that the effect of nitroglycerin is almost completely confined to the larger vessels (McGregor and Fam, 1966). Furthermore, when a coronary branch of a dog is gradually narrowed, thus creating obstruction, nitroglycerin can be shown to augment the collateral flow into the ischemic area. Dipyridamole, which acts principally on the small coronary vessels does not have this effect (Fam and McGregor, 1964).

Conclusion

In conclusion I would like to stress that these observations do not constitute direct evidence of the mechanism whereby the nitrites relieve angina pectoris. It is probable that they are capable of causing some reduction of myocardial oxygen consumption. However, there is increasing indirect evidence which suggests that the site of action of these drugs is principally on the large coronary arteries. Their administration may thus relieve coronary spasm, if this ever causes angina, and more importantly will increase collateral flow into ischemic areas of myocardium when collateral channels have become enlarged. Drugs such as dipyridamole which seem to act on the small vessels, which are the site of autoregulation, are unlikely to have this effect. Indeed, if the autoregulatory mechanism is necessary to direct a limited blood flow to the most ischemic areas of myocardium, such drugs may theoretically be harmful.

References


