CURRENT SURVEY

Anti-anginal drugs

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Summary

This review of studies on anti-anginal agents and their use in the anginal syndrome shows nitroglycerin to be unsurpassed in clinical effectiveness. It has a rapid onset of action. Its duration of action is relatively short but the need for a more prolonged effect has not been demonstrated. Most anginal attacks subside upon resting and the requirement for relief is immediate rather than prolonged. A long-acting anti-anginal agent would have some value if it could prevent precipitation of an anginal episode but there is no convincing evidence to indicate that these drugs have this capability. In general, clinical experience with long-acting nitrites is relatively unsatisfactory.

ANGINA pectoris is a clinical entity characterized by a constricting pain in the chest, often radiating from the precordium to the left shoulder and down the left arm. This pain, usually associated with effort, results from failure of the vascular system to provide an adequate blood supply to the myocardium under periods of increased oxygen demands. Angina can be precipitated by various factors such as physical exertion, emotional stress, heavy meals or, in severe cases, merely by assuming routine procedures, such as shaving and dressing.

Treatment of the anginal syndrome follows two basic courses: immediate relief and prevention. Various drugs have been used to relieve acute attacks and others have been used prophylactically to prevent anginal episodes. The pharmacological action of these anti-anginal drugs is thought by many to be vasodilation of the coronary arteries. Other investigators believe that these drugs act by lessening the work of the heart or by reducing the oxygen requirements of the myocardium. There is evidence to suggest that the latter is the mechanism

of action of nitroglycerin. In normal patients nitroglycerin increases coronary blood flow by dilating the arteries but in patients with angina, coronary blood flow is not increased (Freidberg, 1967). This has been used by some investigators (Bing *et al.*, 1964, in particular) as a test for coronary arterial disease.

For the relief of the acute anginal attack, the standard treatment is the immediate sublingual administration of nitroglycerin; it has an onset of action of 1-2 min. Other sublingual dosage form drugs have been introduced that promise relief equal to nitroglycerin but with a longer duration of action. However, their onset of action is not as prompt as nitroglycerin. These drugs include isosorbide dinitrate (Isordil, Sorbitrate), erythrityl tetranitrate (Cardilate) and trolnitrate phosphate (Metamine). The duration of action of these drugs is approximately four times that of nitroglycerin but this should not be construed as a *significant* advantage. The duration of most anginal attacks is a matter of minutes—not hours. Seldom, if ever, does the pain attributed to the anginal episode last longer than 30 minutes (Burge, 1967). The duration of action of nitroglycerin is approximately 5-30 min (Russek, 1966) and is of sufficient length to provide adequate relief from an anginal episode. The requirements for treatment of an acute anginal attack, therefore, are immediate rather than prolonged action. Although the newer sublingual nitrites¹ have been shown effective for the immediate relief of an anginal attack they are more expensive and have not proven superior to nitroglycerin. In addition, none of the newer sublingual nitrites has an onset of action as short as that of nitroglycerin.

Treatment after onset of an anginal attack,

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¹ Nitrites is a common designation that connotes all organic nitrates whose pharmacological properties are similar to those of the inorganic and organic nitrites.

though effective, does have a drawback in that the patient experiences the attack before treatment is instituted. It has been found that nitroglycerin is effective prophylactically by instructing the patient to take one tablet sublingually 5–10 min prior to an anticipated stress period. This procedure is, of course, limited to those patients who can anticipate stress periods. When nitroglycerin is used *regularly* throughout the day to prevent attacks, it is usually ineffective (Modell, 1966).

Despite the satisfactory results obtained from these short-acting anti-anginal agents, there remains a need for a long-acting drug which could prevent or decrease the frequency of the anginal attack. To fulfil this need, the long acting organic nitrites were introduced. The oral¹ administration of pentaerythritol tetranitrate (Peritrate, Mycardol, Pentral), isosorbide dinitrate (Isordil, Sorbitrate, Vascardin), erythryl tetranitrate (Cardilate), trolnitrate (Metamine), mannitol hexanitrate (Nitranitol) and nitroglycerin (Nitroglyn, Nitrobid, Nitrospan) reportedly provided a prolonged effect. These products were initially received enthusiastically but as they came into greater use they did not measure up to expectations and their value became questionable.

Lack of confidence in this class of drugs has been expressed by various investigators. Nickerson (1965) states: 'This lack of confidence is amply justified by the results of studies that appear to be adequately controlled and allow statistical evaluation of the results. These have almost uniformly shown the long term prophylactic value of an organic nitrate not to differ significantly from that of a placebo.' Nickerson cites Oram & Sowton (1961) and Sandler (1961) to support his argument. Although some studies show favourable results, it should be pointed out that studies which do not use a complete double-blind comparison with an appropriate placebo often can be misleading.

The importance of adequately controlled double-blind studies has been stressed by Charlier (1961) who reviewed studies on triethanolamine trinitrate (Metamine). 'As usual, the first studies, conducted with neither placebo nor double-blind system, were particularly favorable . . . The clinicians whose observations were satisfactorily controlled by use of a placebo and the double-blind technique found that the beneficial subjective effects produced by Metamine were moderate . . . and for Cole *et al.* they were not superior to those given by the placebo (1961).' From the results of well-controlled clinical studies of Metamine, the majority of cardiologists are of the opinion that the slight effects it provides are not sufficient to justify its use.

¹ Oral administration refers to dosage forms which are intended to be swallowed and does not include those intended for sublingual administration.

The most widely used oral anti-anginal drug, pentaerythritol tetranitrate, has been the subject of numerous studies. They arrive at conflicting conclusions on the drug's efficacy. Cole, Kay & Griffith (1957) and Dewar, Horler & Newell (1959) who used the double-blind procedure in evaluating the drug did not consider pentaerythritol tetranitrate superior to placebo. Russek (1966), in a double-blind study, found pentaerythritol tetranitrate produced a significant increase in exercise tolerance when administered before meals. On the other hand, Kalmanson *et al.* (1955) in their double-blind study failed to demonstrate any beneficial effect of this drug on angina pectoris.

Other types of drugs, not of the organic nitrate family, have been investigated for their anti-anginal properties but have also failed to give satisfactory results. In several small scale trials of dipyridamole (Persantin) it did not give significantly better results than placebo (Todd, 1967).

Some promise has recently been demonstrated for propranolol (Inderal), a β -adrenergic receptor blocking agent, in the prevention of anginal episodes. From their review of studies on propranolol Epstein & Braunwald (1966) concluded that in doses of 200–400 mg propranolol significantly decreases the number of anginal attacks. The use of this drug in the treatment of angina, however, requires careful patient selection. Rabkin *et al.* (1966) stress that treatment with propranolol is likely to be effective only in patients whose hearts are functionally relatively sound. Propranolol is hazardous in the presence of cardiac failure, overt or impending, and in heart block because of the blockade of the sympathetic drive. When used for the proper indications, however, these investigators regard propranolol as a safe and most effective agent for the prevention of anginal attacks.

Before a definite assessment of the value of β -adrenergic receptor blocking agents in angina pectoris can be established, further investigation of the efficacy of these agents in angina is necessary.

Route of administration is an important factor in the success or failure of the anti-anginal drugs. Sublingual administration to relieve the acute anginal episode gives far better results than dosage forms that are to be swallowed. Sublingual nitroglycerin has proven to be the most effective drug in treatment of the acute anginal syndrome, but use of its oral form (Nitroglyn, Nitrospan, Nitrobid) is completely without merit. Modell (1966) states: 'Nitroglycerin is very rapidly destroyed in the liver, therefore, any nitroglycerin that gets into the stomach or intestines and is absorbed into the portal circulation is ineffective'. Studies have also shown the oral administration of other anti-anginal drugs such as erythryl tetranitrate (Cardilate), mannitol hexanitrate

(Nitranitol), triethanolamine trinitrate (Metamine) and isosorbide dinitrate (Isordil, Sorbitrate) to be inferior to their corresponding sublingual forms in relief of anginal pain (Riseman, Altman & Koretsky, 1958; Russek, 1966). It would suffice to say the sustained or controlled release form of these drugs is even less reliable than their oral counterparts.

Tolerance develops readily to the nitrites. This property has been observed among factory workers exposed to nitrites. They frequently suffer from severe headaches, dizziness, and postural weakness during the first few days of employment. Tolerance then develops and these symptoms disappear. Tolerance can be minimized by using the lowest effective dose and intermittent administration to prevent continuous exposure to the drug. However, in the case of the long-acting nitrites, something of a therapeutic paradox is presented because of tolerance. The purpose of the prophylactic administration of the long-acting nitrites is to provide continuous protection from an anginal attack. If their effectiveness diminishes with constant use then their true value when administered in this manner would appear to be very limited.

Untoward side-effects to the therapeutic use of nitrites are almost all secondary to their action on the cardio-vascular system. Headache is a common side-effect which usually disappears upon adjustment of the dose, continued use and development of tolerance. A hypotensive effect may be associated with the use of nitroglycerin and certain other anti-anginal agents. This property can be of serious consequence with patients who have suffered a recent myocardial infarct. The use of nitroglycerin could aggravate the hypotensive state induced by the infarct and precipitate shock. Other possible side-effects are dizziness and increased intraocular pressure. The oral anti-anginal agents may, in addition, cause nausea and gastro-intestinal disturbances.

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