The Search for an Ideal Oral Positive Inotropic Agent

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The bicentennial celebration in 1985 of the publication of William Withering’s famous work on the foxglove (Withering 1785) served to remind us of the enormity of his contribution, in that after two centuries, we have yet to find an oral positive inotropic agent to replace digitalis. Several compounds with a variety of ways of producing a positive inotropic effect (Scholz 1984; Johnston 1985; Colucci et al. 1986) are being investigated, and the eventual success of these agents rests on their clinical efficacy and safety. From a clinician’s point of view, the ideal characteristics of a positive inotrope should include its ability to improve cardiac pumping performance in patients with heart failure, which would in turn improve their symptoms and quality of life, without concomitant adverse effects and reduction of life expectancy. Other desirable characteristics, such as ease of administration, reasonable duration of action, and lack of tolerance or tachyphylaxis, will not be discussed in this article.

Of the adverse effects that can be anticipated, two in particular are pertinent to positive inotropic agents. Firstly, in common with the currently available oral agents possessing positive inotropic effects (e.g., digoxin, aminophylline, isoprenaline), the new inotropes have the propensity to cause arrhythmias (Kirlin et al. 1981; Packer et al. 1984; Uretsky et al. 1984; Holmes et al. 1985; Rabinovich et al. 1984). Many, like isoprenaline and aminophylline, are also peripheral vasodilators and can cause marked tachycardia which may lead to inefficient pumping. Those drugs which depend for their positive inotropic effect on their ability to increase the calcium ions available to myofibrils (e.g. by sodium pump inhibition, inward calcium channel stimulation, increase in cyclic AMP) tend to be arrhythmogenic on account of the raised intracellular calcium causing electrolyte imbalance. One might expect inotropes which do not act via an increased intracellular calcium concentration (e.g. those which increase the calcium sensitivity of myofilaments) to be less likely to cause arrhythmias. The value of adding an antiarrhythmic drug for those inotropes that increase intracellular calcium should be explored.

The second relevant adverse effect has so far received less attention. It concerns the likelihood of positive inotropes to cause hypercontractile injury (Reichenbach and Benditt 1970; Tanaka 1980, Laks 1977). Although this observation has been associated only with catecholamines, there is no reason why other equipotent inotropes should be exempt, as suggested by the long-term use of amrinone (Packer et al. 1984). Such myocardial injury results in the destruction of viable myocardium, jeopardizing the function of the already weakened heart. This, together with arrhythmogenicity, is liable to shorten the life-expectancy of patients with heart failure.

The efficacy of new positive inotropic agents must obviously be first established in experiments with isolated muscle strips and intact hearts. Whether the benefits seen in these experimental preparations can be translated to the failing human heart is a key question. There are two major obstacles in the way of in vivo evaluation of the ventricular response to these agents: firstly, currently available indices of contractility do not stand up to scrutiny (Van den Bos et al. 1973; Brutsaert and Paulus 1977; Elzinga and Westerhof 1984), and secondly, the methods of assessing ventricular function proposed by physiologists (e.g. Sarnoff and Berglund 1954; Suga 1971; El-
Their quality of life. This is the group of patients for whom the orally active cardiotonic agents are designed. The outstanding difference in the requirements of this group of patients is that, provided they are optimally treated with diuretics and vasodilators, their hearts are coping adequately at rest, and become inadequate only during exercise. It would therefore be wasteful, if not actually harmful to stress the heart when it is not required, i.e. at rest. It is during exercise that the heart needs the extra "kick". If the basal resting cardiac performance is artifically elevated, then the amount of available pumping reserve, i.e. to take the heart pump to its peak performance, is reduced (assuming that the cardiac pump, like all mechanical engines, has a performance ceiling). Hence the cardiac contribution to exercise may be diminished by inotropic stimulation at rest. Patients in this category need an inotropic agent that is principally effective during stress.

Can such an inotropic agent be developed? The answer is probably yes. Models of therapeutic manoeuvres producing this kind of profile of action exist. Digitalis in therapeutic doses has been shown to be insignificantly inotropic at rest, but during exercise it can exert a true positive inotropic effect in patients with heart failure in sinus rhythm (Tan et al. 1985, 1986). This is probably produced by the separate actions of catecholamines and digitalis in raising the intracellular stores of calcium (Hunter et al. 1983; Smith 1984; Orrego 1984). Another model is seen in beta-blocker treatment of patients with dilated cardiomyopathy, which ironically produces a similar profile of action, probably by exploiting the unique pathophysiological process seen in heart failure (Bristow et al. 1982). The hypothesized mechanism is as follows: beta-blockade produces an up-regulation of beta₁-adrenoceptors (Fowler et al. 1984) without significantly compromising the resting pumping performance of the heart; during exercise the higher concentration of noradrenaline presumably displaces the beta-blockers from the increased numbers of receptor sites, thus effecting augmented pump performance during exercise. For a new inotrope to produce this kind of profile, it must in some way be synergistic with the physiological processes involved in augmenting cardiac performance during exertion. For some drugs, their use in this category of patients may well depend merely on reducing the dosage such that no enhancement of cardiac pumping is seen at rest, but when exercise begins the effects become apparent.

Lastly, it ought to be emphasised that some hearts in failure are already performing at their maximum to maintain a sedentary life, and are unable to respond to inotropic stimulation (Tan et al. 1985b). In such a case, inotropic agents that can mimic the con-