

Leading Article

A new look at digoxin in congestive heart failure and sinus rhythm

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The role of cardiac glycosides in the treatment of congestive heart failure is controversial.¹ Digoxin is the most widely used compound particularly for the patient in atrial fibrillation where it remains the drug of choice for controlling the ventricular rate. For the patient in sinus rhythm, however, there is no firm consensus and opinions range from the almost nihilistic which see no role at all for digoxin to the opposite extreme which see it as first line treatment. There is no doubt that this controversy reflects the paucity of randomized clinical trials and the recent publication of three major studies,^{2–4} therefore, is timely because it is now more than 200 years since Withering's *Account of the Foxglove* first appeared.⁵

In congestive heart failure myocardial contractility is depressed because the binding of calcium by the sarcoplasmic reticulum and its delivery to the contractile proteins is impaired. Cardiac glycosides inhibit the membrane sodium-potassium pump raising the concentration of intracellular sodium which is then available for exchange with extracellular calcium by another membrane transport system.⁶ Thus cardiac glycosides can increase intracellular calcium and enhance contractility. The clinical importance of this mechanism, however, has been uncertain because the increase in intracellular sodium available for calcium exchange is almost vanishingly small. Nevertheless, experiments using intracellular microelectrodes have confirmed small, dose-dependent increases in sodium and a simultaneous inotropic response following exposure to cardiac glycosides. Indeed, an increase in intracellular sodium of only 1 mM is sufficient to double the strength of contraction.^{7,8}

Cardiac glycosides also have important effects on the cardiac conducting tissue and the peripheral circulation.⁹ They slow conduction through the atrioventricular node by increasing both the vagal tone and the sensitivity of the node to vagal effects.

Peripheral vascular responses to cardiac glycosides are complex. There is a direct vasoconstrictor effect and also a neurogenic vasodilator effect which acts through sensitization of the carotid baroreceptors.^{10,11} Clinically, the vasoconstrictor action dominates and when heart failure is severe enough to produce cardiogenic shock the increase in afterload may offset any potential benefit of inotropic stimulation.¹²

The inotropic action of cardiac glycosides has been confirmed in muscle bath experiments¹³ and also in the normal human heart.¹⁴ In the failing heart, however, it has been more difficult to demonstrate a useful inotropic response.¹⁵ Early studies described the effects of digoxin withdrawal with inconsistent results, some investigators reporting significant clinical deterioration,¹⁶ others reporting no palpable change.¹⁷ Similar inconsistency has characterized the results of placebo-controlled cross-over studies in patients in sinus rhythm. Thus, Dobbs *et al.*¹⁸ found that 16 of 46 heart failure patients deteriorated on placebo and 8 completely recovered when digoxin was reintroduced. Fleg *et al.*¹⁹ on the other hand, detected no digitalis-induced clinical benefit in a similar study while Lee *et al.*²⁰ found that appreciable clinical improvement was restricted to patients with severe heart failure and a gallop rhythm. Based on these results it is hardly surprising that cardiologists in this country and elsewhere have been unable to agree upon indications for digoxin therapy for the patient in sinus rhythm.

We now have data from three large randomized studies which suggest a potentially useful role for digoxin in congestive heart failure and sinus rhythm. The Captopril-Digitalis Research Group² randomized 300 patients on frusemide therapy to additional treatment with digoxin, captopril or placebo. Only digoxin produced a significant improvement in left ventricular function (as judged by ejection fraction) although this was not associated with a significant improvement in exercise tolerance. Interestingly (and conversely), captopril improved exercise tolerance without affecting left ventricular ejection fraction. The same year, the German and Austrian Xamoterol Study Group³ reported a trial in which 433

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patients were randomized to receive placebo, xamoterol or digoxin in the ratio 1:2:1. It is important to emphasize that these patients had only mild to moderate heart failure and less than 20% of the patients were on diuretics. Nevertheless, digoxin produced significant improvement in dyspnoea and oedema associated with a 17% (statistically insignificant) improvement in exercise tolerance. Responses to xamoterol (a new beta 1 partial agonist) were similar although the 34% improvement in exercise tolerance was significant, possibly because the larger numbers randomized to this drug prevented a type 2 statistical error. Most recently, the Milrinone Multicenter Trial Group⁴ reported the results of a trial in which 230 patients in sinus rhythm with moderately severe heart failure (all on diuretics) were randomized to treatment with digoxin, milrinone, both or placebo. After 3 months, digoxin improved left ventricular function (as judged by ejection fraction) and this was associated with a significant increase in exercise tolerance. Moreover, the frequency of decompensation from heart failure fell from 47% with placebo to 15% with digoxin. Results with milrinone (a new phosphodiesterase inhibitor) were broadly similar.

These data confirm that digoxin improves left ventricular function in congestive heart failure and sinus rhythm and leads to variable clinical improvement which is most marked when heart failure is severe. At present patients with severe heart failure are usually treated with diuretics and angiotensin converting enzyme (ACE) inhibitors but recent work has shown that further improvement in resting and exercise haemodynamics can be achieved by the addition of digoxin.^{21,22} Thus a reasonable policy would be to reserve digoxin for patients in sinus rhythm in whom

the response to diuretics and ACE inhibitors is unsatisfactory. In patients of this type digoxin can be expected to produce a useful improvement in both left ventricular function and exercise capacity.

Concern is often expressed about the narrow therapeutic range of digoxin and the risks of toxicity.²³ However, in the recent randomized trials digoxin was remarkably well tolerated and in none of them were side effects different from placebo, except for a small increase in ventricular ectopy in the report from the Captopril-Digitalis Research Group. Nevertheless, there remains some concern about the long-term effects of inotropic stimulation in general and digoxin in particular.²⁴ Bigger *et al.*²⁵ in a review of pooled data from four acute infarction studies concluded that there was a persistent risk associated with digoxin which could not be explained by baseline differences between treatment groups. The MILIS investigators,²⁶ on the other hand, were able to attribute the excess mortality in patients treated with digoxin to the severity of infarction. None of the recent trials has identified an increased risk of death in patients randomized to digoxin and although long-term data are not available it seems unlikely that a drug which has been widely used for more than 200 years would be the cause of significant excess mortality.

At present digoxin is the only orally active inotropic agent licensed for use in congestive heart failure. Its primary indication is for rate control in atrial fibrillation but, based on the results of recent randomized trials, it is now clear that many patients in sinus rhythm will also benefit from treatment with digoxin, particularly those with advanced heart failure in whom the response to diuretics and ACE inhibitors is inadequate.

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