Regular Review

William Withering and digitalis, 1785 to 1985

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This year marks the bicentenary of the publication of a book that has become a classic in medical history: William Withering's *An Account of the Foxglove, and Some of its Medical Uses: with Practical Remarks on Dropsy, and Other Diseases*. Records indicate that the foxglove had been used for various purposes for many centuries, but by 1745 the drug had fallen into disrepute through injudicious use. The first accurate description of its therapeutic effect in cardiac oedema is contained in nine case reports appended by Erasmus Darwin to his son's graduation thesis published in 1780.[1] It was Withering, however, who in 1776 asserted that *Digitalis purpurea* merited more attention than modern practice bestowed on it, and it was he who drew the drug to Darwin's attention. Withering's account of his own experience in 163 patients during 10 years of study is a masterpiece of careful observation, honest recording, and discerning interpretation. His work undoubtedly contributed to the restoration of the drug to the influential *London Pharmacopoeia*, and it stimulated a train of research that continues to this day.

Withering was born in Wellington, Shropshire, in 1741 and graduated in medicine from Edinburgh University in 1766. Soon after he moved to Stafford to become first attending physician at the newly built infirmary for the poor. In 1775—at the suggestion of Darwin and with the prospect of a better income—he moved to Birmingham, where he became attached to the staff at the General Hospital. In addition to medicine, his interests included botany, chemistry, and mineralogy, and his industrious nature is shown by the contributions he made to these other disciplines despite a heavy clinical commitment and his own ill health. Thus his botanical studies led to the first complete text in English on the plants of the British Isles, published in 1776. He translated the works of Bergman, professor of chemistry at Uppsala, which dealt with the chemical analysis of waters, and as a result of his own researches discovered barium carbonate (witherite).

Withering first concerned himself with the foxglove in 1775 when his opinion was asked about "a family receipt for the cure of dropsy . . . kept a secret by an old woman in Shropshire." The medicine comprised 20 or more herbs, but he was quick to recognise that foxglove was the active component. To standardise the dose he used only leaves gathered from the plant in its flowering state. For the same reason he chose to administer it as a powder or infusion rather than a decoction. His detailed account of his use of digitalis from 1775 to 1784 provides a vivid picture of his increasing acquaintance with the drug. He gives a complete description of its toxic effects—"sickness, vomiting, purging, giddiness, confused vision, objects appearing green and yellow; increased secretion of urine, with frequent motions to part with it; and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death." At first, he "thought it necessary to bring on and continue the sickness, in order to ensure the diuretic effects." As he became more familiar with the drug, however, he modified his practice—"let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped at the first appearance of any of these effects."

Withering was most impressed with the diuretic effects of the drug but he also observed that digitalis had "a power over the motion of the heart to a degree yet unobserved in any other medicine." By the early part of this century it had become accepted that the primary effect of digitalis was on the heart and the drug had established a place as an antiarrhythmic for atrial fibrillation and flutter, and as a positive inotropic agent for cardiac failure.

Today digitalis is prescribed as digoxin (the active constituent of the leaves of *D lanata*) or sometimes digitoxin (from *D purpurea*). Other cardiac glycosides have been added to their number—for example, ouabain from *Strophanthus gratus*. The pharmacokinetics of these drugs have been well studied; in particular, the dependence of digoxin excretion on renal function is well known. Some progress has been made in elucidating their mechanism of action. Digoxin binds to Na^+-K^+ adenosine triphosphatase (ATPase), the sodium pump; indeed, the interaction between digoxin and this enzyme shows all the characteristics—specificity, affinity, reversibility—of a drug receptor relation.[2] The binding of digoxin to Na^+-K^+ ATPase has been associated with the positive inotropic effects of the drug. Inhibition of the enzyme is thought to increase intracellular free calcium, making it available for muscle protein contraction. A more controversial view is that digoxin stimulates Na^+-K^+ ATPase at physiological concentrations of potassium.[3] Despite this increased understanding two substantial problems remain from Withering's era—drug toxicity and the question of efficacy of digitalis in all patients with chronic heart failure.

Withering's account gives an estimate of the incidence of

digitalis toxicity in his hands.[4] During the latter years, 1780 to 1784, it was around 18%. Studies among patients being admitted to hospital in the 1970s gave figures between 20% and 30%,[5] while an outpatient study in the Oxford area has given an incidence of around 16%.[6] We are doing little better today than Withering did in his time. Several assays are now widely available for accurately determining plasma digitalis concentrations, and therapeutic values have been defined. Unfortunately, these measure the distribution of the drug in the body rather than its effect on the tissues and there is considerable overlap of concentrations between patients who show signs of toxicity and those who do not.[7] The factors which increase the likelihood of toxicity may be broadly divided into those in the plasma and those in the tissues.[6] Plasma factors include hypokalaemia, hypomagnesaemia, acid base balance, renal function, and concurrent drug treatment, all of which influence the tissue binding of digitalis. Tissue factors include age concomitant disease and severity of the underlying cardiac illness, which influence tissue sensitivity to the drug. The second group is probably the more important, and the influence of these tissue factors on response to digitalis is difficult to predict. Nomograms have been devised for calculating dosages of digoxin based on age, weight, plasma potassium concentration, and renal function, but as in Withering's day there is no substitute for careful observation of the patient.

The second problem concerns the efficacy of digitalis when prescribed to patients with chronic heart failure in sinus rhythm. Laboratory experiments on erythrocytes have shown adaptation to long term treatment with digitalis.[8,9] When treatment with digitalis is started the number of available functioning sodium pump units per cell falls, the intracellular sodium concentration rises, and the uptake of rubidium-86 (a measure of sodium pump activity) falls. These changes are apparent within two or three days of starting treatment. After two or more months of continued treatment, however, the number of functioning pump units returns to normal and intracellular sodium concentrations and uptake of ^{86}Rb return to pretreatment levels. How far this apparent tolerance to digitalis should be extrapolated to the therapeutic effect of the drug on the heart depends on two unresolved questions: firstly, the usefulness of the erythrocyte as a model for cardiac tissue and, secondly, the relation of inhibition of the sodium pump to the biochemical action of the drug.

What data are there from clinical studies? Mulrow *et al* identified 16 articles from 1960 to 1982 that specifically addressed the question of efficacy of digitalis in patients with congestive cardiac failure and sinus rhythm. Nine assessed the effect of simply withdrawing the drug; three compared the effects of diuretics alone with digoxin plus diuretics; three compared digoxin with placebo; and one assessed patients before and after a period of digitalis monotherapy.[10] They evaluated these studies according to the strict methodological criteria recommended for clinical trials assessing drug efficacy. The digitalis withdrawal studies suggested that the drug could be discontinued in 48-100% of patients, but these studies contained some important deficiencies of design, and in some cases the successful withdrawal of the drug may have been due to its inappropriate use in the first instance. The trials comparing treatment with digoxin and diuretics were rendered inconclusive by their design. The digitalis versus placebo studies were more rigorous in approach. Dobbs *et al* reported that 16 out of 46 patients deteriorated with placebo, but they included patients with atrial fibrillation who may have accounted for many of those who deteriorated.[11] The study by Fleg and colleagues was marred by the lack of randomisation of treatment but suggested that a cautious trial of withdrawal of digoxin may be warranted in selected elderly patients with stable congestive heart failure.[12] The study by Lee *et al* satisfied all the design criteria for assessing drug efficacy and suggested that a subgroup of patients with severe heart failure and a protodiastolic (S_3) gallop benefited most from treatment with digitalis.[13] Their findings await confirmation.

Mulrow *et al* concluded that there is virtually no definitive evidence on which to determine the place of digitalis in patients with congestive heart failure and sinus rhythm.[10] The failure of these studies to provide answers—largely because of faults in trial design—is, to say the least, disappointing. More recently Taggart *et al* have described a double blind placebo crossover trial of digoxin withdrawal from 22 patients entered after fulfilling defined admission criteria.[14] Nearly all had mild heart failure (New York Heart Association, class II), and all had been stable for at least three months. Fourteen patients showed no clinical change whether taking digoxin or placebo; five patients deteriorated taking placebo, three taking digoxin, a difference that was not statistically significant. Unfortunately, the results of this study were complicated by the fact that three of the patients who developed heart failure (one with digoxin, two with placebo) did so during the first treatment phase and did not proceed to the alternate treatment period. Mulrow *et al* suggest that in future investigators should assemble and study patients at the initial diagnosis of congestive cardiac failure rather than examining them after withdrawal of treatment.[10]

Thus 200 years after Withering's book much remains to be learnt about digitalis; and the methods by which progress is made—careful observation and interpretation—remain unchanged.

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