

A Fond Farewell to the Foxglove? The Decline in the Use of Digitalis

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ABSTRACT

Since William Withering's report on the foxglove in 1785, digitalis, in 1 form or another, has remained a mainstay in the treatment of congestive heart failure and as a means of rate control in atrial fibrillation. Recently, with the introduction of potent diuretics and other agents for the treatment of these conditions, there has been a deemphasis on the role of digitalis despite its therapeutic value. Continued evidence of the frequent usefulness of digitalis in both conditions suggests that this venerable drug should remain within the therapeutic armamentarium of cardiologists and other physicians. (*J Cardiac Fail* 2010;16:45–48)

Key Words: Digitalis, congestive heart failure, atrial fibrillation.

It was not until the beginning of the 20th century that physicians could express some well-founded confidence in the effectiveness of some of our therapeutic agents. This was best expressed by Lawrence J. Henderson (1878–1942), who is credited with the statement that “Somewhere between 1910 and 1912 in this country a random patient with a random disease consulting a doctor chosen at random had, for the first time in the history of mankind, a better than fifty-fifty chance of profiting from the encounter.”¹ The sad state of medical therapy before this had been commented on earlier by Oliver Wendell Holmes (1809–1894) in 1 of his essays on medical science: “I firmly believe that if the whole *materia medica as now used* could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes.”²

The popularity of homeopathy during the 19th century was probably related to the fact that the miniscule doses of medicines prescribed by the adherent physicians protected their patients from the all-too-often occurring toxic effects of many of the medicines popular during this period. The great William Osler (1849–1919) was well aware of the uselessness of many of the medicines recommended during his lifetime, as well as their frequent toxicity. He had no qualms about being branded as a “therapeutic

nihilist” because of his reluctance to dispense many of the medicines in vogue during his time.³ One of the rare exceptions to his exclusionary approach to medications was digitalis. Osler's most distinguished protégé, George Dock, was also a skeptic. He would tell his students that he was guided by the expression that a young physician has 20 remedies for every disease, whereas an older one has 20 remedies for all diseases.⁴ However, in his list of 20 for 1900 he included digitalis, which has survived in popularity for many years, whereas the use of such nostrums such as arsenic, strychnine, calomel, and balsam, included in his lists, has faded.

The enthusiasm for digitalis has been on the wane, which comes as something of a surprise for older physicians who grew up professionally when digitalis was looked on as a strong ally when it came to treating congestive heart failure as well as controlling ventricular rate in atrial fibrillation. Fifty years ago, our therapeutic arsenal was rather limited when it came to other drugs of use in these conditions. Besides digitalis, there was quinidine, of course, and then the invaluable mercurial diuretics that had been introduced in the 1920s, and little else.

So dependent were physicians on the use of digitalis in heart disease that its administration became something of an institution in itself, perhaps even an art form for those who used to wield it in pursuit of therapeutic success. A half-century ago, rapid digitalization was frequently achieved with lanatoside-C (Cedilanid) administered intravenously. Several oral forms were in general use. Physician preference depended on differences in absorption, persistence of effect, and propensity for inducing toxicity. Digitoxin, digoxin, and digitalis leaf were the major contenders, and supporters of each could resemble religious

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zealots in their differing advocacies. Digitoxin attracted adherents because it was fully absorbed from the gut, perhaps making loading dosages more predictable. Because of its longer lasting effect, it was argued that patients would not lose digitalization if they forgot to take their daily dose. On the other hand, cases of digitalis toxicity induced by digitoxin would be more prolonged than with digoxin. Digoxin is only 50% to 80% absorbed, and this variability put off some practitioners. It was shorter lasting than digitoxin: although patients might become underdigitalized by failing to take their daily dose, they would benefit by a more rapid recovery should toxicity occur. A cruder preparation, digitalis leaf, was favored by some because they thought that the effects of overdosage on the stomach might precede the centrally induced vomiting and potentially lethal effects of over dosage on cardiac rhythm.

Whatever preparation a physician favored, he or she was admonished to be expert in its utilization, and the importance of digitalis was rarely questioned. If you knew how to use digitalis, in whatever form you preferred, you knew just about all you could about treating heart failure and atrial fibrillation.

Over the years, digoxin won out among the available oral preparations and, when digitalis is used today, it is this formulation that cardiologists and others employ. But even this form of the drug seems to be losing out to other medications with which we have been blessed in treating both heart failure and atrial fibrillation. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, aldosterone antagonists, and a variety of new potent diuretics have eliminated mercurials from the formulary and seriously question the use of digitalis as well.

A detailed review of the extensive literature concerning the use of digitalis in current medical practice is beyond the scope of this article. However, a few observations may be in order.

In atrial fibrillation, where ventricular rate control is a major aim of therapy, use of digitalis in recent years has been discounted because of the general impression that, although rate can be well-controlled at rest, with exercise this may not be the case.⁵ Nonetheless, in the AFFIRM Study (The Atrial Fibrillation Follow-up Investigation of Rhythm Management) in which efficacy of rate control at rest and exercise with 3 different drugs, singly or in combination, was evaluated, digoxin alone had a 58% success rate compared with β -blockers (59%) and calcium channel blockers (38%).⁶ The highest rates of success (70% to 78%) were achieved by digoxin in combination with 1 or 2 of the other drug classes.

The reputation of digitalis in the treatment of congestive heart failure (CHF) has also suffered in recent years. In the 2005 guidelines of the American Heart Association and the American College of Cardiology for the treatment of CHF, digitalis is barely mentioned.⁷ Two years later, in a published roundtable discussion of the treatment of acute heart failure, none of the experts even mentioned digitalis.⁸ For many cardiologists, the report of the Digitalis Investigation Group in

1997 was a final confirmation of digitalis's lack of effectiveness.⁹ In this large study of more than 6000 patients in CHF characterized by low ejection fractions ("systolic failure"), digitalis added to other medications had no effect on mortality; this seemed to settle the matter in many minds. Other significant findings, such as digitalis reducing need for hospitalization or reducing the progression of heart failure, were generally overlooked. Also noteworthy are the findings of other studies released about the time of the Digitalis Investigation Group report showing the benefits of digitalis in CHF even with patients in sinus rhythm, a group traditionally thought poorly responsive to such treatment.¹⁰⁻¹²

Given such findings, as well as new knowledge about the metabolism of digoxin, the ability to measure serum levels and the ability to treat digitalis intoxication now with specific antibodies to digoxin all make a case against the premature rejection of its role in the treatment of CHF.

The demonstrable utility of digitalis notwithstanding, there seems to have been an undeniable decline in its clinical use. By 2007–2008, it was no longer 1 of the 10 most popular drugs prescribed by cardiologists.¹³ (Multiple attempts by the author to obtain further quantitative information on production and sales of digitalis preparations from pharmaceutical manufacturers were unsuccessful.)

Such ruminations about the current status of digitalis lead back to a reconsideration of the source of its reputation as 1 of the great botanical gifts to mankind for more than 200 years. (Recommended is Aronson's reproduction of the original report with marginal notations to guide the modern reader non-conversant with 18th-century terms and concepts).¹⁴ William Withering's own words about his discovery still ring familiar to many of today's physicians:

In the year 1775 my opinion was asked concerning a family receipt for the cure of the dropsy. I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures after regular practitioners had failed... This medicine was composed of twenty or more different herbs; but it was not difficult for one *conversant in these subjects* [italics added] to perceive that the active herb could be no other than the Foxglove.

How many modern physicians, learning of some miracle cure of an obscure person in the hinterlands with a concoction of 20 different herbs, would have the slightest idea of how to go about determining what the active ingredient might be? The fact is that many of the 18th-century medicines available to physicians of the period were derived from native plants and it was the practitioners' duty to be aware of them. Withering, in particular, was well-grounded in botany. He had long been an enthusiast about the subject and at the time of his first encounter with the foxglove as a therapeutic agent, he had already published a massive highly acclaimed study on the plant life of Great Britain.¹⁵

Before Withering's use of foxglove in dropsy, it had been used as a remedy for various other disorders. Among them, foxglove was used as a purgative to empty the bowels,

although its action as an emetic was much more pronounced and a more constant sign of toxicity when this occurred. Withering's great insight was contained in a sentence omitted from the previous quote: "I was informed also that the effects produced were violent vomiting and purging; for the *diuretic effects* [italics added] seemed to have been overlooked."

By focusing on the amount of urine produced by treatment with digitalis rather than on the expulsion of fluids either through vomiting or diarrhea, Withering was able to establish the usefulness of the active principle he extracted from the foxglove. For those who are of the impression that this was an epiphany occurring over a short span, reference to his original report will show that it consisted of 207 pages of carefully accumulated documentation obtained over a 10-year period (1775–1785).

As one reads through this remarkable document, Withering's pharmaceutical skills were as impressive as his medical ones. Perhaps being the son of a successful apothecary exposed Withering to some of this methodology. He determined that it was the leaves of the plant rather than the roots, stems, flowers, or seeds that contained the active principle. He noted a seasonal variation in the strength of the drug in the powder he prepared from the leaves. He prepared different forms of the drug for administration to his patients, such as a liquid ("infusion") or making up pills by incorporating the powder in soap or gum ammoniac.

At first he prescribed the drug to the point of vomiting but later realized that an adequate diuresis could be achieved before this toxic manifestation occurred. He determined which types of cases were more likely to respond (eg, those with hydrothorax [pleural effusions] that were often likely due to congestive heart failure and those that would not: those with ovarian cysts, consumption, or hydrocephalous).

Some have suggested that Withering was ignorant of the mechanism of foxglove's action. On the contrary, although he never once mentions the kidneys, in his section entitled "Inferences" toward the end of his monograph, he states "That it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends." Finally, in describing the toxic effects of the drug, other than vomiting, he notes the disturbances of vision (green or yellow) as well as what was probably advanced heart block by detecting a pulse rate of 40 in a patient (#106) who had been overdosed.

How well did Withering's foxglove perform? He describes 163 cases in widely varying detail; some case

reports occupy several pages, whereas 25 consist of 5 lines or less. I attempted to determine success according to diagnosis, seeking to separate out those who, to this cardiologist, were almost undoubtedly suffering from CHF from the rest with other etiologies of their dropsy (eg, liver disease, kidney disease, ovarian cysts, possibly intra-abdominal cancers). The identification of those most likely to have heart disease depended mainly on history, symptomatology, and the presence of pleural effusions ("hydrothorax"). Because this work was all done pre-Laennec, there were no auscultatory findings to provide such leads as to causation. Pulse rate was noted infrequently and blood pressure, of course, was not measured at all.

Eleven cases were eliminated from this analysis by the author for lack of sufficient information to suggest either cardiac or other causes of dropsy. The results among the remaining 152 patients were favorable in 64%. When those identified as most likely to have been in heart failure were separated out (Table 1) the success rate rose to 89%. Considerable success among the others (55%) no doubt indicates a number of cardiac cases among them, not meeting the rather strict criteria adapted for this analysis.

Were such data presented in an article submitted to any modern journal, they would no doubt be immediately rejected. What did Withering know about a randomized, prospective, double blind study to determine therapeutic efficacy? Fortunately for millions of patients over the last 200 years, this was no impediment to his wonderful contribution.

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Table 1. Withering's Success in Treating Dropsy: 152 Cases

Patients	Success (%)	Failure	Total
Definite cardiac	39 (89)	5	44
Others	59 (55)	49	108

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