William Withering's legacy – for the good of the patient

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ABSTRACT – The lessons that the physician William Withering learned from his studies of digitalis are still relevant today. This paper highlights four of these lessons and updates them using the tools of clinical pharmacology and pharmacoepidemiology. First, Withering learned that failure to prepare digitalis from the foxglove in a standard manner resulted in a product with unpredictable clinical effects. Preparation of medicines from plants since then has not followed similar good practice and medicines have often not been granted marketing authorisation because of variability in their quality. Second, differences in the response to digitalis were noted by Withering, but he had little idea of their basis. Clinical pharmacology has shown that for drugs such as digitalis differences are caused by variability both in receptor sensitivity and in drug disposition. Third, the dose-response characteristics of digitalis were well known to Withering. Modern techniques of measuring response, such as the use of biomarkers, have made such studies easier, although clinical observations remain the gold standard. Fourth, Withering documented many of the adverse effects of digitalis. The use of various modern databases has facilitated the analysis of clinical toxicology and thus of risk-benefit profiles.

KEY WORDS: adverse reactions, bioavailability, biomarkers, clinical pharmacology, digitalis, pharmacodynamics, pharmacokinetics

William Withering was born in Wellington, Shropshire in 1741 and died in 1799 of pulmonary tuberculosis. He was a true polymath, being not only a physician of national repute, but also an expert botanist and a mineralogist, with both a genus of plants and a mineral named after him. But he is best known for his work on digitalis; his book, *An account of the foxglove and some of its medical uses*, was published in 1785 and is, by any standards, a remarkable work.[1]

It has been said that if digitalis were to come before a medicines regulatory committee today, it would be refused a licence. This can be disputed, for as a former Withering Lecturer, Michael Rawlins, said of Withering's book:

> *Its contents would do justice to an Expert Report accompanying a Product Licence application to the drug regulatory authority of any state in the European Union.*[2]

In his book, Withering describes how he:

- collected and prepared the leaves of the purple foxglove (*Digitalis purpurea*) to obtain a product of reasonable consistency
- demonstrated that some individuals were more responsive to digitalis than others
- investigated the dose-response characteristics of digitalis, with respect to both slowing the heart rate and inducing a diuresis
- identified most of the adverse effects of digitalis and their relation to dose, and how toxicity could be minimised by dose reduction

Withering's impressive understanding of his newly discovered drug serves as a model for much of today's therapeutics, and it is no exaggeration to describe him as the father of clinical pharmacology.

This paper will take each of the lessons that Withering learned from studying digitalis and show how it has influenced modern clinical pharmacology and thus the regulation of medicines. The paper draws extensively on the writings of Jeffrey Aronson on Withering and digitalis.[3]

Lesson 1: Medicines from plants – variations in bioavailability

The production of medicines from plants has a long and variable history that is bedevilled by problems of impurities and poor standardisation, which makes Withering's efforts of over 200 years ago all the more remarkable:

> *I was well aware of the uncertainty which must attend on the exhibition of the root of a biennial plant and therefore continued to use the leaves. These I found to vary much at different seasons of the year, but I found that if gathered at one time of year, namely when it was in its flowering state and carefully dried, the dose could be determined as exactly as any other medicine. The more I saw of the great powers of this plant, the more it seemed necessary to bring the doses to the greatest degree of accuracy.*[1]

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Unfortunately, not all these lessons have been learned and remembered. Over the past 10 years, one of the most contentious areas of therapeutics has been the drug treatment of depression with tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Concerned about the adverse effects of these drugs, many depressed subjects have had recourse to herbal antidepressants, in particular St John's wort (SJW). SJW is widely used as an antidepressant in Germany, where more SJW than fluoxetine (Prozac) is sold for the treatment of depression, and in 1998 the sales value of SJW in Europe was $6 billion.

The herbal preparation consists of the dried flower tops or other parts of SJW, which are usually harvested shortly before or during the flowering season. However, the concentrations of the main active principle of SJW, hypericin, varies as much as 10-fold in different formulations, depending on which part of the plant is used, variations in growth conditions, and the time of year that it is gathered.[4]

SJW has pharmacological effects by virtue of its actions on the neurotransmitters serotonin, noradrenaline, and dopamine. However, SJW has important properties other than its antidepressant action, namely the ability to interact with other medications taken at the same time. It inhibits and then induces the metabolism of several important isozymes of CYP450. Thus, marked changes in the levels of such commonly used medicines as cyclosporin, warfarin, and constituents of oral contraceptive have been well documented in patients starting SJW.[4] SJW also induces the activity of the transporter p-glycoprotein, which is involved in the disposition of digoxin.

Several applications have been made to medicine licensing authorities to market preparations of SJW for the treatment of depression but all have failed – one reason being the variability in the content of active principle in the various batches.

A second modern example of variations in bioavailability concerns digoxin.[5] In 1969, Burroughs Wellcome, one of the main manufacturers of digoxin, decided to improve the formulation of their proprietary brand of digoxin, Lanoxin. The amount of digoxin in the tablet remained unchanged, but several of the excipients in the tablet were altered. The clinical importance of these changes went undetected for some time and it was only due to skilful detective work that the reason was unearthed for a lack of response to Lanoxin in some patients. Four-fold variability in the bioavailability of different batches of Lanoxin was eventually found, causing great variability in plasma digoxin levels in patients due to the differing rates of digoxin release from tablets in the stomach and intestine. In 1975, British pharmacopoeia standards for digoxin were published to prevent a repeat of this problem.

Lesson 2: Interindividual variation in response to digoxin

Withering was aware that not all patients responded in the same beneficial way to digitalis administration. He knew little, of course, of how digoxin exerted its therapeutic effects and even less of its disposition within the body.

Today, one of the basic tenets of clinical pharmacology is that:

drug + receptor → drug-receptor complex → pharmacological effect

Variability in response to digoxin can therefore depend on variation in the sensitivity of the receptor on which digoxin acts, ie in its pharmacodynamics, or on variation in its disposition within the body, ie in its pharmacokinetics.

Pharmacodynamics

Four levels of action can be described:

1 At the *molecular level* there is strong evidence that digitalis inhibits the ubiquitous magnesium-dependent membrane-bound enzyme Na^+/K^+-ATPase and thus alters the intracellular disposition of Na^+, K^+ and indirectly Ca^{2+}.
2 At the *cellular level*, this results in an increased rate of contractility of cardiac muscle fibres (although this is not so in acute myocardial infarction or cor pulmonale, for reasons that are not entirely clear).
3 At the *whole heart level*, this results in an increase in cardiac output. In hypertrophic obstructive cardiomyopathy, however, due to the outflow obstruction, this increase may result in a worsening of the clinical situation rather than an improvement.
4 At the *whole body level*, the beneficial effects of digitalis manifest as alleviation of the symptoms and signs of heart failure.[3]

Marked variability in each of these stages has been documented.

Pharmacokinetics

Advances in our understanding of the pharmacokinetics of digitalis have been even more profound, and central to this is an appreciation of the role of the transporter protein p-glycoprotein.

Transporter proteins are key determinants of drug transport across cell membranes of the intestine, pancreas, liver hepatocytes, kidney and blood-brain barrier, where they are expressed in the apical portion of epithelial cells. These proteins influence both the influx and efflux of drugs across membranes. Much is now known of the molecular structure of these proteins, of their genetic control, and of the gene families that encode individual members. Genetic polymorphisms in several transporter proteins have been documented and their clinical relevance explored.[6]

The transporter protein p-glycoprotein is expressed in the apical segment of the epithelial cells of the jejunum, colon, proximal convoluted tubules of the kidney, biliary canaliculi of hepatocytes, and brain capillaries. P-glycoprotein acts as an efflux pump for many drugs, including digoxin, at these various sites. Over-expression of p-glycoprotein is associated with multidrug resistance (MDR) to many anticancer drugs as it removes these drugs from the intestine to the gut lumen. Thus, p-glycoprotein is also known as the MDR transporter.

With respect to digoxin, p-glycoprotein is an efflux transporter in the gut and at the blood-brain barrier, but less so within the kidney. In MDR knockout mice, ie mice that do not

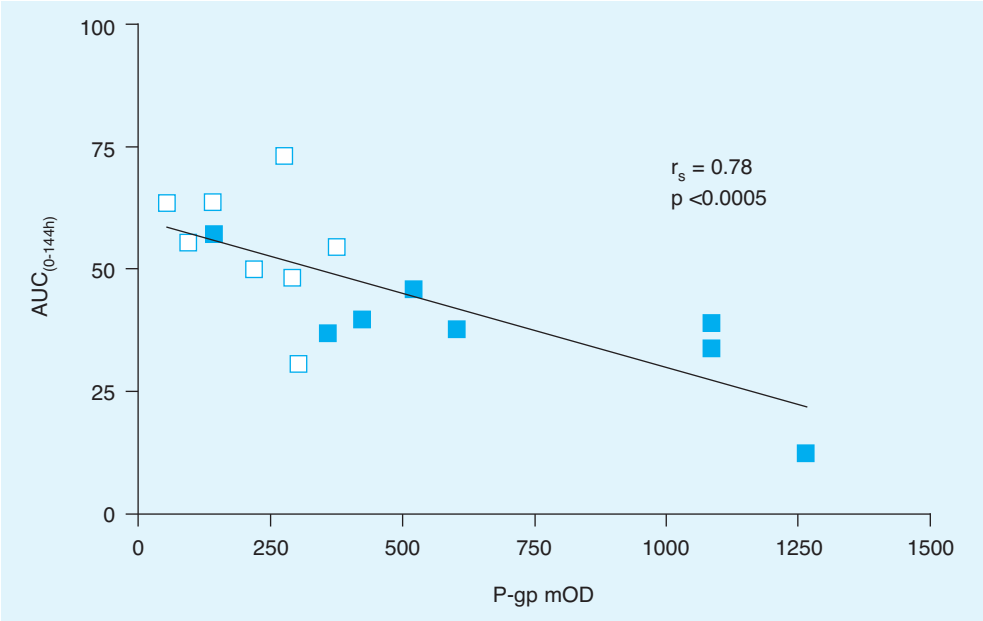

Fig 1. Correlation between area under the curve (AUC) of orally administered digoxin (1 mg) and expression of p-glycoprotein (n=16) measured by Western blot. Open squares = without rifampicin; filled squares = with rifampicin (600 mg).[7]

express p-glycoprotein activity, administration of digoxin results in a 30-fold increase in brain digoxin levels and a four-fold increase in digoxin plasma levels compared to control mice.[6]

In man, Greiner *et al* showed a significant correlation between the plasma area under the curve (AUC) of administered digoxin and the expression of p-glycoprotein in jejunal biopsies.[7] Further, when these subjects were given the inducing agent rifampicin and jejunal biopsies were taken before and after its administration, three- to four-fold increases in p-glycoprotein activity were found and the correlation between the plasma AUC of administered digoxin and p-glycoprotein activity was maintained (Fig 1).

Thus, the genetics of p-glycoprotein and the effects of other drugs that induce or inhibit p-glycoprotein activity are central to our understanding of the pharmacokinetics and thus the interindividual variability of the response to digoxin.

Lesson 3: Dose-response characteristics of digitalis

The two main issues that Withering grappled with were the indications for digitalis administration and the appropriate dose. It is worth remembering that while Withering found that digitalis was remarkably effective in treating cases of dropsy, and that in doing so, he noted a slowing of the heart, the diagnoses, let alone the pathophysiology, of heart failure and atrial fibrillation were beyond the understanding of 18th century physicians.

Fig 2 shows Aronson's estimation of the efficacy of digitalis in the 162 cases of dropsy treated by Withering.[3] Withering encountered considerable toxicity, but Aronson's estimation also show that as Withering became more adept at selecting dosage regimens, the incidence of adverse effects decreased.

The debate continues even today as to the appropriate dose of digitalis, and whether its dose-response characteristics in heart failure and atrial fibrillation are similar. The main problem is how to measure its efficacy; atrial fibrillation poses fewer problems than heart failure. While the gold standard for assessment of the therapeutic efficacy of a drug remains changes in mortality or in quality-of-life measurements, such as improvement in disease-related symptoms or in activity or need for hospitalisation, require long and large studies of new drugs or in dose finding.

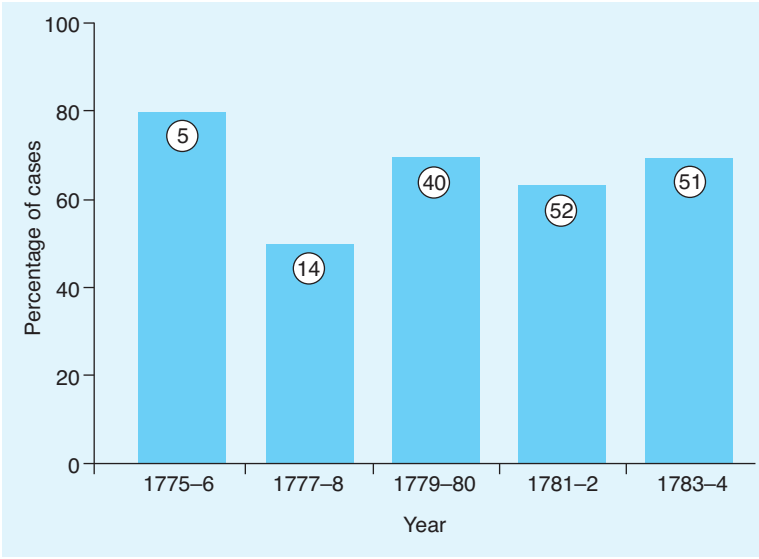

Fig 2. Percentage rates of therapeutic efficacy achieved by Withering with the foxglove, classified by year of use. The numbers in each bar refer to the number of cases treated during the relevant years.[3]

Thus, there is great interest in the use of surrogate measurements (reliable endpoint substitutes (physical signs or laboratory measurements), which should correlate with the frequency and intensity of the disease endpoint both as an epidemiological marker and as a therapeutic response) and biomarkers (laboratory measurements used as a surrogate measurement) in therapeutic drug evaluation.[8] The ideal marker should be biologically plausible, be detectable in most subjects at all stages of the disease, change towards normal when an effective agent is given, predict the ultimate clinical response in patients taking the drug, and discriminate between patients who will do well and those who will not.

Many biomarkers for heart failure have been proposed over the years; one of the more interesting and potentially valuable is B-type natriuretic peptide (BNP). BNP is released from ventricular myocytes, augments urine volume and sodium excretion, and inhibits the sympathetic nervous system and the renin angiotensin system. It has also been used as a possible treatment for heart failure.[9]

Two studies illustrate the potential usefulness of BNP measurements in situations with which Withering would have been familiar. First, the BNP for Acute Shortness of Breath Evaluation (BASEL) study investigated 452 patients presenting to the emergency room of a medical centre:[10] 225 patients were assigned to a diagnostic strategy involving measurement of BNP, while 227 were assessed in the standard manner. A plasma BNP concentration of >100 pg/ml was used as a discriminator for the diagnosis of heart failure from shortness of breath due to other causes. When used with other clinical information, rapid measurement of BNP in the emergency room improved the evaluation and treatment of patients with acute dyspnoea, reducing the time to discharge and total cost of treatment with no adverse effects on mortality or rate of subsequent hospitalisation (Table 1).

Table 1. B-type natriuretic peptide (BNP) for evaluation of acute shortness of breath.[10]

	BNP group	Standard group	p
Hospitalised (%)	75	85	0.008
Requiring intensive care (%)	15	24	0.01
Median time to discharge (days)	8.0	11.0	0.001
Cost of treatment ($)	5,410	7,264	0.006
30-day mortality (%)	10	12	0.45

Table 2. Prognostic value of B-type natriuretic peptide (BNP) measurement at first clinic visit in 3,346 persons without heart failure, followed for mean of 5.2 years.[11]

1 SD increment in BNP associated with:	p
27% increased risk of death	0.009
28% increased risk of first cardiovascular event	0.03
77% increased risk of heat failure	<0.001
66% increased risk of atrial fibrillation	<0.001
53% increased risk of stroke	0.002

Second, a subset of 3,346 asymptomatic patients (without heart failure) in the Framingham study were followed for a mean of 5.2 years.[11] BNP level was measured at the first screening visit to determine its prognostic value. Table 2 shows that each incremental increase in BNP level correlates significantly with both mortality and cardiovascular morbidity. Interestingly, excess risk was apparent at BNP levels well below current thresholds for the diagnosis of heart failure.

BNP levels taken in isolation, however, must be interpreted with caution. Whether data such as that obtained by Wang *et al*[11] help in clinical management was questioned in a leading article published alongside the original article:

> *Looking at BNP in isolation may be akin to seeing smoke trailing out of the window of a house without having any notion of what is on fire, where that fire is, or how it can best be extinguished.*[9]

Lesson 4: Adverse reactions to digitalis

As Withering gained more experience with the use of digitalis, he noted fewer adverse effects.[1] Whether or not this related to different dosage regimens is more problematical, but we do know that over the years he experimented with different preparations of digitalis which probably had varying degrees of bioavailability.

The issue of the risk-benefit balance of digitalis is very much alive today. I have argued that the use of biomarkers such as BNP might be useful in documenting the benefit of digitalis. Are there equivalent tools to help our understanding of safety issues? The safety of medicines still depends very much on careful clinical observation and documentation, combined with biomarkers of toxicity. What has changed over the years is the sophistication of the way we study adverse reactions.

It is widely appreciated that when a medicine is granted a marketing authorisation, the understanding of its overall safety profile is very incomplete, relying on what can be extrapolated from animal pharmacology and from the limited clinical trial evidence that is available at that time. An appreciation of the safety profile of a new medicine can only be gained after it is marketed, and tools are required to capture this information. These tools are spontaneous adverse reaction reports, clinical databases, and clinical studies, both observational and experimental.

So, Withering's first port of call today if he were interested in the clinical toxicology of digitalis would be to access the reports of adverse reactions reported to a regulatory authority such as the Medicines and Healthcare Regulatory Agency. Since 1963, when the UK Yellow Card database was set up, until the end of 2005, some 628 reports of adverse reactions to digoxin (104 cardiac and 94 gastrointestinal) were reported, 36 of which have been fatal (14 cardiac and 3 gastrointestinal). It might be considered that this is a remarkably small number, but it is known that all such spontaneous reporting systems suffer from under reporting, that such schemes have great difficulty in distinguishing adverse drug reactions from similar common symptoms

that occur frequently in the population, and that for old drugs such as digitalis, prescribers are asked only to report severe and unusual reactions. In this respect, it is interesting that 20 cases of reproductive and breast disorder, including gynaecomastia, and 28 cases of eye disorders, mainly perturbation of colour vision, have been reported on Yellow Cards.

Further investigation of the adverse events following digitalis therapy could be carried out using the General Practice Research Data Base (GPRD) which contains some four million ongoing clinical records.

To study the cardiac side effects, however, it would be necessary to mount a clinical study, either an observational study (cohort or case-control) or a controlled clinical trial, since this is the best way of distinguishing adverse drug effects from similar events that are commonly seen in the community. Cardiovascular toxicity following therapy with rofecoxib (Vioxx) has recently been defined in a clinical trial;[12] spontaneous reports failed to document this toxicity.

Conclusion

The subtitle of this article is 'for the good of the patient'. By going back to the lessons that William Withering taught us over 200 years ago, and putting them in a modern context, this paper attempts to fulfil his legacy.

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References

1 Withering W. *An account of the foxglove and some of its medical uses.* London: CGJ and J Robinson, 1785.
2 Rawlins M. Pharmacovigilance: paradise lost, regained or postponed? *J R Coll Physicians* 1995;29:41–9.
3 Aronson JK. *An account of the foxglove and its medical uses 1785–1985.* Oxford: Oxford University Press, 1985.
4 Henderson L, Yue QY, Berqvist C *et al.* St. John's wort: drug interactions and clinical outcomes. *Br J Clin Pharmacol* 2002;54:349–56.
5 Munro-Faure AD, Fowle ASE, Fox J *et al.* Recognition of variable bioavailability as an international problem: a review of earlier studies. *Postgrad Med J* 1974;50(Suppl 6):14–8.
6 Mizuno N, Niwa T, Yotsumoto Y *et al.* Impact of drug transporter studies on drug discovery and development. *Pharmacol Rev* 2003;55: 425–61.
7 Greiner B, Eichelbaum M, Fritz P, *et al.* The role of intestinal P-glycoprotein in the interaction between digoxin and rifampicin. *J Clin Invest* 1999;104:147–53.
8 Jortani SA, Prabhu SD, Valdes R. Strategies for developing biomarkers for heart failure. *Clin Chem* 2004;50:265–78.
9 Mark DB, Felker GM. B-type natriuretic peptide-a biomarker for all seasons? *N Engl J Med* 2004;350:718–20.
10 Mueller C, Scholer A, Laule-Kilian K *et al.* Use of B-type natriuretic peptide in the evaluation and management of acute dyspnoea. *N Engl J Med* 2004;350:647–54.
11 Wang TJ, Larson MG, Levy D *et al.* Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;350: 655–63.
12 Bresalier RS, Sandler RS, Quan H *et al.* Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092–102.