THE NORTHERN HOSPITAL

DIGOXIN

English Christmas Card, 1889.

…As the more obvious and sensible properties of plants, such as colour, taste, and smell, have but little connexion with the diseases they are adapted to cure; so their peculiar qualities have no certain dependence upon their external configuration. Their chemical examination by fire, after an immense waste of time and labour, having been found useless, is now abandoned by general consent. Possibly other modes of analysis will be found out, which may turn to better account; but we have hitherto made only a very small progress in the chemistry of animal and vegetable substances. Their virtues must therefore be learnt, either from observing their effects upon insects and quadrupeds; from analogy, deduced from the already known powers of some of their congenera, or from the empirical usages and experience of the populace.

The first method has not yet been much attended to; and the second can only be perfected in proportion as we approach towards the discovery of a truly natural system; but the last, as far as it extends, lies within the reach of every one who is open to information, regardless of the source from whence it springs.

It was a circumstance of this kind which first fixed my attention on the Foxglove.

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 the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove…

William Withering, "An Account of the Foxglove" 1785.

William Withering was a world class botanist as well as physician and so in the year 1775 he was well placed to make the discovery that the digitalis plant, was beneficial to those who suffered from the "dropsy" , or congestive cardiac failure as we would label it today. He was a true man of the Eighteenth century Enlightenment, and was member of the famous "Lunar Society" of Birmingham, a group of brilliant people from all walks of life who gathered once a month on the night of the full Moon (so as to assist in their walks home after the dinner, in an age without street lighting), in order to discuss the very latest developments in the Arts, the sciences and the industrial revolution, in which the city of Birmingham was truly leading the way. He noted that patients with dropsy seemed doomed, resistant to all the treatments of physicians and apothecaries, (of which he was also one). So when he heard rumours of an old woman in Shropshire who was reported to be having remarkable success in treating people with dropsy with a secret herbal brew he decided to investigate and the rest is well recorded history. A careful man however, (in the same spirit as Charles Darwin and Isaac Newton) he would not publish his world changing findings on the Foxglove till many years after his discovery, really only being prompted to do so (as also for Charles Darwin and Isaac Newton) by the fact that others were thinking along the same lines. He thought that as others were beginning to understand the beneficial effects of the Foxglove he would need to publish right away not only in order to gain recognition for the discovery but also in order to educate physicians on its proper use - he was also we acquainted with the considerable toxic

effects of digitalis when used inappropriately by inexperienced practitioners. In his preface to "An Account of the Foxglove" he wrote:

"AFTER being frequently urged to write upon this subject, and as often declining to do it, from apprehension of my own inability, I am at length compelled to take up the pen, however unqualified I may still feel myself for the task….

The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable….."

Amoung the many case reports of his own he also gathered many reports from other practitioners on both the benefits and the toxic effects of digitalis. One amusing report he received was news of a certain American Physician named Salerne who experimented on his unfortunate turkey and discovered the GIT side effects of chronic digitalis poisoning:

"M. Salerne, a physician at Orleans, having heard that several turkey pouts had been killed by being fed with Foxglove leaves, instead of mullein, he gave some of the same leaves to a large vigorous turkey. The bird was so much affected that he could not stand upon his legs, he appeared drunk, and his excrements became reddish. Good nourishment restored him to health in eight days.

Being then determined to push the experiment further, he chopped some more leaves, mixed them with bran, and gave them to a vigorous turkey cock which weighed seven pounds. This bird soon appeared drooping and melancholy; his feathers stared, his neck became pale and retracted. The leaves were given him for four days, during which time he took about half a handful. These leaves had been gathered about eight days, and the winter was far advanced. The excrements, which are naturally[xvi] green and well formed, became, from the first, liquid and reddish, like those of a dysenteric patient.

The animal refusing to eat any more of this mixture which had done him so much mischief, I was obliged to feed him with bran and water only; but notwithstanding this, he continued drooping, and without appetite. At times he was seized with convulsions, so strong as to throw him down; in the intervals he walked as if drunk; he did not attempt to perch, he uttered plaintive cries. At length he refused all nourishment. On the fifth or sixth day the excrements became as white as chalk; afterwards yellow, greenish, and black. On the eighteenth day he died, greatly reduced in flesh, for he now weighed only three pounds".

George Bernard Shaw once famously wrote, "The man who has fed the chicken every day throughout its life at last wrings his neck instead, showing that more refined views as to the uniformity of nature would have been useful to the chicken". Given our happy Christmas traditions - as well as the Medical profession's cheerful propensity for cruel animal experimentation - Mr Shaw's warning equally applies to the unfortunate turkey! Indeed there is also a message for us - whilst we happily feed our patient's digoxin every day, we must nonetheless maintain a refined sense of nature by appreciating Dr Withering's drug's formidable potential for lethal toxicity!

DIGOXIN

The beautiful Foxglove plant, (Digitalis purpura), from which the cardiac glycoside digoxin was originally isolated, (Wikipedia)

Introduction

Digoxin is one of the oldest drugs of the modern lexicon.

Its primary use in the ED relates to **second line** therapy for ventricular rate control in rapid AF or rapid atrial flutter.

If has considerable toxicity in both the acute and chronic settings, and so its prescription must always be carefully considered.

See also separate documents on:

- **Digoxin Toxicity (Acute and Chronic) - (in Toxicology folder)**
- **Oleander poisoning - (in Toxicology folder)**
- **Digoxin-Fab Fragments (in Drugs Folder)**

History

The English botanist, geologist, apothecary and physician William Withering (1741 - 1799) is credited with the discovery of the plant alkaloid digoxin as a therapeutic agent.

He was a prominent member of the famous **Lunar Society** of Birmingham, an informal learned society of friends that met once a month to discuss the latest developments of the Arts, sciences and the industrial revolution, then in full sway.

Members included such prominent persons as Matthew Boulton, Erasmus Darwin, (grandfather of Charles) Joseph Priestley, James Watt, Josiah Wedgwood, and William Withering.

William Withering published his medical landmark, "**An Account of the Foxglove**" in **1785.**

Chemistry

Digoxin is a cardiac glycoside obtained from the leaves of *Digitalis lanata* plant.

Preparation

Tablets:

- 250 micrograms (white tablets)
- PG preparation - 62.5 micrograms (blue tablets).

  (Four of the blue tablets = one white tablet).

Ampoules:

- Digoxin 500mcg/2ml

Paediatric Elixir (solution):

- 50mcg/ml.

Mechanism of Action

Digoxin inhibits the enzyme sodium- potassium ATPase, that regulates the quantity of sodium and potassium within cells. It exchanges intracellular sodium for extracellular potassium.

Inhibition of the enzyme therefore leads to an increase in the intracellular concentration of sodium and this, by stimulation of sodium-calcium exchange leads to an increase in the *intracellular* concentration of **calcium.**

The increased intracellular concentration of calcium is responsible for the positive inotropic effects of digoxin.

The beneficial effects of digoxin result from direct actions on cardiac muscle, as well as indirect actions on the cardiovascular system mediated by effects on the autonomic nervous system, which include an increase in vagal tone and a decrease in sympathetic tone.

Pharmacodynamics

Clinical effects include

1. Slowing of the heart rate:
    - Reduces AV nodal conduction by an increase in **vagal tone** and a reduction in sympathetic activity.
    - Digoxin may also reduce sympathetic tone.
2. Increases the force of myocardial contraction:
    - This action is more pronounced in decompensated heart failure with systolic dysfunction.
3. Promotes a diuresis in patients with congestive cardiac failure.
    - Secondary to improved cardiac output.

Note that digoxin is **not** effective in:

- Rapid ventricular rates associated with increased sympathetic tone (e.g. exercise, hyperthyroidism, fever).
- Converting AF to sinus rhythm
- Preventing recurrence of AF after cardioversion

ECG effects:

Digoxin usually has an effect on the ECG and may result in:

- Prolonged PR interval
- ST depression or T wave inversion (with the typical "reverse tick pattern").

It should be noted that these changes do *not* necessarily indicate digoxin toxicity or myocardial ischaemia.

Pharmacokinetics

Absorption

- Digoxin is well absorbed orally. It can also be given IV

  Digoxin is **not** administered IM due to unpredictable absorption and local pain and irritation).

- Its oral bioavailability is 60-80%.
- Peak serum levels usually occur at 6 hours.
- Onset of effect occurs **0.5 - 2 hours** after an initial **oral** dose of 500 - 750 micrograms maximal effect occurs after 2–6 hours after oral administration.
- Onset of effect occurs **5 - 30 minutes** after an initial **IV** dose of 400 - 600 micrograms; Maximal effect occurs after 1–4 hours after IV administration.

Distribution

- Its volume of distribution is large (5-10L/kg) indicating that it is extensively bound to body tissues.
- The Vd is increased in the elderly and the obese.
- Of the small proportion of digoxin circulating in plasma, approximately 25% is bound to protein.
- The highest digoxin concentrations are seen in the **heart, liver and kidney**, that in the heart averaging 30-fold that in the systemic circulation.

  Although the concentration in skeletal muscle is far lower, this store cannot be overlooked since skeletal muscle represents 40% of total bodyweight

Metabolism and elimination

- It is predominantly eliminated **unchanged by the kidneys.**

  There is only minimal hepatic metabolism.

- In patients with *normal kidney function*, the half-life of digoxin is at least **24 hours.**

  In patients with impaired kidney function, the half-life of digoxin may be **greatly prolonged.** These patients take much longer to reach a steady state and their maintenance dose is lower. Digoxin plasma concentration should be monitored.

- Following initiation or change in digoxin dose, it takes at least 5 days (five half-lives) to achieve a new steady state.

Indications

These include:

In the ED:

1. Second line therapy for the control of rapid ventricular rates in cases off:

   - Atrial flutter
   - Heart failure

Outside of the ED:

2. Chronic heart failure due to systolic dysfunction:

   There are two indications for the use of digoxin in patients with heart failure:

   - Patients with heart failure and atrial fibrillation to control rapid ventricular rate
   - Patients with sinus rhythm when heart failure is not adequately controlled by optimal doses of ACE inhibitor, beta blocker, loop diuretic and aldosterone antagonist.

Contra-indications/precautions

These include:

- Second- or third-degree heart block (without pacemaker)
- Rapid AF involving **accessory pathways** (e.g. Wolff-Parkinson-White syndrome)

- Thyroid dysfunction:

  Hyperthyroidism:

  - ♥ May decrease digoxin concentration and increase sympathetic tone; monitor digoxin concentration and alter dose when required, or combine with another agent; dosage adjustment may be required when condition is corrected.

  Hypothyroidism:

  - ♥ May increase digoxin concentration; monitor digoxin concentration and alter dose as required; dosage adjustment may be required when condition is corrected.

- Caution with **electrolyte disturbances**:

  There is an increased risk of digoxin toxicity in situations of:

  - ♥ Acidosis
  - ♥ Hypokalaemia
  - ♥ Hypomagnesaemia
  - ♥ Hypercalcaemia

- Aortic stenosis:

  - ♥ Digoxin may worsen cardiac function in severe aortic stenosis because it increases the force of myocardial contraction.

- Hypertrophic obstructive cardiomyopathy

- DC Cardioversion:

  - ♥ Digoxin increases risk of arrhythmias after DC cardioversion; withhold digoxin for 1-2 days before elective cardioversions or use **lowest effective energy** in emergency situations.

- In ACS or myocarditis, digoxin increases risk of arrhythmias.

- Use digoxin cautiously in sick sinus syndrome (risk of severe bradycardia or sinoatrial block).

- Toxicity is more likely in the elderly and renal failure

- ♥ **Dosages need to be reduced in these situations.**

- Adverse drug interactions:

  - ♥ Treatment with drugs that **slow cardiac conduction**, **cause bradycardia** or cause **arrhythmias** may potentiate the toxic cardiac effects of digoxin; use combinations carefully and monitor cardiac function.

Pregnancy:

Digoxin is a class A drug with respect to pregnancy.

Class A drugs are those drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Breast feeding:

Safe in breast feeding.

Adverse Effects

Acute digoxin poisoning results in a delayed onset (hours) of hyperkalaemia and cardiovascular toxicity that can be lethal without digoxin antibodies.

Chronic digoxin poisoning is often missed and is associated with an appreciable 7 day mortality.

Toxic effects of digoxin include:

1. GIT:

   These are usually the *earliest signs* of toxicity.

   - Anorexia, nausea, vomiting and diarrhea occurring within 2 - 4 hours of ingestion.

2. CVS:

   Enhanced automaticity:

   - Ventricular ectopic contractions, (less commonly atrial)
   - Atrial tachycardias, often with A-V blocks
   - VT

- VF

Bradyarrhythmias:

- Sinus bradycardia
- Conduction delays / blocks
- Pre-existing AF that has become very slow, (note, AF and atrial flutter are *not* typically *caused* by digoxin toxicity. It is the ventricular *rate* that is affected)

Hypotension:

3. Metabolic:

    - Hyperkalemia, (due to blockade of sodium / potassium pump).

      Hyperkalemia of any magnitude is an important early sign of serious digoxin toxicity.

4. CNS:

    - Lethargy
    - Confusion

5. Ophthalmic:

    Visual disturbances may include:

    - Reduced acuity
    - Yellow halos (xanthopsia)
    - Altered color perception (chromatopsia).

Dosing

Rapid digoxin loading [5]

For maximal early benefits, digoxin requires loading doses, which can be administered intravenously or orally.

The total **loading** dose with digoxin varies from patient to patient but is usually between:

- **0.75 - 1.5 mg** with **intravenous** administration

And

- **1 - 1.5 mg** with **oral** administration.

Rapid intravenous loading:

For ventricular rate control in atrial fibrillation and flutter, the most rapid means of digitalization is the intravenous route.

- An initial intravenous dose of **0.25 to 0.5 mg** of digoxin is given over **several minutes.**

Followed by:

- **0.25 mg every 6 hours** for a **total loading dose of 0.75 to 1.5 mg** (i.e 10 to 12 mcg/kg lean body weight).

Intravenous digoxin begins to act in 5 to 30 minutes with a peak effect in 1 to 4 hours.

Rapid oral loading:

Rapid oral digitalization can be accomplished by giving:

- **0.5 mg** initially

Followed by

- **0.25 mg** every **6 hours** for a total loading dose of **0.75 to 1.5 mg.**

Slow digoxin loading and maintenance:

Slow oral digitalization can be achieved by starting a maintenance dosing without the need for an initial loading dose.

- Give **0.0625 to 0.25 mg** daily, (according to age, eGFR)

- A steady state will be achieved after five cycles of the drug half-life which is approximately 7 to 10 days in the average subject.

Monitoring:

Digoxin has a narrow therapeutic range; adverse effects are related to its plasma concentration.

The generally accepted therapeutic range is:

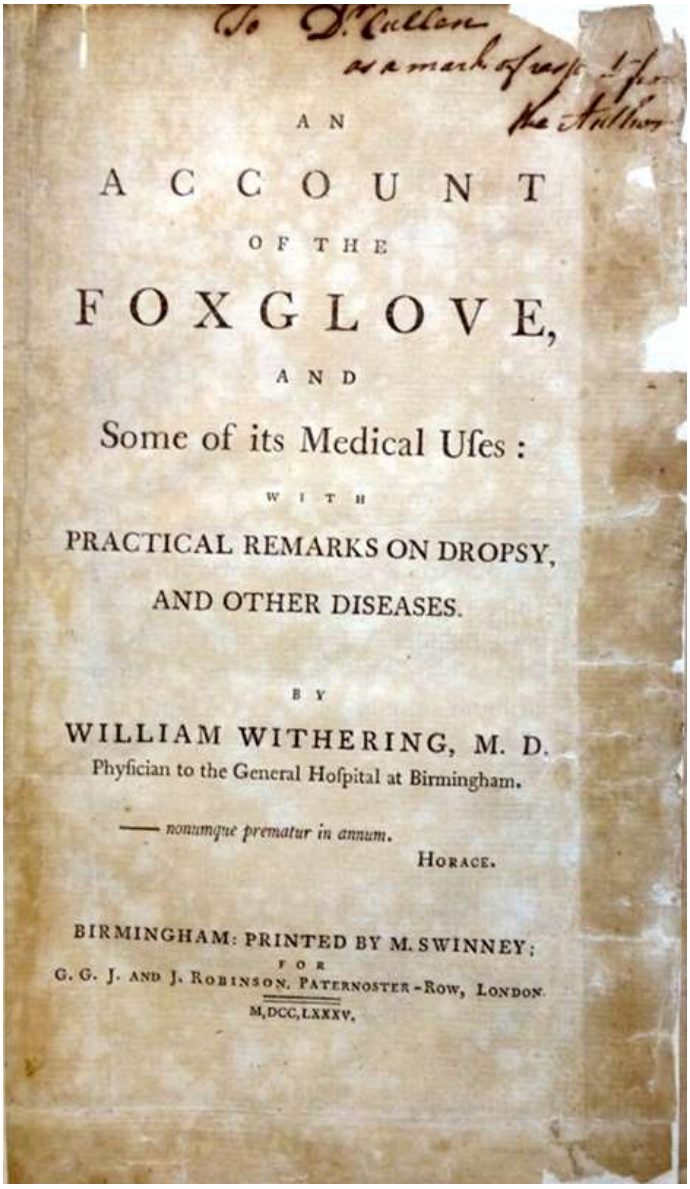
- **0.6 - 2.6 nanomol/L (or 0.5 - 2 microgram/L)**

However, toxic effects can occur at “therapeutic” concentrations, in the elderly or in those with electrolyte disturbance, hypoxia or hypothyroidism or renal failure.

Blood samples should be obtained at least **6 hours,** but optimally 12 hours, after the oral administration of digoxin to ensure completion of distribution from the blood to the tissues.

William Withering, oil on canvas, 1792. C.F von Breda, National Portrait Gallery, London

The discovery of digoxin, by William Withering was a classic example of the serendipitous nature of many brilliant discoveries, a matter of the right person, being in the right place at the right time!



To Dr Cullen
as a mark of esteem for
the Author

AN

ACCOUNT

OF THE

FOXGLOVE,

AND

Some of its Medical Uſes:

WITH

PRACTICAL REMARKS ON DROPSY,

AND OTHER DISEASES.

BY

WILLIAM WITHERING, M. D.
Phyſician to the General Hoſpital at Birmingham.

—— nonumque prematur in annum.

HORACE.

BIRMINGHAM: PRINTED BY M. SWINNEY;
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M, DCC, LXXXV.

Left: Original copy of William Withering's "An Account of the Foxglove" 1785. Right: a fold out depiction from the same work of the digitalis purpurea plant.

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Further Reading:

The Foxglove, "The Old Woman From Shropshire" and William Withering, JACC Vol. 5, No.5 May 1985: 3A-9A

Dr J. Hayes

Reviewed June 2015.