CASES IN PRIMARY CARE LABORATORY MEDICINE

Pitfalls of testing and summary of guidance on safety monitoring with amiodarone and digoxin

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BMJ 2007;334:312-5

doi: 10.1136/bmj.39090.709537.47

Patients on a range of drug therapies are often not monitored appropriately, even though this can improve patient safety

Considerable guidance is available on the safety monitoring required for many commonly used drugs. In some cases, where a clinical effect correlates with drug concentrations, this involves monitoring concentrations of the drug in blood (therapeutic drug monitoring). In other cases, such monitoring is of limited value, although knowing drug concentrations can help in diagnosing toxicity. Secondary effects of the drug on other body systems may also be monitored by using other tests or measurements.

Audits of compliance with drug safety monitoring recommendations in a range of prescribing situations have shown that monitoring of compliance remains an important area for improvement as a contributor to patient safety.¹⁻⁵

This article considers two scenarios involving the cardiovascular drugs digoxin and amiodarone and the monitoring required to detect their therapeutic and adverse effects. It also reviews the evidence based and consensus guidance that is available.

Case 1

A 71 year old man with longstanding congestive heart failure and atrial fibrillation was reviewed routinely by his general practitioner. The patient was being managed with perindopril 8 mg daily, combined with digoxin 187.5 µg daily for rate control of his atrial fibrillation. One month previously he had started taking frusemide 40 mg daily because of worsening ankle oedema associated with his heart failure. He was receiving long term anticoagulation with warfarin, stabilised at a dose of 5 mg daily.

At review he had slight ankle oedema but no other clinical signs of heart failure. His pulse was 86 beats/minute in atrial fibrillation and his blood pressure was 136/84 mm Hg. Renal function and digoxin measurement were reported as sodium 135 mmol/l, potassium 3.8 mmol/l, urea 7.2 mmol/l, and creatinine 105 µmol/l (estimated glomerular filtration rate 63 ml/min/1.73 m²). His serum digoxin concentration was 1.8 nmol/l (therapeutic range 1.0-2.6 nmol/l).

SUMMARY POINTS

- Drug safety monitoring in routine practice is often suboptimal
- Consensus guidance for safely monitoring a wide range of drugs is available
- Safe prescribing of drugs also requires a basic understanding of physiological, pathological, and pharmacological influences on the action of a drug and of its pharmacokinetics
- Blood concentrations of drugs often do not correlate closely with activity or toxicity, which can be influenced by several other factors
- "Therapeutic ranges" are produced as guides to a drug's activity, potential toxicity, or both: prescribers should know how to use these ranges

Three weeks later the patient presented with recurrent nausea over the previous four days, with vomiting on two occasions. His renal function results were similar to two weeks before, with a normal serum potassium of 4.1 mmol/l, although a digoxin measurement was reported as 2.7 nmol/l. The doctor telephoned the laboratory to discuss the large apparent rise in the digoxin concentration and for advice on further management.

This discussion revealed that the first blood sample had been taken when the patient had been seen initially in an evening surgery and the second when he had been reviewed in a morning surgery. The doctor understood that the patient took his medicines in the morning. A repeat digoxin sample taken eight hours after dosing and measurement of serum magnesium were organised. The repeat digoxin result was 2.0 nmol/l and the patient's magnesium was reported as being 0.4 mmol/l (normal range 0.75-0.95 mmol/l).

The patient was admitted to hospital for supervised intravenous magnesium sulphate supplementation. His dose of digoxin was omitted for two days and then reduced to 125 µg daily and he was started on oral magnesium glycerophosphate replacement.

Case 2

A 64 year old woman had been started six weeks previously by her local cardiologist on a loading regimen of amiodarone for symptomatic paroxysmal atrial fibrillation which had continued to recur despite initial

treatment with sotalol. She had been treated with anti-coagulants at the time of diagnosis six months before, and her international normalised ratio (INR) had been maintained close to a target of 2.5 on a daily dose of 6 mg of warfarin, which had been reduced to 4 mg because of a rise in her INR after her loading doses of oral amiodarone. She presented to her general practitioner with a history of a further short (30 minutes) episode of palpitations and light headedness typical of her previous attacks. This had developed after an episode of diarrhoea and vomiting attributed to a “bug” that other family members had had. Her doctor noted that she was in atrial fibrillation with an irregular pulse of 96 beats per minute and organised a blood sample for measurement of serum amiodarone.

Following local guidance her doctor also checked a routine thyroid function test and liver profile. The thyroid function results were reported as thyroid stimulating hormone 0.4 mIU/l (reference range 0.4-5.0 mIU/l) and free thyroxine (FT4) 30 nmol/l (reference range 11-23 nmol/l). When the doctor telephoned her local laboratory to discuss whether the patient required antithyroid treatment or review of her amiodarone treatment, she was advised that the laboratory would add free tri-iodothyronine (FT3) to the thyroid profile, and that amiodarone measurement was unlikely to be helpful in this situation unless non-compliance was suspected. The FT3 was returned as 4.2 pmol/l (reference range 2.8-7.1 pmol/l).

After discussion with the cardiologist, the patient was reassured that more time might be needed for her amiodarone to reach adequate concentrations in tissue. The patient had one further short episode of palpitations over the next six weeks, after which she had no further symptoms. Her warfarin dose was subsequently reduced further to 3 mg daily because of a further rise in her INR.

Discussion

These two cases illustrate several pitfalls in therapeutic drug monitoring and safety monitoring when digoxin

Box 1 | What safety monitoring is required in a patient receiving digoxin in primary care?

- Measure plasma digoxin to diagnose toxicity or to monitor for potential toxicity developing from a change in dose, the patient's clinical state, or other drug therapy
- Serum potassium and renal function indices should be measured at intervals depending on the patient's clinical state and other drugs taken
- Samples for digoxin measurement should be taken at least 8-12 hours after the last dose, and 8-10 days after any change in dose
- Plasma monitoring is not necessary in clinically and biochemically stable patients

and amiodarone are used.

Case 1

In the first case, a serum sample was taken for digoxin only a few hours after the dose and produced a result compatible with toxicity, in a normokalaemic patient who was subsequently found to be hypomagnesaemic. Timing of the sample is important for digoxin measurement. Current recommendations are for the sample to be taken 8-12 hours after the previous dose. In addition, a digoxin result within the “therapeutic range” does not exclude digoxin toxicity, as individual susceptibility varies considerably.

Potassium, magnesium levels

Various cations affect the excitability of different nerve and muscle cells in the body, including the myocardium. Changes in the serum concentrations of potassium, magnesium, or calcium may lead to arrhythmias. The cardiac consequences of severe hypokalaemia or hypomagnesaemia are both important, particularly as hypomagnesaemia can worsen pre-existing hypokalaemia, and the likelihood of problems is increased by coronary artery disease and in patients taking digoxin.⁶ Low serum potassium concentrations can reduce the renal excretion of digoxin and increase myocardial uptake of digoxin; this is relatively well known, and hypokalaemia induced digoxin toxicity is fairly well recognised in clinical practice.⁷ Although in this case the patient's serum potassium concentration remained within the population reference range despite his loop diuretic, possibly as a result of the angiotension converting enzyme inhibitor, he had developed diuretic induced hypomagnesaemia. Hypomagnesaemia predisposes to digoxin toxicity and also leads to hypocalcaemia and hypokalaemia. Hypomagnesaemia seems to cause hypokalaemia via the Na/K ATPase pump, which depends on magnesium and is responsible for retention of potassium. Hypomagnesaemia causes defective release of parathyroid hormone, resulting in hypocalcaemia.

Hypomagnesaemia, although quite common in hospitalised patients, is under-recognised in clinical practice. The patient may develop muscular tremors, tetany, or altered mental state, but these symptoms may be misinterpreted. Magnesium depletion can result from decreased absorption or, more

Commonly used drugs need safety monitoring

commonly, increased loss from the intestines (for example, diarrhoea) or renal losses. Diuretic induced hypomagnesaemia is common, particularly in elderly patients taking digitalis,⁸ and increases susceptibility to the toxic effects of digoxin, which may occur in patients who are within the “therapeutic range.”⁹ As magnesium salts are poorly absorbed orally, this patient was admitted for intravenous replacement before being given oral magnesium.

Guidance

The evidence based guidance for safety monitoring in patients taking digoxin is summarised in box 1. Although routine digoxin measurement is not recommended in clinically and biochemically stable patients,¹⁰ existing guidelines emphasise changes in clinical state, the concomitant use of drugs that may impact on toxicity,¹¹ and recognition of situations predisposing to toxicity¹²—notably renal insufficiency.¹³ Even if no recognised concomitant medications or medical conditions could have altered the pharmacokinetic profile or indirectly altered its cardiac effects by pharmacodynamic interactions, the presence of toxic symptoms such as nausea, vomiting, visual disturbance (yellow-green discoloration), or severe dysrhythmias may prompt an urgent measurement.

Case 2

In the second case, amiodarone produced thyroid test results resembling biochemical thyrotoxicosis, which is a recognised complication of treatment with amiodarone, although it is rarer than amiodarone-induced hypothyroidism in countries with high environmental iodine content such as the United Kingdom.¹⁴ Amiodarone interferes with the peripheral conversion of FT4 to FT3 and may produce a rise in FT4 to levels above the reference range, with a fall in FT3.¹⁵ In parallel, an acute illness in this case can produce various effects on thyroid hormone results, including a fall in thyroid stimulating hormone (TSH), described under the term non-thyroidal illness.¹⁶

Few if any laboratories routinely measure FT4, FT3, and TSH in standard thyroid profiles; many use a TSH measurement to screen for primary thyroid disease

Box 2 | What safety monitoring is required in a patient receiving amiodarone in primary care?

- Minimum safety monitoring at baseline and every six months on patients treated with amiodarone if levels are within the population reference range:
Thyroid profile (TSH, FT4, and FT3 where applicable)
Liver enzymes (aspartate aminotransferase, AST) and renal function (“urea and electrolytes”) Clinical evaluation
- Annual chest x ray, electrocardiogram, and clinical assessment
- Prothrombin ratio monitoring weekly during the first seven weeks of warfarin treatment, after which warfarin should be adjusted depending on response

before performing further tests. In the case of patients receiving amiodarone, measurement of FT3 is required for interpreting results when FT4 or TSH values are outside reference limits, and it is important that information about drugs taken is available to the laboratory so that the correct thyroid tests can be selected and erroneous interpretation avoided. The fall in this patient's warfarin requirements was consistent with the decrease in renal clearance of warfarin during treatment with amiodarone¹⁷; clearance may take weeks to months because of the large volume of distribution (up to 5000 litres in an adult) and the consequently long half life of the drug (up to 60 days during chronic treatment). Similarly, although oral loading with 400-600 mg daily is used in the initial weeks of treatment, achieving full anti-arrhythmic activity may take many weeks.

Use of amiodarone can result in many other adverse effects, especially at doses of greater than 200 mg daily. Many organ systems other than the thyroid are affected, including the lungs (pneumonitis, fibrosis), liver (raised liver enzymes), nervous system (neuropathy), and skin (discoloration). Although several clinical monitoring strategies are suggested (box 2), after initial treatment the need for ongoing treatment should be considered, and where possible the dose should be decreased or rationalised if other effective treatments are available.

Evidence note

The therapeutic interactions and toxicities of digoxin and amiodarone have been identified from observational studies. Studies of monitoring practice are limited by their setting, as practices vary between and within countries, between primary and secondary care, and over time as practice evolves. Nevertheless, the high reported figures for mistimed samples or samples that are inappropriate for monitoring digoxin, or for incomplete monitoring for amiodarone, from the more recent of these studies provide strong circumstantial evidence that incorrect monitoring remains an important patient safety issue. A review of interventions indicates that a combination of education and active interventions can change requesting practices,¹⁸ although the guidance found on monitoring relies primarily on expert and consensus opinions that are based on observational studies of the incidence of toxicity and at-risk groups for toxicity.

USEFUL WEBSITES

- Lab tests on Line (www.labtestsonline.org.uk)—a comprehensive guide to laboratory tests and their use for patients
- Cochrane Library (www.nelh.nhs.uk/cochrane.asp)—information and systematic reviews on evidence based medicine. The Cochrane Collaboration is beginning reviews on laboratory diagnostic testing
- Journal of Clinical Pathologists (www.jclinpath.com)—electronic access (by subscription) to the Journal of Clinical Pathology, with full content of the questions and answers examined in this article
- Clinical evidence (www.clinicalevidence.com)—summaries of current evidence based management guidelines
- PRODIGY (www.prodigy.nhs.uk)—clinical decision making guidelines principally for general practitioners
- E Medicine (www.emedicine.com)—comprehensive resource for medical practitioners with links to public information classified by disease type

We thank Mrs Susan Richardson for typing this manuscript, A Taylor who coauthored the original review answers, and the clinical practice section of the Association of Clinical Biochemists (in particular I D Watson, C van Heyningen, and D Freedman) for commenting on this document. We also thank D Housley (Association of Clinical Biochemists), R Gama, (Association of Clinical Pathologists), and N Campbell (Royal College of General Practitioners), who kindly reviewed the original work and added valuable comments in addition to those of the steering group, and I Watson, who coauthored the original guidance.

Competing interests: None declared.

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Accepted: 2 January 2007

BMJ UPDATES

Permanent pacing is a powerful placebo for people with vasovagal syncope

Research question

Is pacing an effective treatment for adults with refractory vasovagal syncope?

Answer

Probably not, although even the best trials are still too small to be conclusive

Why did the authors do the study?

Permanent pacing is one option for adults with vasovagal syncope who don't respond to medical treatment, but the evidence from individual trials is mixed. These authors wanted to synthesise all the published data on pacing to find out if it works or if the early promise shown in some small trials was simply the result of a placebo effect.

What did they do?

They searched systematically for randomised controlled trials of permanent pacing for adults with refractory vasovagal syncope. They searched databases of published and unpublished trials in any language, hand searched reference lists of trials and review articles, and contacted experts and authors for any trials they might have missed. All included trials were assessed for

quality using a standard method.

The authors pooled data from the trials using three different analysis techniques. They did further analyses to look for heterogeneity and publication bias and did a sensitivity analysis to test the robustness of their findings.

What did they find?

Nine randomised trials met their inclusion criteria and included a total of 430 adults. The methods were too heterogeneous to pool data meaningfully from all nine trials, so the authors separated them in to three groups: four open label (unblinded) trials comparing pacing with medical treatment, three open label trials comparing one active pacing modality with another, and two double blind trials comparing active pacing with inactive pacing (a placebo). Active pacing reduced patients' symptoms in both groups of open label trials (odds ratios for recurrent syncope 0.09 (95% CI 0.04 to 0.22) and 0.04 (0.01 to 0.23)), but not in the two trials that were rigorously double blind (0.83 (0.41 to 1.70)). The authors estimate that 76% of the benefits reported by the open label trials were due to an expectation or placebo effect, which was all but wiped out in trials that hid the allocated treatment from both the patients and their doctors.

What does it mean?

These findings suggest that when patients know they have an active pacemaker in they get better because they expect to, not because the pacemaker is actually doing them any good. It's also possible that investigators measure outcomes more favourably for patients they know to be actively treated. When both these biases are removed by double blinding, the treatment no longer seems to work. There is still room for doubt, however. The double blind trials included only 129 patients between them and may not have been powerful enough to detect small but clinically relevant benefits.

Since vasovagal syncope is generally benign, and often gets better on its own, these authors say permanent pacing is a poor first choice of treatment for most people. A rigorously double blinded trial including at least 500 patients is required to find out if pacing is a useful treatment for anyone.

Sud et al. The expectation effect and cardiac pacing for refractory vasovagal syncope. *Am J Med* 2007;120:54-62

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