Monitoring Response to Drug Treatment

Introduction

Clinicians are frequently asked to monitor the effects of drug treatment with the objective of ensuring safe and effective therapy. In this issue we present the first in a series of articles which focus on optimal monitoring of drug treatment.

Monitoring takes many forms and there is evidence that in many situations it is done inappropriately (too much or too little or at the wrong time) or not targeted at specific parameters that are clinically useful. A New Zealand study showed that over 50% of serum digoxin concentrations were not taken at the correct time to allow meaningful interpretation of the result, and 5% of the measurements led to inappropriate dose adjustments.[1] Other studies have shown excessive and unnecessary monitoring of antiepileptic drug concentrations and we now know that routine monitoring of CK and liver function tests in people taking statins is unnecessary. On the other hand, failure to check the CBC in a person taking clozapine or not attaining therapeutic drug concentrations in a person taking lithium can have severe consequences. Monitoring is also much more than objective laboratory testing as it often includes the participation of the patient by their informed reporting of signals of clinical response or adverse drug reactions.

Despite comprising at least 30 – 40% of all blood tests in general practice,[2] monitoring is relatively poorly studied and is often associated with non-specific and even vague guidelines. Improvements in monitoring by clinicians and patients are likely to improve benefits, reduce adverse events and reduce costs.

Some examples of monitoring include:

- Monitoring laboratory tests (e.g. LFTs, CBC) to check for early signs of an adverse drug reaction.

  Objective monitoring for adverse effects.

- Monitoring drug concentrations (e.g. digoxin, lithium) to attain therapeutic response without dose related toxicity, or to confirm compliance.
- Monitoring for signs or symptoms which may be indicative of a side effect or adverse drug reaction, e.g. delirium or constipation with a tricyclic antidepressant, or muscle pain with a statin.

  Subjective monitoring for adverse effects

- Monitoring biochemical markers as a response to treatment and/or toxicity, e.g. lipid profile with statins, INR with warfarin, TSH with thyroxine.
- Monitoring clinical response to treatment, e.g. preventers and relievers in asthma therapy.

"Know the abnormality that you are going to follow during treatment. Pick something you can measure."

Meador C. A Little Book of Doctors' Rules.
Lyons: IARC Press, 1999

This article provides a general introduction to some of the principles of monitoring the response to drug therapy in order to ensure optimum response without significant adverse effects. In future issues suggested monitoring strategies will be described for specific drug and therapeutic categories.

Monitoring Strategies

An overriding principle of monitoring is that there should be justification and some degree of assurance that the practice will actually meet the objectives the test. Furthermore, the test must be correctly performed, e.g. in the right time frame, and be interpreted correctly to be meaningful.

Monitoring Strategy (adapted from Glasziou et al[2])

- Is the test a good predictor of relevant clinical outcomes or adverse effects?

  Will routine monitoring of CBC detect drug-induced agranulocytosis? Are clinical symptoms more reliable?

- Can the test detect changes in risk early?

  Is the CBC likely to pick-up on a downward trend in the blood count as an early sign of the problems?

- Is there an optimum interval for monitoring?

  Is the blood dyscrasia more likely to occur within a certain timeframe that may dictate the duration of monitoring?

- Is random testing useful or can it be made acceptable by repeated measurements?

  What is the value of a one-off CBC? Is there any value in monitoring more frequently?

- Is the test accessible and acceptable to patients and cost effective for health care providers?

  If checking the CBC is very unlikely to detect an outcome is it worthwhile?

- Are there any additional risk factors which provide further justification for testing?

  Will a history of blood dyscrasias or concurrent use of a medicine with a similar adverse effect profile provide justification to change the monitoring parameters?

Objective monitoring for adverse effects.

Many drugs have laboratory monitoring recommendations mentioned in their data sheets. However, if the above criteria are applied the supporting evidence for many monitoring schedules is relatively weak. In addition, vague statements such as periodic checking of liver function or occasional checking of electrolytes are generally unhelpful as they lack precise guidance.

The antithyroid drug carbimazole can cause agranulocytosis but this is relatively rare and it usually occurs rapidly without an indicative downward trend in the blood count. Therefore a routine CBC every few months or random testing are very unlikely to identify the event. Early signs of infection such as a sore throat or fever are much more reliable predictors of agranulocytosis so the emphasis should be placed on educating the patient on early warning signs rather than blood tests.

In contrast clozapine induced agranulocytosis is much more common, usually occurs early in treatment and can often be detected early by regular blood tests which can show a downward trend in the neutrophil count. More is known about the "natural history" of clozapine induced agranulocytosis which justifies the rigorous and specific monitoring regimen.

If the effect is relatively common, such as hypothyroidism induced by lithium, regular measurement of TSH is justified as the condition can be detected before significant symptoms appear allowing the introduction of thyroid replacement therapy or an alternative drug.

Monitoring drug concentrations

Therapeutic drug monitoring (TDM) by measuring serum concentrations is useful for a relatively small range of drugs that meet specific criteria. For most drugs, the serum concentration does not correlate well with therapeutic effect and treatment is guided solely by clinical response. For drugs that do have a good correlation between concentration and effect, TDM can assist monitoring and guide dose adjustment in addition to assessing clinical response.

Generally, criteria for TDM are as follows:

- There is a narrow range between a sub-therapeutic serum drug concentration (SDC) and a toxic SDC. This is referred to as the drug's therapeutic range.
- There is a predictable relationship between the SDC and therapeutic or toxic effects.
- The measurement of SDC must be better or enhance other methods of monitoring.
- There is an unpredictable relationship between the dose administered and the SDC.
- There is a suitable assay for the drug.

Lithium is a good example where TDM is useful if not essential for optimal treatment. Serum lithium concentrations are clearly related to clinical effect; if the concentration is too low a clinical response is unlikely but if the concentration is too high the risk of toxicity is increased. The range that includes clinical response without toxicity is the therapeutic concentration range. Unfortunately, due to interindividual variability in drug handling, it is not possible to accurately predict what lithium concentration will be attained from any given dose. Therefore TDM can be used to titrate the initial dose to give a target drug concentration and the dose can be further adjusted according to clinical response or adverse effects. If response is sub-optimal, the SDC may guide the magnitude of a dose increase without significant risk of adverse effects. Subsequently, measurement of SDC can be used to check compliance or assess the impact of drug interactions that may change lithium concentrations. Other drugs which are candidates for TDM include digoxin, some antiepileptic drugs, theophylline and some antibiotics. In future issues specific monitoring strategies will be discussed.

Subjective monitoring of adverse effects

Patients and carers should be informed about what to look for and report early signs of possible adverse effects. This has to be done in the context of explaining the benefits of treatment.

A person taking a statin should be informed to report myalgia especially if this is of sudden onset, is severe or worsens or appears with an increase in dose. A subsequent check of the CK may indicate the need to reduce the dose or consider alternative treatment. In this case subjective reporting of symptoms may indicate the potential value of an objective laboratory test.

The situation with statins is well known but it should be realised that all drugs have adverse effects that are potentially preventable if the early warning signs are recognised. Many adverse effects are very predictable as they are dose related and an extension of the drug's pharmacological effect.

Advice directly to the patient about what to look for, or a simple note in the patient's records, can be valuable in detecting adverse effects at an early stage and possibly preventing more serious consequences. For example, if a patient in residential care is prescribed haloperidol for psychoses and agitation, a flag can be made in the patient's notes to "monitor" for common adverse effects such as constipation and hypotension. Early identification of these effects can reduce drug related morbidity.

Some examples of subjective monitoring parameters with possible causes and action points are given in Table 1. This will be expanded in future issues.

References:

1. Sidwell A, Barclay M, Begg E, Moore G. Digoxin therapeutic monitoring; An audit and review. NZMJ;2003:116:U704

2. Glasziou P, Irwig L, Mant D. Monitoring in chronic disease: a rational approach. BMJ 2005;330:644-648

Table 1: Some examples of subjective monitoring parameters with possible causes and action points

Drug or drug class	Monitoring parameter, possible cause and action.
Drugs causing leucopenia	Infection, sore throat, fever *Check CBC*
Drugs with anticholinergic effects	Constipation, urinary retention, drowsiness *Reduce doses or modify drug treatment*
Anihypertensives	Postural hypotension, dizziness; especially on diuretics. *Modify doses or drugs, check electrolytes*
Serotonin Re-uptake Inhibitors	Agitation and restlessness in early treatment. Dose may be too high or drug unsuitable. *Reduce dose or change drug. Review diagnosis.*
NSAIDs	Darkened stools may indicate GI bleeding. *Check for blood in stools. CBC.*
Digoxin	Changes in vision, especially colour vision may indicate digoxin toxicity or hypokalaemia *Check serum digoxin concentration, renal function and electrolytes*
Phenytoin	Ataxia may indicate toxicity due to high blood concentrations. *Check serum concentration of phenytoin and compliance*
Amiodarone	Intractable cough – may indicate pneumonitis *Chest X-ray*