Monitoring drug therapy

Andrew W Hitchings

Abstract

It is important to monitor drug therapy because the effects of a particular drug regimen can vary significantly between individuals. Wherever possible, therapeutic effect should be monitored using a clinical endpoint (i.e. a measure that directly reflects how the patient feels, functions or survives). In practice, it is often not feasible to use a clinical endpoint to guide therapy, particularly for preventive treatments. The next best option is to use a surrogate endpoint: a measure that changes so as to predict whether the clinical endpoint will be achieved. For a few drugs, neither a clinical nor a surrogate endpoint is available. In these instances, if the drug has a narrow therapeutic index and there is a predictable relationship between its concentration and its effects, it may be appropriate to measure its concentration in the blood. This article discusses approaches to monitoring drug therapy using clinical and surrogate endpoints, and plasma concentration monitoring. Specific guidance is provided for plasma concentration monitoring of digoxin, gentamicin, vancomycin, phenytoin, lithium and theophylline.

Keywords Biomarkers; clinical markers; drug monitoring; drug therapy; surrogate endpoints

Key points

- Drug therapy should be monitored due to the potential for inter-individual variability in drug response
- Wherever possible, drug therapy should be monitored using a clinical endpoint — a characteristic or variable that reflects how a patient feels, functions or survives
- When it is not possible to use a clinical endpoint to guide therapy, a surrogate endpoint can be used — a characteristic or variable that changes in such a way as to predict whether the clinical endpoint will be achieved
- Measurement of plasma concentrations is indicated for only a few drugs — those in which effects of the drug are difficult to measure, the relationship between plasma concentration and clinical effects is predictable or the therapeutic index is narrow
- When measuring the plasma concentration of a drug, usually take the sample at steady state (at least five half-lives after starting the dosage regimen), and always record the time of the sample in relation to the last dose

What is monitoring?

When we prescribe a medicine, we do so in the expectation that its benefits will outweigh its risks. Subsequently, some assessment is invariably required to confirm whether our judgement holds true for that individual. We can simply ask the patient to return if their symptoms do not improve or if they experience adverse effects. Alternatively, we can objectively assess the drug's effects. Occasionally, we measure the concentration of the drug in the blood. These are all forms of monitoring. This article will focus on monitoring the beneficial effects of drug therapy, but prescribers should also be aware of the importance of monitoring as a means of detecting early signs of adverse drug effects.

Why monitor drug therapy?

The relationship between a prescribed dosage regimen and its resultant clinical effects is complex. It can be influenced by the patient's concordance with the treatment plan (affecting the amount of drug entering the body), the manner in which the drug is handled within the body (pharmacokinetic variability) and the effect the drug has on that individual (pharmacodynamic variability). Together, these sources of variability create uncertainty over how a particular patient will respond to a particular treatment regimen. This can be resolved only by monitoring the effects of therapy in that individual.

How can drug therapy be monitored?

Monitoring using clinical and surrogate endpoints

In general, monitoring parameters are most likely to be informative if they are closely related to the clinical outcome that the treatment is intended to produce (Figure 1). Indeed, wherever possible, it is best to monitor the clinical endpoint itself. A *clinical endpoint* can be defined as a 'characteristic or variable that reflects how a patient feels, functions, or survives'.[1] For example, when a benzodiazepine is administered to allow an interventional procedure to be performed, the clinical endpoint — sedation — is usually readily apparent. The drug dosage can be titrated to achieve the required level of sedation.

Often, however, measuring the effect of the drug on the clinical endpoint is impractical or cannot readily be used to guide therapy. This could be because the clinical endpoint is an event that cannot be detected until it is inevitable or irreversible, as is typically the case in preventive therapy (e.g. anticoagulation to reduce the risk of stroke in atrial fibrillation). Alternatively, it can be because the clinical endpoint is a delayed event, which cannot be measured until after treatment has finished. For example, the clinical endpoint in the treatment of pneumonia — cure of the infection, most reliably confirmed by the resolution of symptoms and radiographic consolidation — may not be measurable until weeks after the treatment course has ended. In these situations, we should seek to attempt to identify a suitable *surrogate*

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Competing interests: none declared.

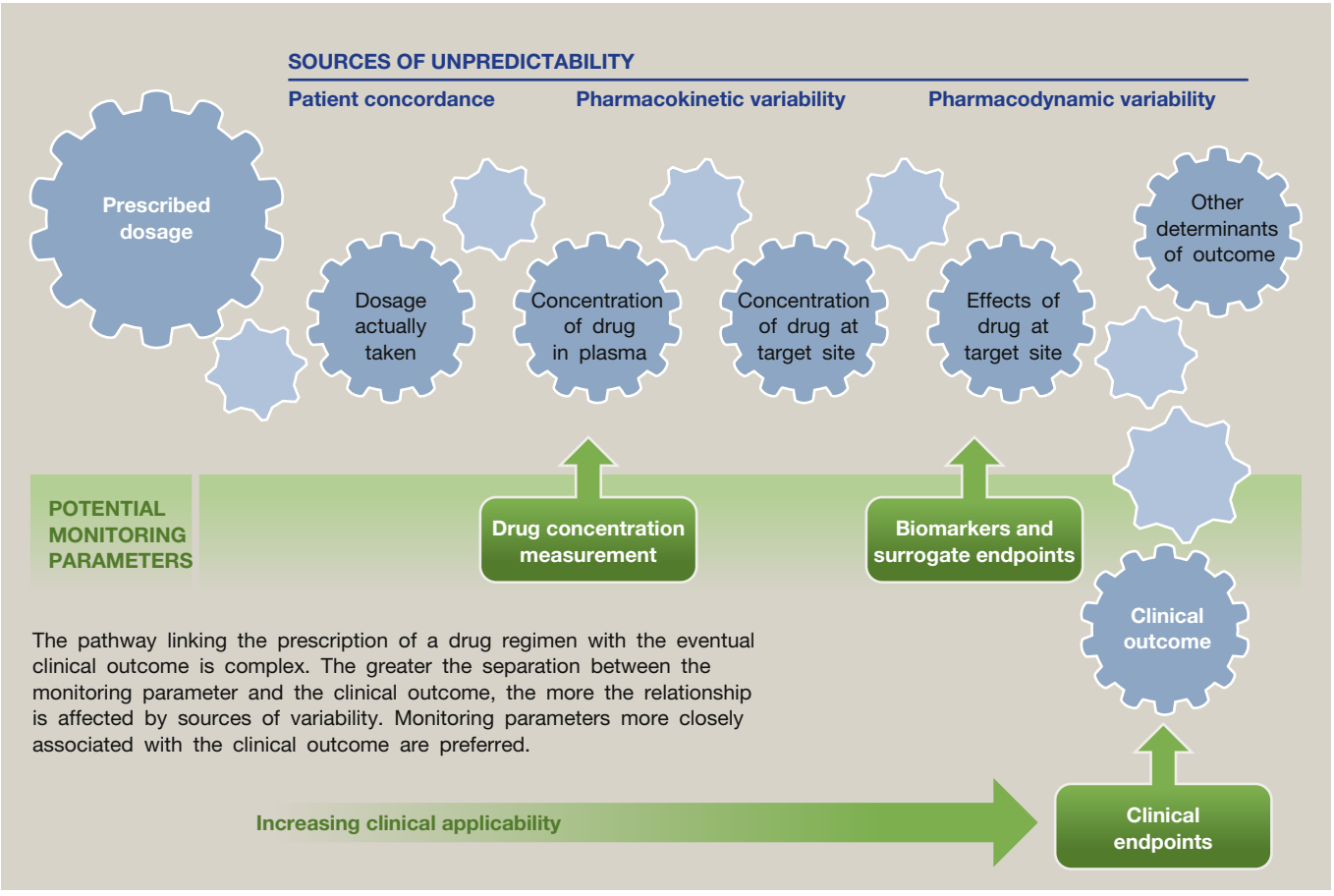

Figure 1

endpoint. A surrogate endpoint is a clinical variable, such as a blood test or examination finding, that does not itself affect the way the patient feels, functions or survives, but which changes in such a way as to predict whether the clinical endpoint will be achieved. Surrogate endpoints may be:

- **Directly related to the clinical endpoint** as an intermediate step in the causal pathway: for example, blood pressure (surrogate endpoint) is directly related to the risk of heart attack or stroke (clinical endpoint).
- **Indirectly related to the clinical endpoint**, not as part of the causal pathway but changing in parallel to it: for example, correction of an abnormal body temperature (surrogate endpoint) can provide an indication of the likelihood of curing an infection (clinical endpoint).

Any biological characteristic that is *objectively measured* as a marker of physiological, pathological or therapeutic pathways (e.g. white cell count) can be termed a *biomarker*.[1] When used to measure the effect of treatment, the biomarker is acting as a surrogate endpoint. Thus, from a semantic perspective, biomarkers and surrogate endpoints can be considered related but not synonymous terms (Figure 2).

Monitoring using drug concentration measurements

A variety of factors can complicate the interpretation of plasma drug concentration, as illustrated in Figure 3, such that this is generally considered the monitoring parameter of 'last resort'. Criteria have been proposed to help identify drugs for which plasma concentration measurement is likely to be worthwhile.[2]

1. **The clinical and pharmacodynamic effects of the drug are difficult to monitor** – i.e. it is not feasible to measure the clinical endpoint directly, and no suitable surrogate endpoint exists. For example, it would clearly be inappropriate to measure the plasma concentration of a glucose-lowering agent, given that a suitable surrogate endpoint – blood glucose concentration – is readily available.
2. **The relationship between plasma concentration and clinical effects is predictable** – we should know the range of plasma concentrations at which there is a high probability of beneficial effects and a low risk of toxicity (the target range). For example, there is a good correlation between the plasma concentration of phenytoin and its clinical effects, with a well-defined target range. This, combined with its narrow therapeutic index (see below), makes a compelling case for monitoring plasma phenytoin concentration to guide dosage adjustment. For other antiepileptic drugs, regular plasma concentration monitoring is generally not necessary in routine practice.
3. **The therapeutic index is 'narrow'** – i.e. the ratio between the lowest concentration associated with toxicity, and the lowest concentration associated with benefit, is low. This