Introduction to monitoring

What is what you prescribed actually doing?

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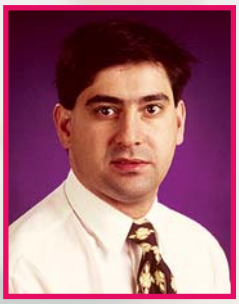

This is the ninth article in the series on general practice prescribing.

BACKGROUND Having written a prescription for the patient, it is important to monitor for the effects of the drug.
OBJECTIVE This article discusses the importance of patient monitoring as part of the prescribing process, and in particular, what factors to monitor.
DISCUSSION Monitoring of drug therapy is an important part of the prescribing process in enhancing the drug's effectiveness. This is partly due to the large variability in patient response to any given dose of a drug. The drug's effect as well as adverse effects should be actively sought, and dosage alterations made in order to enhance the drug's effect. In some cases, this involves directly monitoring for the drug's effects, and in other cases using surrogate markers.

For most clinicians, what we have covered so far in this prescribing series seems to be all there is to it: you consider what to write, you write the prescription and the patient comes back if they have any problems. Unfortunately, this is a common fallacy in the prescribing process. Although this is appropriate for short term prescriptions for intermittent ailments, more and more the work of general practitioners is managing chronic illnesses, and it is the appropriate monitoring of the prescription that enhances the benefit of all of the steps undertaken so far. Furthermore, it is this monitoring step that is the worst performed in the prescribing process.

Despite the spiel from pharmaceutical companies that their new drugs will work in all patients (and have a similar adverse reaction profile to placebo) it is a well documented fact that individual patients will have an individual response to any prescribed medication. Some may benefit with or without adverse reactions, whereas others may experience no beneficial effect at all, and others only adverse effects. Patients are individuals, and their response to medications is variable.

We are only now beginning to understand some of the reasons behind this variability. Some of it has to do with the way the patient's body handles the medications (eg. genetic differences in hepatic cytochrome P450 enzymes), the genetic differences in the receptors with which the drug interacts, and a lot has to do with drug compliance which varies for many reasons such as experienced adverse effects, lack of efficacy, cost and sociocultural issues. The bottom line is that the prescription of each drug is a therapeutic trial that may be a success or failure, and unless you review the patient and monitor for the drug's effects, you will not know if the trial worked. Furthermore, by monitoring then altering the prescription, you may be able to turn a failed trial into a success.

Many GPs may be reluctant to bring patients back for further follow up because of concerns about over servicing. Although this may be an appropriate concern for the treatment of short term illnesses, for chronic conditions monitoring is simply a good investment. Many studies have shown that the use of medications such as angiotensin converting enzyme (ACE) inhibitors and statins in high risk groups are cost effective, but long term compliance is poor for a variety

of reasons. Hence, ensuring these medications are used appropriately ensures cost effectiveness.

So how do we go about monitoring prescriptions and what exactly do we monitor for? Have a look at the case of Edna.

Case history – Edna

Edna is 76 years old. She suffers from hypertension and has had a previous stroke. She has been seeing you for some time complaining of osteoarthritis of the knees. She has tried paracetamol, and has found the relief to be inadequate. You decide to prescribe her celecoxib 100 mg twice per day. Her other medications are aspirin 100 mg, fosinopril 20/hydrochlorthiazide 12.5 mg.

It is well documented that the response of osteoarthritis symptoms to NSAIDs is quite variable, with some patients having little relief and others considerable improvement in pain and mobility. There have been numerous meta-analyses on this subject,[1–3] but it appears that about 60% of patients have clinically significant improvement (ie. 50% reduction in symptoms) in their pain and immobility.[4] The other 40% do not really get effective analgesia, but may well suffer from the adverse effects of NSAIDs. Furthermore, unless patients are reviewed and efficacy is enquired about, they are unlikely to be tried on other forms of therapy that may be more effective for them (eg. a combination of paracetamol with a weak opiate).

The adverse effects of medication such as celecoxib in a patient such as Edna are well documented. She may have an increase in blood pressure[5] which places her at a greater risk of recurrent stroke, she may have a worsening of renal function or acute renal failure as a result of the 'triple whammy' effect in combination with an ACE inhibitor and diuretic,[6] and there have also been recent reports of neuropsychiatric reactions with COX-2 inhibitors.[7] The CLASS study also documented an approximate 10–15% incidence of dyspepsia and abdominal pain.[8]

Table 1. Treatments with symptomatic effects

Drug	What is frequently monitored	What should also be monitored
Parkinson treatment	Symptom improvement, nausea, vomiting	Postural hypotension
NSAIDs	Pain relief, dyspepsia	Blood pressure, renal function, weight (for fluid retention) in at risk patients
Diuretics for cardiac failure	Symptoms of cardiac failure, electrolytes	Postural hypotension
Nitrates	Anginal symptoms	Postural hypotension
Oxybutynin	Improvement in urinary incontinence	Confusion or worsening of dementia in elderly, constipation, dry mouth, blurred vision
Low dose tricyclic antidepressants for insomnia	Effect on sleep	Confusion or worsening of dementia in elderly, constipation, dry mouth, blurred vision, daytime sedation, postural hypotension
Digoxin	Heart rate, symptoms of cardiac failure, plasma concentration	Anorexia, nausea
SSRIs	Depression	Plasma Na^+ in elderly at high doses, sexual dysfunction
Antipsychotics	Psychiatric symptoms	Depending on the agent and dose: weight gain, cardiac effects, eg. postural hypotension, QT prolongation, extrapyramidal effects
Sibutramine	Weight	Heart rate, blood pressure

Variability in response

This issue of variability in response to a particular drug therapy is an important one in therapeutics. For certain medications such as the thiazolidinediones (can anyone actually pronounce that word!) for diabetes (eg. pioglitazone and rosiglitazone), various agents for dementia (eg. donepezil or even beta blockers) there appear to be certain patients that are simply nonresponders. As discussed previously, genetic reasons are thought to underlie these differences in response. Hence, it has been suggested, for example, that patients commenced on rosiglitazone should be trialled on 4 mg per day initially, then if a response is seen, the dose could be increased to 8 mg for greater efficacy. If there is no improvement in the glycaemic control after 6–8 weeks of treatment, there is unlikely to be any benefit in dose escalation. Similarly, there are other patients who have a dramatic response to initial doses of thiazolidinediones and require reduction in the dosage of other medications in order to avoid repeated hypoglycaemia.

Symptomatic medications

The issue of monitoring for a response is particularly pertinent for treatments that provide symptomatic benefit only. Table 1 lists examples of such treatments, what is usually monitored in these patients, as well as what should be monitored for, but is frequently forgotten. Other examples not listed include hormone replacement therapy for menopausal symptoms, most dermatological treatments, inhaled bronchodilators, as well as many gastrointestinal treatments for complaints such as dyspepsia and constipation.

It can be seen from the list that many of

Table 2. Treatments with long term effects

Drug	Clinical effect: prevention of	Surrogate marker	Other monitoring
Antihypertensives	Long term complications	Blood pressure	Depending on agent, eg. ACE inhibitors/thiazides: renal function, electrolytes, beta blockers: heart rate, dihydropyridines: ankle swelling
Statins	Ischaemic events	Cholesterol	Symptoms of myalgia
Warfarin	Ischaemic events	INR	Symptomatic evidence of bleeding, development of contraindications
Bisphosphonates	Fractures	Bone mineral density (BMD)	Gastro-oesophageal symptoms
Corticosteroids for immune disease	Disease complications	CRP, ESR, auto-antibodies	Depending on dose: BP, BSL, BMD, proximal muscle strength, weight, cataracts, infections and others
Inhaled corticosteroids for asthma	Asthma complications	Peak flow, lung function testing	Inhaler technique
Antimania drugs, eg. lithium	Disease relapse	Serum levels	Depending on agent, eg. lithium: symptoms of polydipsia/polyuria, tremor, weight gain
HIV drugs	Disease complications/AIDS	CD4 counts, viral load	Depends on drug used

the commonly prescribed symptomatic treatments have significant toxicity. A good example is oxybutynin. Anticholinergic agents have only modest efficacy in reducing the incidence of urge incontinence (approximately one less episode of incontinence per 48 hour period[9]) but can have serious adverse effects in the elderly. Hence, whether the patient actually gets any benefit from such medication should be investigated and therapy ceased if the patient does not respond. Other medications such as hormone replacement therapy are very effective for reducing hot flushes (approximately 77% reduction in incidence of flushes[10]) but again, because of concerns about the long term toxicity of these medications, should not be continued unnecessarily.

Preventive medications

Other medications are used to prevent long term complications, eg. antihypertensives or statins. For these agents it is difficult to monitor the actual effect of the drug (absence of ischaemic complications) hence surrogates are used, eg. blood pressure or lipid levels, respectively. Table 2 lists examples of such drugs, their clinical effects, commonly monitored surrogates, as well as other things that should be monitored for. The most important thing to remember for these drugs is that the effect being monitored is only a surrogate, and as such may be an imperfect measure of the clinical effect of the drug.

Some medications may overlap between requiring symptomatic or surrogate monitoring. A good example is the antiepileptics. If the seizure frequency is high, then the occurrence of symptoms can be used to monitor for the effects of drug therapy. However, if the seizures are infrequent, then drug levels are often used to guide therapy. Again, it needs to be emphasised that drug levels are an imperfect marker of drug effect and need to be interpreted in light of clinical findings. Another example is diabetic medications where blood sugar monitoring is used both for alleviation of short term symptoms and as a surrogate for the likelihood of long term complications.

Other medications appear to require no monitoring for their effect. A good example is aspirin for ischaemic conditions (where a standard dose is prescribed) and there is no monitoring of its antiplatelet effect. Other examples include the use of ACE inhibitors, or beta blockers postmyocardial infarction. However, these agents still need monitoring for their adverse effects.

Conclusion

Monitoring of drug therapy is an important part of the prescribing process in enhancing the drug's effectiveness. The drug's effect as well as adverse effects should be actively sought and dosage alterations made in order to enhance the drug's effect. In some cases, this involves directly monitoring for the drug's effects, and in other cases using surrogate markers.

In the next issue of AFP we will look at a common area of poor drug monitoring: prescribing in nursing homes.

Conflict of interest: none declared.

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