Individualising therapy

The right dose, dosage form, frequency and duration

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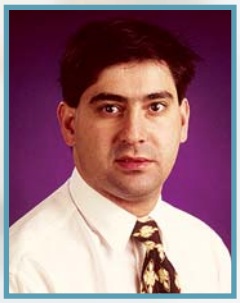

This is the sixth article in the series of general practice prescribing. This article focusses on individualising drug therapy.

BACKGROUND Having chosen which drug to prescribe, the prescription now needs to be individualised for the patient in front of you.
OBJECTIVE This article discusses the factors that have to be considered when individualising drug therapy for each patient.
DISCUSSION Before considering writing a prescription it is important to develop a personalised approach for the individual patient. The prescription should also then be individualised as to the route of administration, dosage, dosage form, frequency, and duration of the medication being prescribed.

So far in this prescribing series we have discussed how to approach prescribing in terms of therapeutic goals and approach, as well as how to choose the drug we are going to prescribe. One of the commonest mistakes in prescribing, however, is to take the 'one size fits all' approach and not to consider the patient in front of you as an individual. In this issue of AFP we will look at the how to individualise drug therapy.

When you are considering individualising a prescription, you need to think about the following issues: mode of administration, dose, dosage form, frequency, and duration.

In general practice, the mode of administration is usually oral, although occasionally other routes need to be considered particularly with nursing home patients who may not be able to tolerate oral medications.

Dosage

The need to individualise the dose is fairly obvious to most prescribers. There may be different dosage recommendations for a particular medication according to the indication it is being used for, eg. aspirin as antiplatelet versus anti-inflammatory, or for the age group it is being prescribed to (eg. morphine dosing). Occasionally the dosage is according to weight, eg. paracetamol, and this is especially common in the paediatric setting. Less commonly, the dosage needs to be altered according to a reduction in clearance capacity such as reduced dosage of digoxin or allopurinol in renal impairment, and rarely because of the co-prescription of another medication causing a pharmacokinetic drug interaction. Sometimes, when prescribing a drug such as digoxin you need to take all of these factors into account:

- the initial loading dose is weight based
- determination of the maintenance dose requires consideration of the indication (patients with cardiac failure appear only to need a serum concentration of 0.5–0.8 ng/mL[1] compared to patients with atrial fibrillation where a higher serum concentration is usually required)
- the presence of renal impairment (digoxin is predominantly renally cleared and dosage needs adjustment in the elderly or those with renal impairment), or
- interacting medications (amiodarone, spironolactone or verapamil result in daily digoxin requirements being approximately halved).

This probably explains the high incidence of inappropriate dosing with digoxin! Furthermore, once the initial dose is

established, it may need to be changed once any of these parameters is altered.

Form of the medication

The next consideration is the dosage form of the medication. This may be as basic as whether it should be prescribed as a tablet, capsule or syrup formulation of an oral medication. There is usually little difference between tablets and capsules and there is often no choice, as a drug may only be available in one or the other formulation. The main difference between tablets and capsules is usually patient preference. However, the pharmacokinetics of syrups can be quite different to other oral preparations. This is usually not important in the case of antibiotic syrups such as amoxycillin, but can be an issue with other medications such as sodium valproate where the syrup has a much more rapid absorption and is more likely to cause gastric irritation.

Another important consideration with dosage form is whether the medication has controlled release characteristics or not. As we saw in last month's issue of AFP, many of the available calcium channel blockers have a short half life requiring multiple daily dosing and this problem has been overcome by the development of once per day formulations. A drug may have a controlled release preparation for a number of other reasons: sodium valproate is enterically coated, and although this makes a small difference to its absorption characteristics, the main benefit has to do with the reduced gastrointestinal irritation; the carbamazepine CR preparation still has to be administered twice per day, but results in much less fluctuation in the serum concentration which can be useful in reducing concentration dependant adverse events in some patients; the venlafaxine XR preparation is not only once per day, but may be associated with improved tolerability as well. For other medications, however, the controlled release preparation is a gimmick to maintain the market edge when other generic agents become available, eg. Natrilix (indapamide) SR.

Dose frequency

The next factor that may need individualisation is the dosage frequency. Most of the time, this is determined by the indication for which the medication is used, or by the drug's pharmacokinetics, eg. cephalexin is administered twice per day for acute cystitis, but six hourly for mild pyelonephritis or cellulitis. The greatest individualisation is usually required when administering symptomatic treatments, eg. analgesia for pain, levodopa therapy for Parkinson disease.

Treatment duration

The last factor to consider is treatment duration. For many treatments, this is lifelong, so you should also think of the duration as how long the patient should be taking the medication for before the treatment is reviewed. The area in which treatment duration is always a consideration is antibiotic therapy, and Therapeutic Guidelines Antibiotics[2] is an excellent source of information regarding this.

Putting it all together

So how do we put all of these considerations together?

Case history: Beryl

Beryl is 84 years old and has known metastatic breast cancer. She has recently been discharged from hospital to her nursing home with a pathological vertebral fracture.
The nursing staff contact you saying that she was discharged on regular paracetamol/codeine combination, and that although this works initially, it does not last the full six hourly frequency that it is prescribed for.
Beryl had some morphine in hospital and is documented to have responded well to it.

Beryl's current analgesia becomes ineffective toward the end of the dosage period and you cannot make it more frequent because of the concern about paracetamol toxicity. So you consider changing her across to morphine as your P-drug of choice given that she has had a favourable response to it in hospital. What prescription would you write? If Beryl's pain was very severe then intravenous dosing would result in effective analgesia within minutes, however, this requires very careful titration of dose and observation. In most cases, the subcutaneous or oral route would be chosen, and provided that Beryl is not vomiting and able to absorb morphine, there would be little advantage in the subcutaneous route. The choice of route of administration would have important implications for the initial dosage chosen as the parenteral dose is approximately a third of the equivalent oral dose.

As Beryl's pain is fairly acute, sustained release morphine preparations would not be appropriate because they do not allow for safe and effective rapid titration of dosage. Beryl is currently receiving 60 mg of codeine every six hours, and this is equivalent to approximately 3 mg of parenteral or 10 mg of oral morphine. This dose does result in effective analgesia, however, its duration is insufficient. The way to individualise the prescription according to Beryl's needs would be to give a similar equivalent dose on each occasion but to give it more frequently, eg. 5–15 mg of morphine every 2–3 hours. By prescribing the dosage and frequency as a range rather than a fixed value, this allows nursing staff (or the patient or carer in other circumstances) to practise judgment and individualise the dose further according to how the patient is feeling at the time when the drug is required.

The duration of therapy obviously depends on how long the lesion is painful for. The other consideration is how long should this current prescription be in place for, before it is reviewed by you. With most cases of acute pain such as this, review within 24 hours is a good idea, which may simply be by phone.

Once a regular dosing pattern is established the prescription could be altered to a sustained release morphine prescription taken less frequently, with additional 'as required' immediate release morphine doses for breakthrough pain.

Individualising drug therapy may not just be about choosing the correct initial dose, formulation and frequency, but should also encompass the overall approach to the management of a patient.

Case history: Myrtle

Myrtle is 78 years old and has NIDDM. She lives alone at home apart from her turtle (Hurtle). She checks her blood sugar levels (BSLs) once or twice per week, and seems to have excellent values, but her HbA_1C is 8.6%.

The last few times that you have seen her, you have found that she has been short of breath. You sent her to the outpatient service of the local hospital where they diagnosed congestive cardiac failure resulting from previous myocardial infarcts, and have sent her back to you with the recommendation of commencing an angiotensin converting enzyme (ACE) inhibitor and for tighter control of her diabetes. Her current medications are:

- Frusemide 40 mg per day
- Metformin 1000 mg per day

Out of the eight ACE inhibitors on the Australian market, you should by now have one that is your P-drug ACE inhibitor. The approach to commencing an ACE inhibitor in Myrtle is different to prescribing for a 40 year old hypertensive patient. Table 1 lists risk factors for ACE inhibitor induced drug toxicity such as first dose hypotension, renal impairment and hyperkalaemia. It is not uncommon for many elderly patients to have underlying renal impairment, or co-prescription of diuretics or NSAID/COX-2 medications, resulting in a number of these risk factors. These do not necessarily constitute contraindications to ACE inhibitor therapy, but the prescriber needs to be aware that such patients are at a higher risk of adverse reactions, hence the starting doses need to be lower, and the increase in dosage needs to be performed carefully with close review. The usual approach would be to commence with the lowest available dosage of the drug and to review the patient and their renal function within 1–2 weeks.

When individualising ACE inhibitor therapy, the other consideration is how high to push the dose. The Australian Medicine's Handbook,[3] Therapeutic Guidelines: Cardiovascular[4] as well as the National Prescribing Service website[5] provide useful guides to ACE inhibitor dosing. For conditions such as heart failure there is usually a target maintenance dose to aim for. This is because most of the studies have been performed with these higher doses of ACE inhibitors. There is also evidence that patients given higher doses of ACE inhibitors do have better symptomatic outcomes such as shortness of breath and re-admission to hospital.[6] However, the dosage of ACE inhibitor that is prescribed for Myrtle depends on how well she tolerates it and the impact that it has on her blood pressure and her renal function.

The other recommendation from the outpatient specialist was to have tighter control of Myrtle's diabetes. Many guidelines recommend that the HbA_1C be below a certain value such as 7%.[7,8] Before writing the prescription for a sulphonylurea a number of factors need to be taken into account. Reductions in HbA_1C can be attended by an increased risk of hypoglycaemia and the risk-benefit of this needs to be individualised for Myrtle. She lives alone (I can't see Hurtle being of much use in a hypoglycaemic coma!) and there is uncertainty about whether she is accurately or reliably performing her BSL monitoring. Hence, her risk of adverse outcomes should she develop significant hypoglycaemia, would be higher than for other patients; therefore you may choose to start at a much lower dose and increase the dose only very gradually. Other issues that need to be thought about before considering more aggressive control of Myrtle's diabetes are her cognitive functioning, ability to recognise and treat hypoglycaemic attacks, vision, and most importantly her own personal preferences. All these factors should be considered before individualising therapy regarding her diabetic control. Clearly the approach to the management of Myrtle's BSLs would be different to how you might manage a much younger patient with more family supports.

Table 1. Risk factors for ACE inhibitor toxicity

- dehydration or high diuretic dose
- age >75 years
- serum Na+ <130 mmol/L
- systolic BP <100 mmHg
- pre-existing renal impairment
- concomitant use of NSAIDs or COX-2s, or K+ sparing diuretics, or K+ supplements

Conclusion

Individualising drug therapy is about taking into account specific patient factors to write a personalised prescription for the patient in front of you. In order to do this, you need to consider how to alter the overall approach to the management, as well as the drug mode of administration, dose, dosage form, frequency, and duration in each case. For certain conditions such as the treatment of acute cystitis in a nonpregnant woman, little individualisation may be required, but for other conditions such as the treatment of severe cancer pain, all of these issues need to be addressed.

In next month's issue of AFP, we will address how to check the suitability of the prescription to ensure that the patient does not have any specific contraindications.

Conflict of interest: none declared.

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