Choosing a drug from within a class

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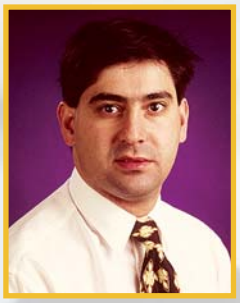

In the last issue of Australian Family Physician, we discussed how considerations of efficacy, safety, suitability and cost help us choose between different drug classes for a particular indication. Not surprisingly similar considerations are involved when choosing between different drugs within the same class.

Hypertension is a good example to illustrate the importance of these four factors in therapeutic decision making, because there are a large choice of agents available, and also because it is an area where individualisation of therapy is very important, hence considerations of safety and suitability come to the fore.

BACKGROUND Having decided on a drug class, an individual drug needs to be chosen.
OBJECTIVE This article discusses the same four factors used in deciding the generic drug within a class as well as between different drug classes: efficacy, safety, suitability, and cost.
DISCUSSION The example of hypertension will be used to illustrate the choice of individual drugs within beta blockers and calcium channel blockers. Although a large number of options exist within each class, by considering the above factors, the choice is narrowed to only 1–2 preferred options. These drugs should then be added to the P- or Personal-drug list. By only prescribing agents on the P-drug list, the prescriber will become more familiar with their dosing, adverse effects, and interactions, resulting in improved patient outcomes. Also when a new drug becomes available, it clearly needs to be better for the patient in terms of these factors, before it is added to the P-drug list.

Consider the case of Beryl. You decide that based on the hypertension and the fact that she has ongoing angina on exertion, she should be prescribed a beta blocker. Well, which one do you choose? There are a large number of different beta blockers available on the Australian market. Table 1 lists some of the differences between them. In terms of efficacy, all of the beta blockers on the list would be similar except for those with intrinsic sympathomimetic activity (ISA). These agents (pindolol and oxprenolol) reduce exercise induced tachycardia and resting heart rate to a lesser extent than beta blockers without ISA, and have not been shown to benefit patients after myocardial infarction.

In terms of safety, all of the beta blockers listed would have the usual con-

Case history

Beryl is 76 years old and had a myocardial infarction six months ago. She has had an uncomplicated course apart from some ongoing angina when she exerts herself. Her cardiologist feels that medical management is appropriate, and will review her in two years. You note that on the past few occasions she has seen you, her blood pressure has been persistently elevated, and on this occasion is 150/95.

Her current medications are:

Aspirin 150 mg per day

Trandolapril 4 mg per day

Simvastatin 20 mg per day

traindications of reversible airways disease, bradycardia, sick sinus syndrome, heart block, and uncontrolled heart failure in this setting. There are a few other differences of importance. All of the beta blockers apart from atenolol, metoprolol and bisoprolol are nonselective, hence they may be more likely to cause bronchospasm, peripheral vasoconstriction and alteration of glucose and lipid metabolism. This is important in a patient who has a smoking history and may have some susceptibility to beta-2 blockade. The other issue is the lipid solubility of the beta blocker, as less lipid soluble beta blockers may be less likely to enter the brain and may cause fewer sleep disturbances and nightmares.

When considering suitability, the main difference between the beta blockers is the number of daily doses. The differences between the costs of the different agents are listed in Table 1. The drugs that have an indication for the treatment of heart failure (bisoprolol, carvedilol) are substantially more expensive than ones that do not.

As you can see from this analysis, the agent which is beta-1 selective with low lipid solubility, (and hence less likely to cause adverse reactions) and is also administered once per day is atenolol. It is also one of the least expensive agents to use.

There are circumstances in which you may want to choose one of the other agents. For example, if Beryl had any heart failure as well, then using one of the agents with demonstrated efficacy for this indication (metoprolol, carvedilol, bisoprolol) may be preferable. There appears to be little role for medications such as oxprenolol or pindolol, apart from case series describing the use of pindolol in neurocardiogenic syncope.[1,2]

In the first article in this series (AFP January/February 2003) there was mention of the use of 'personal drugs' or P-drugs. P-drugs are the drugs you have chosen to prescribe regularly, and which you have become familiar with. The P-drug concept should include the indication for the drug as well as the dosage form, dosage schedule, and duration of treatment. P-drugs enable you to avoid repeated searches for a good drug in daily practice.[3] And, as you use your P-drugs regularly, you will get to know their effects and side effects thoroughly, with obvious benefits to the patient. You may think that using P-drugs is obvious and intuitive, but surveys have shown that many clinicians use a wide variety of different agents for the same indication, eg. 5–6 different ACE inhibitors for hypertension. Although it is true that different agents may need to be prescribed to account for patient preference, or allergies, it is clear that prescribing such a large number is unnecessary, and that some patients are likely to be receiving suboptimal care.

So how do you apply the concept of P-drugs to the choice of prescribing beta blockers? As you can see from Table 1 and the discussion above, atenolol may be a preferred beta blocker for the management of hypertension. It would also be your beta blocker of choice for the management of angina. You may choose to put metoprolol on your P-drug list as well as a second line agent to atenolol for angina, in patients who have a low blood pressure, where the use of an agent with a shorter half life may be preferable. The other details for your P-drug list would include details of dosing (eg. commence with 25–50 mg per day), when and what to review (check blood pressure and heart rate in two weeks), as well as how to alter dosing (if no response push to 100 mg per day. Do not cease abruptly).

Once you have decided to use atenolol as your beta blocker of choice, then you continue using it, and get more and more familiar with its dosage, side effects, and monitoring requirements. Then when a new beta blocker comes on to the market, it needs to be clearly superior to the one you currently have on your P-drug list, in terms of efficacy, safety, suitability, or cost for the patient before you consider changing. Unfortunately, most of the information you receive may not be objective data upon which to base these decisions, and that is why independent sources of information such as the National Prescribing Service, the Australian Medicines Handbook, or the new drugs section of Australian Prescriber can be so helpful.

Let's look at another example: the confusing issue of calcium channel blockers (CCBs). Table 2 lists the options currently available on the Australian market apart from the recently arrived lercanidipine (Zanidip). Most of the drugs have been shown to have efficacy in terms of preventing cardiovascular endpoints in large scale trials,[4–7] with the

Table 1. Comparison of ß-blockers

Drug	Receptors antagonised	ISA*	Lipid solubility	Number of daily doses	Approximate daily cost
Atenolol	ß1	-	-	1	$0.20
Bisoprolol	ß1	-	-	1	$3.00
Carvedilol	a1, ß1, ß2	-	++	1	$3.80
Labetalol	a1, ß1, ß2	-	+	2	$0.40
Metoprolol	ß1	-	+	1-2	$0.20
Oxprenolol	ß1, ß2	+	+	2-3	$0.40
Pindolol	ß1, ß2	++	+	2-3	$0.60
Propranolol	ß1, ß2	-	++	2-3	$0.20

* ISA: intrinsic sympathomimetic activity
Modified from: Australian Medicines Handbook

Table 2. Comparison of calcium channel blockers

	Verapamil	Verapamil SR	Diltiazem	Diltiazem CR	Nifedipine tablets	Nifedipine OROS	Felodipine ER	Amlodipine
Efficacy	BP reduction	BP reduction	Clinical outcomes*	Clinical outcomes*	BP reduction	Clinical outcomes*	Clinical outcomes*	Clinical outcomes*
Safety	Constipation, Heart block, Worsening CCF	Constipation, Heart block, Worsening CCF	Heart block, Worsening CCF	Heart block, Worsening CCF Ankle swelling	Flushing, Headache, Ankle swelling	Flushing, Headache, Ankle swelling	Flushing, Headache,	Ankle swelling
Suitability Contra-indications	ß-blockers CCF	ß-blockers CCF	Caution with ß-blockers CCF	Caution with ß-blockers CCF	CCF	CCF		
Suitability	+++	+++	++	++	+	+	+++	–
Drug interactions								
Doses/day	3	1	3	1	2	1	1	1
Daily cost	~$0.50	~$0.60	~$0.75	~$1.00	~$0.75	~$1.00	~$1.00	~$1.30
Patient cost/ prescription	Nil	Nil	Nil	Nil	Nil	~$2.90	Nil	~$5.10

* Clinical outcomes means reduction in myocardial infarction, stroke and other complications of hypertension

exception of verapamil and nifedipine tablets. In terms of safety, different CCBs tend to have different adverse reactions: verapamil and diltiazem tend to cause more depression of myocardial contractility and heart block, whereas the more peripherally acting dihydropyridines cause more ankle swelling, flushing and headaches. Clinical trials do not show a clear advantage of one dihydropyridine over another in terms of adverse reactions[8–10] (a more critical issue in terms of adverse reactions is the starting dose and how high the dose is pushed).

In terms of suitability, verapamil should not be prescribed with a beta blocker or a patient with heart failure, and diltiazem only with careful monitoring for bradycardia and worsening congestive cardiac failure. Nifedipine has also been shown to be contraindicated in patients with heart failure,[11] but this study has not been repeated with the sustained release preparation. Felodipine[12] and amlodipine[13] have been shown not to increase morbidity or mortality of heart failure.

Another suitability issue is the possibility of drug interactions. Verapamil and diltiazem can inhibit cytochrome P450 3A4, while the others do not. However, because of its high first pass clearance, felodipine can be subject to clinically significant drug interactions with other substances including grapefruit juice.

As for dosing, all the agents in Table 2 with the exception of amlodipine have a short half life, hence either have to be taken multiple times per day, or administered in a sustained release formulation.

The cost of the CCBs often reflects the formulation being used. Older multiple daily dosing formulations are cheaper than the newer sustained released preparations, but this probably represents false economy given the predictable difficulties with compliance. Nifedipine OROS and amlodipine carry an additional patient payment because of their cost.

So which CCB(s) would you put on your P-drug list for hypertension? From Table 1 it is obvious that there are many choices and that some of them are not as good as others. Clearly agents that require to be given only once per day with proven benefit in reducing cardiovascular endpoint are preferable. If you prescribe beta blockers for hypertension, then diltiazem would be less suitable than the dihydropyridines. Among these agents, only felodipine can be taken once per day without the need for additional patient payments. However, felodipine is more prone to drug interactions. You can see that there may not be a perfect P-drug for every situation, and that you may have to choose two P-drugs to account for different patient suitability and cost factors.

What about lercanidipine? Well, you should only prescribe it if there is data clearly proving superiority to the agents that you have chosen in terms of efficacy, safety, suitability, and cost. Although it is a once per day agent there are no clinical outcome studies, hence it should be used only if the more proven agents are not well tolerated. You can see how the P-drug concept can save you a lot of time in deciding between different drugs to prescribe, especially with the myriad of new drugs emerging.

Conclusion

The same considerations of efficacy,

safety, suitability and cost can be used to choose between drugs within a particular class. Once you have determined which drug you are going to prescribe for a particular indication, then you should add this drug to your P-drug list, and become familiar with it. This can save you time when it comes to prescribing and result in improved patient outcomes, as well as helping you make the correct prescribing decisions with the emergence of new drugs in the same class.

In next month's issue of AFP we will look at how to individualise your P-drugs for each patient.

Conflict of interest: none declared.

Resources

For a review of cytochrome P450 interactions try the simple summary in Australian Prescriber: Martin J, Fay M. Cytochrome P450 drug interactions: Are they clinically relevant? Aust Prescr 2001; 24:10-12 or the website where the pharmacologists go: http://medicine.iupui.edu/flockhart/.

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