

Which drug class and why?

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This is the fourth article in the series on general practice prescribing. This article focusses on the choice of drug class.

BACKGROUND Having made the diagnosis, decided on therapeutic goals and the therapeutic approach, the next step is choice of drug class.

OBJECTIVE This article discusses the four factors to be considered when choosing an appropriate drug class: efficacy, safety, suitability and cost.

DISCUSSION The first consideration in choosing a drug class is the relative efficacy compared with other agents for the particular therapeutic goal. Safety is a broad issue involving adverse reactions, toxicity, tolerance and dependence, teratogenicity, and consideration of special at risk populations. Suitability involves consideration of contraindications to the medication as well as other factors such as the requirements for monitoring, drug formulation and the number of daily doses. Cost includes consideration of drug acquisition as well as the total cost of therapy, including by whom the cost is borne.

So far in this prescribing series we have discussed the issues of therapeutic goals and therapeutic approaches. Now we get to the juicy bit of how to choose between different drugs to prescribe. In this issue we will cover the choice between different drug classes, and in the next issue of Australian Family Physician, different drugs within a class. The choice in both cases is based on four factors: efficacy, safety, suitability and cost, and we will be using different examples in each issue to illustrate the case.

Imagine yourself buying a car: it has to get you from point A to B, and it can do that with varying degrees of efficacy in terms of the reliability of the car, the amount of acceleration it has, its responsiveness, handling and fuel efficiency. You also want the car to be safe. At different stages in your life, the importance of safety will differ: when you are young a sports car that comes off second best

hitting a cyclist is okay, but when you have children, you go for the Volvo 4WD station wagon with extra heavy duty side impact protection and 22 front, side, rear, top, and bottom air bags! You then have to think about budgetary constraints, obviously. There is also another issue though when choosing cars, which I can only describe as personality: certain cars are made for some and obviously not others. Some people I know just wouldn't drive that Volvo even if it was given to them for free!

Well, the issue is much the same for drugs. Look at the case of Harold. The therapeutic goal in treating Harold's atrial fibrillation would be to improve the symptoms it is giving him, and to prevent complications such as stroke. The therapeutic approach would be to either aim for rate control and anticoagulation or rhythm control and anticoagulation (there is no evidence that rhythm control

Case history

Harold is an active 79 year old man who lives with his wife. He has had hypertension for years and has been taking a beta blocker. He presents to you complaining of transient weakness of his left leg, which you diagnose as a transient ischemic attack (TIA); you also find him to be in slow atrial fibrillation. You organise a CT head scan that shows he has had previous undiagnosed strokes.

alone helps prevent strokes). What would you prescribe to prevent a stroke: aspirin, warfarin or other?

Efficacy

First let's consider the issue of efficacy: in metaanalysis of clinical trials, warfarin is associated with an approximate 70% risk reduction of the incidence of stroke, com-

pared to only approximately 20% with aspirin.¹ In Harold's case his yearly risk of a stroke without treatment would be approximately 8%,^{2,3} hence with warfarin his risk of stroke would go down to approximately 2.4% (5.6% yearly absolute risk reduction) and with aspirin his risk would still be approximately 6.4% (only 1.6% absolute risk reduction).

For drugs to be approved by the Therapeutics Goods Administration (TGA), they have to have proven efficacy. The important issue is really relative efficacy compared to the use of other agents. In the example of Harold, anticoagulation with warfarin is clearly more efficacious in preventing strokes than aspirin, but this is not the only issue.

Safety

A common reason why clinicians do not anticoagulate patients such as Harold is concerns about bleeding.⁴⁻⁶ The bleeding risk associated with aspirin use is approximately 0.5–1.0% per year. Metaanalysis of trials demonstrate there is an approximate 0.45% gastrointestinal,⁷ and 0.04% intracerebral⁸ risk of bleeding per year. There is evidence from cohort studies to suggest the absolute rate of bleeding is greater in elderly patients.⁹ There is some evidence of a higher incidence of bleeding at higher doses,^{10,11} but it is clear that complications do occur at a substantial rate at doses of 100–150 mg per day.

The annual bleeding rate with warfarin is considerably higher than with aspirin. The average risk of major haemorrhage is estimated to be approximately 3% per year,¹² but this varies with age, blood pressure, likelihood of falls, and excessive anticoagulation or factors predisposing to it such as confusion, dementia, etc.¹³ A number of scoring tools have been developed to help predict the risk of haemorrhage in patients taking warfarin in whom absolute contraindications such as falls or alcohol abuse do not apply (Table 1).^{14,15}

Although it can be said that all drugs now approved by the TGA are effica-

cious, it cannot be said that they are all safe (despite the claims made for some pharmaceuticals by their manufacturers). All drugs have some element of toxicity. Most prescribers would be familiar with predictable or idiosyncratic adverse drug reactions. Other aspects of safety to consider are:

- the potential for chronic toxicity (eg. pulmonary fibrosis with amiodarone, nitrofurantoin or methotrexate)
- acute toxicity (eg. digoxin, lithium, theophylline)
- issues of dependence and withdrawal, and
- the possibility of teratogenicity.

One also needs to consider whether there are particular at risk populations who are more likely to suffer from the drug's toxicity (Table 2).

Suitability

Next let's consider the suitability of different forms of anticoagulation for Harold. Aspirin comes as an easy to administer once per day tablet, and even if he forgets to take it for a day, because of its irreversible platelet inhibition, there is no loss of efficacy. Warfarin on the other hand, requires regular monitoring as well as greater patient education regarding the importance of compliance and drug and food interactions. Given that Harold is active, has no contraindications to war-

farin, and does not have a history of falls, warfarin would be suitable for him. Other pertinent issues to consider would be regarding transport, support from his wife, and his ability to alter warfarin doses according to telephone advice.

The suitability of a medication is usually thought of as contraindications that a patient has to it, eg. history of falls with warfarin. It is not just about contraindications, however, and is a much broader issue when selecting between different drug classes. It may also have to do with the requirements for additional investigations associated with the use of a particular drug such as electrolyte monitoring with loop diuretics, serum concentrations with digoxin, phenytoin, perhexiline (especially in a patient with needle phobia). Other issues are the formulation of the medication, the number of daily doses and the packaging of the medication, such as in the case of paediatric antibiotic syrups where the taste can be an important issue! Suitability may also have to do with whether the medication comes in a 'one size fits all' dose, or whether it has to be carefully titrated to effect. Suitability also has a psychological component such as in the case of cancer patients who refuse to take morphine because they feel that it represents giving up, or decisions regarding drug

Table 1. Five point warfarin bleeding index¹⁴

Score 1 point each for

- age ≥65
- history of gastrointestinal bleeding
- history of stroke
- any of: diabetes, recent myocardial infarction, haematocrit <30%, creatinine >.12 mmol/L

Risk of bleeding in patients on warfarin treatment

Time after commencement	Low risk (0 points)	Intermediate risk (1–2 points)	High risk (3–4 points)
6 months	3%	8%	16%
12 months	3%	8%	30%
48 months	3%	12%	53%

Table 2. At risk populations for particular medications

Medication	Adverse reaction	At risk group
ACE inhibitor, angiotensin II antagonists	Acute renal impairment	Elderly Dehydration or high diuretics dose Na ⁺ <130 mmol/L Pre-existing renal disease Taking NSAIDs or COX-II inhibitors
Sulphonylureas, insulin	Hypoglycaemia	Living alone Cognitive impairment
Metformin	Lactic acidosis	Cardiac failure, hepatic failure, renal impairment
Tricyclic antidepressants	Overdose death	Suicidal patients
Oral bisphosphonates	Oesophagitis	Gastrooesophageal reflux
Paracetamol	Hepatotoxicity	Poor oral food intake Hepatic enzyme inducers
Bupropion	Seizures	Past head injury
NSAIDs, COX II inhibitors	Acute renal failure	Elderly Hypovolemia due to dehydration or diuretics Co-prescribed diuretic and ACE inhibitor/angiotensin II antagonist Pre-existing cardiac, hepatic, renal failure
Statins	Rhabdomyolysis	Renal impairment
Spironolactone	Hyperkalaemia	Renal impairment
Perhexiline	Neuropathy Hepatotoxicity	Cytochrome P450 2D6 poor metaboliser
Pethidine	Altered mental state seizures, cardiac arrhythmias	Renal impairment
Dextropropoxyphene, eg. Capadex, Digesic	Altered mental state, seizures, cardiac arrhythmias	Renal impairment
Allopurinol	Rash and other adverse effects	Renal impairment
Anticholinergic drugs, eg. tricyclic antidepressants, oxybutinin	Confusion	Elderly Cognitive impairment

therapy being influenced by previous favourable or unfavourable experiences with drugs or diseases, eg. family members who have had intracerebral haemorrhage from being prescribed warfarin, or strokes from not being anticoagulated for atrial fibrillation.

Cost

The cost of a medication warrants an entire series of articles to itself. In brief, cost has to do with the overall cost of prescribing the medication, ie. including the cost of monitoring, adverse effects, lack of efficacy, as well as consideration of by whom the cost is being borne. Although aspirin is a much cheaper option initially in terms of drug acquisition and monitoring costs, because warfarin is more efficacious, it may be more cost effective in carefully selected populations because of the cost of stroke victim management that it can save the community.

Conclusion

In summary, warfarin is likely to be more efficacious for Harold, but it also has a higher risk of bleeding. There are no contraindications making it unsuitable for him, but ultimately whether the attendant monitoring is unsuitable for him, is his decision. The cost of treatment is not really an issue for Harold, because the medication is inexpensive, and the monitoring is subsidised by the government.

The same considerations of efficacy, safety, suitability and cost apply to the choice between all drug classes for a particular indication. Table 3 summarises the drug choices for the treatment of reflux oesophagitis.

Although the decision of which drug class to prescribe for a particular indication or therapeutic goal may appear daunting given the availability of different medications, by considering the issues of efficacy, safety, suitability and cost of each class, the choice is made much easier.

In next month's issue of AFP we will consider choices between different agents within a particular drug class.

Table 3. Comparison of different drug classes for reflux disease

Drug class	Efficacy	Safety	Suitability	Cost
Antacid	+	++	-	6 cents/tablet
H ₂ antagonist	++	+++	++	70 cents/day
Proton pump inhibitor	+++	+++	+++	\$1.60 per day

n Which drug class and why?

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