Book review

Health care and notions of risk. R.B. Clark.

Melbourne: Therapeutic Guidelines; 2004.

72 pages. Price including GST $33; students $25.30; plus postage

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This book is a consumer view of medical adverse events, patient participation in healthcare decision-making, risk perception and patient safety in the Australian healthcare system. It is based on an analysis of the Australian Patient Safety survey which was a comprehensive study of Australians' attitudes to participation in health care and perceptions of safety. The book explains the likelihood and types of medical adverse events, models of consumer involvement in healthcare decision-making and the views of consumers about the safety of health services.

Medicine-related adverse events are the main category of adverse events reported, but the lack of resources and the exposure to infection were the most important consumer issues in relation to safety. Chapter 5 discusses the factors which predict adverse events. It is interesting that consumers perceived nursing homes, residential aged care, hospitals and doctors' surgeries as places where adverse events were likely to occur.

Younger people aged 18–34 years are significantly more likely to report an adverse event than the older age groups. According to the author, this may be due to younger people feeling more empowered in healthcare decision-making, but more data are needed to clarify why this is the case.

The final chapter of the book attempts to place the findings of the study within a policy context. A key finding is that the lack of resources and exposure to infection have contributed to a recent fall in confidence in relation to the safety of health care. Another finding with implications for health policy is consumers' preference for a shared decision-making model. Sharing information reduces the risk of experiencing an adverse event.

The book concludes that the value of this Australian study is that future studies may be able to focus on vulnerable groups. These include people with poor health and those who have a number of hospital admissions.

I can recommend this book to all those interested in consumer perceptions of risk, safety and quality and participation in health care. It will also be valuable to those interested in greater consumer participation in the policy, planning, delivery and evaluation of health care.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Adefovir dipivoxil

Hepsera (Gilead Sciences)

10 mg tablets

Approved indication: hepatitis B

Australian Medicines Handbook section 5.3

Although Australian children are now immunised against hepatitis B, infection still occurs in adults and is endemic in Aboriginal and Torres Strait Islander communities. Some people who are infected develop chronic hepatitis B which may lead to cirrhosis and liver failure. Patients with chronic hepatitis B can be treated with injections of interferon. Lamivudine, a nucleoside analogue, can be used as an oral treatment.

Adefovir is a nucleotide analogue of adenosine monophosphate. Cells convert adefovir to adefovir diphosphate which competes with the normal substrate of the viral DNA polymerase. The concentration of adefovir diphosphate needed to inhibit the enzyme in hepatitis B virus is lower than the concentration which inhibits human DNA polymerase. When adefovir diphosphate gets incorporated into viral DNA, it inhibits replication by preventing elongation of the nucleic acid chain.

As adefovir is not well absorbed it is given as a prodrug. Adefovir dipivoxil is taken once a day and is converted to adefovir (bioavailability 59%) by hydrolysis. Most of this adefovir is later excreted unchanged in the urine.

Patients who **do not have** detectable hepatitis B e antigen[1] (HBeAg) may have an increased risk of progressive liver damage. A multicentre study randomised 123 of these patients to take adefovir dipivoxil and 61 to take a placebo for 48 weeks. Concentrations of viral DNA reduced significantly in 51% of the adefovir group but not in any of the patients given a placebo. Although 33% of the placebo group had improved liver histology, this was significantly less than the 64% who improved with adefovir dipivoxil.[2]

Another study of 515 patients who **did have** detectable HBeAg produced similar results. While viral DNA concentrations were not reduced by placebo, they were undetectable in 39% of patients taking adefovir dipivoxil 30 mg and in 21% of those taking 10 mg. Liver biopsies after 48 weeks of treatment showed improvement in 59% (30 mg) and 53% (10 mg) of the adefovir group and 25% of the placebo group.[3] As adverse effects are more frequent at higher doses the recommended daily dose of adefovir dipivoxil is 10 mg.

In the clinical trials adverse events occurred with a similar frequency in patients taking adefovir dipivoxil or placebo. Common adverse events include asthenia, headache, abdominal pain and diarrhoea. Adefovir dipivoxil can be prescribed for patients with hepatic impairment, but the dose requires adjustment in patients with renal impairment. Nephrotoxicity may occur during long-term therapy so renal function should be monitored particularly if the patient takes other treatments, such as non-steroidal anti-inflammatory drugs, which affect the kidney.

The effectiveness of lamivudine in chronic hepatitis B is reduced because the virus becomes resistant to the drug. So far, the virus has not developed significant resistance to adefovir. A small study in patients with HIV infection who also had lamivudine-resistant hepatitis B found that adefovir dipivoxil significantly reduced the concentrations of viral DNA.[4]

The available drugs for hepatitis B have not yet been compared directly so it is difficult to know which will produce the best outcomes for patients. While liver histology improved in the patients who responded to adefovir dipivoxil, we do not know if this will reduce the long-term complications of chronic hepatitis B. The optimum duration of treatment is uncertain, and up to 25% of patients will develop an exacerbation of their hepatitis after they stop taking adefovir dipivoxil.

References

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Anakinra

Kineret (Amgen)

100 mg/0.67 mL in pre-filled syringes

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2.2

The current treatment of rheumatoid arthritis involves the early use of disease-modifying antirheumatic drugs (DMARDs).[1] If these drugs are not effective a biological agent may be considered. These agents are aimed at the pro-inflammatory cytokines which are involved in the pathogenesis of rheumatoid arthritis.

The structure of anakinra differs by only one amino acid from the structure of the naturally occurring human interleukin-1 receptor antagonist. This difference is to enable genetically engineered *Escherichia coli to* produce anakinra.

Anakinra antagonises interleukin 1α and 1β at the interleukin-1 type 1 receptor. As these interleukins are inflammatory mediators, competition for their receptor may prevent joint damage.

Patients have to subcutaneously inject anakinra every day. The maximum plasma concentration is reached in 3–7 hours. Anakinra is probably cleared by the kidneys and has a half-life of 4–6 hours.

In a clinical trial involving 472 patients, anakinra was compared to injections of a placebo. After 24 weeks the rheumatoid arthritis was less active in patients randomised to receive anakinra. They had fewer swollen joints, less pain and a shorter duration of morning stiffness.[2] This trial was extended for a year with patients from the placebo group being switched to treatment with anakinra. A total of 218 patients completed the extension. Efficacy was maintained in 46% of the patients who continued treatment with anakinra and 40% of the patients who had switched from placebo.[3]

During the extension phase 29% of the patients discontinued treatment. Half of these withdrawals were caused by adverse events such as a flare-up of the arthritis or abnormal blood counts.[3]

Adverse effects also accounted for most of the withdrawals from a safety study of anakinra. This study randomised 1414 patients to take anakinra or placebo in addition to their other treatments. Approximately 78% of the patients completed six months of treatment. The most common adverse effect of anakinra was injection site reactions. Patients should vary the site of injection to try and reduce such reactions. Serious infections such as pneumonia occurred more frequently than with placebo.[4] Patients should have their white blood cell count checked before and during treatment.

Although the safety study[4] included patients taking other DMARDs, anakinra is only approved in Australia for prescription with methotrexate. This combination was compared with methotrexate in a six-month study involving 419 patients. Adding anakinra produced a response in 38–46% which was significantly greater than the 19% of patients who responded to methotrexate alone.[5]

While the trials show that anakinra has greater efficacy than placebo its benefits depend on how efficacy is measured. Several

trials used the American College of Rheumatology criteria for a 20% improvement (ACR20).[6] However, if the criteria for success is set higher the results are less impressive. For example, if the goal is a 50% improvement in the patient's symptoms, only 18% of patients will achieve it. If the goal is a 70% improvement, only 3% will achieve it after 48 weeks of therapy.[3]

As the response may be related to the dose of anakinra[5], it is important to know that some patients in the trials took more than the recommended daily dose of 100 mg. This dose was not specifically tested in some of the published trials.[2,3,5]

While the biological agents will benefit some of the patients who have not responded to DMARDs, the variations in study design mean the best option is not clear. Anakinra does not appear to be more effective than etanercept or infliximab, but comparative studies are needed.

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Atazanavir sulfate

Reyataz (Bristol-Myers Squibb)

150 mg and 200 mg capsules

Approved indication: HIV infection

Australian Medicines Handbook section 5.3.4

HIV infections are best managed with combinations of antiviral drugs.[1] As treatment may involve taking medication several times a day, there is an interest in simpler regimens. Atazanavir is a protease inhibitor which only needs to be taken once a day. The daily dose should be taken with food as this increases bioavailability. Steady state concentrations are reached in 4–8 days. Most of the dose is metabolised and then excreted in the faeces.

A dose-ranging study compared atazanavir with nelfinavir in previously untreated patients. The 467 patients also received lamivudine and stavudine. After 48 weeks approximately 35% of all patients had less than 50 copies of viral RNA/mL and CD4 cell counts had increased.[2]

Another study compared atazanavir with nelfinavir in 420 previously untreated patients who were also given didanosine and stavudine. After 48 weeks 36% of the patients taking 400 mg atazanavir daily and 39% of those taking nelfinavir had less than 50 copies of viral RNA/mL. CD4 cell counts increased in all treatment groups.[3]

In patients who have previously been treated with a regimen containing a protease inhibitor, atazanavir may be less effective than adding lopinavir and ritonavir to therapy with two nucleoside reverse transcriptase inhibitors. After 48 weeks 35% of the 144 patients taking atazanavir had less than 50 copies of viral RNA/mL compared with 53% of the 146 patients taking lopinavir and ritonavir.

If atazanavir is used in a combination with ritonavir a lower dose is prescribed because of a drug interaction. As atazanavir is metabolised by cytochrome P450 3A4 it has the potential for several other interactions. It should not be prescribed with calcium channel blockers, HMG-CoA reductase inhibitors ('statins'), ergot derivatives, sildenafil, midazolam and triazolam.

Atazanavir inhibits an enzyme involved in bilirubin conjugation. Many patients will therefore have elevated bilirubin concentrations and up to 11% may develop jaundice while taking atazanavir 400 mg daily.[2]

Other adverse effects reported in clinical trials include nausea, rashes and heart block. Hyperlipidaemia may be less of a problem than it is with other protease inhibitors. As with other protease inhibitors, HIV can become resistant to atazanavir.

While atazanavir does have the advantage of a single daily dose, the best use of the drug in combination regimens, particularly in previously treated patients, will require further study.

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Cholera vaccine

Dukoral (Aventis Pasteur)

glass vials containing 3 mL for dilution

Approved indication: cholera immunisation

Australian Medicines Handbook section 20.1

Vibrio cholerae and *Escherichia coli* are responsible for many cases of diarrhoea around the world. Although cholera is endemic in some countries vaccination is not routinely recommended for travellers. Some vaccines have not been very effective.

This new product contains inactivated forms of three strains of *Vibrio cholerae*. It also contains a recombinant form of the binding portion of the cholera toxin. As this toxin is similar to the enterotoxin produced by the enterotoxigenic strains of *Escherichia coli*, the vaccine may have the ability to prevent some cases of traveller's diarrhoea.

The vial of vaccine is supplied with a sachet of sodium hydrogen carbonate which acts as a buffer. Patients dissolve the granules of the buffer in water then add the contents of the vial and drink the mixture. They should not have food or drink for one hour before and one hour after taking the mixture. The dose is repeated after at least a week, but children aged 2–6 years are recommended to have a third dose. Most people will be protected against cholera approximately one week after completing the course.

The vaccine was studied in Bangladesh as long ago as the 1980s. These studies found that for older children and adults two doses were as good as three. The protective efficacy of a two-dose regimen was 77% after a year. The protective efficacy then declines with time. If exposure to cholera continues, a booster is recommended after two years in adults and after six months in young children. Although there have been studies of the vaccine for the prevention of traveller's diarrhoea, this is not an Australian approved indication.

Patients may complain of loose stools and abdominal discomfort, but these adverse effects occur at similar frequencies in patients given a placebo. The clinical trials did not specifically assess interactions with other vaccines, but it is recommended that oral typhoid vaccines are not used within eight hours of cholera vaccine.

Although many Australians travel overseas there are only about six cases of cholera a year. The National Health and Medical Research Council advises that avoiding contaminated food and water is more important than vaccination against cholera.[1] Most tourists have a low risk of infection, but the vaccine may be considered for people at high risk, for example healthcare professionals working in endemic areas or refugee camps overseas.

Reference †

1. National Health and Medical Research Council. The Australian Immunisation Handbook. 8th ed. Canberra: Department of Health and Ageing; 2003.

Enfuvirtide

Fuzeon (Roche)

vials containing 90 mg/mL as powder for reconstitution

Approved indication: HIV infection

Australian Medicines Handbook section 5.3

Fusion inhibitors are a new class of drugs that prevent HIV from penetrating cells. By binding to an HIV transmembrane glycoprotein they stop the virus from fusing with the CD4 receptors on the patient's cells.

Enfuvirtide is given twice daily by subcutaneous injection. It reaches its peak concentration about four hours after the injection. As enfuvirtide is a peptide it is metabolised into amino acids. It has a half-life of approximately four hours.

Highly active antiretroviral therapy has improved the outlook for patients infected with HIV.[1] However, HIV can become resistant to antiviral drugs so that treatment fails to adequately suppress viral replication. Introducing a drug of a new class may help to regain control of the infection.

Clinical trials of enfuvirtide have included patients infected with HIV which had become resistant during at least three months of antiviral treatment. A trial, involving 512 Australian and European patients, randomly added enfuvirtide to an optimised regimen of other drugs for HIV. After 24 weeks the concentrations of viral RNA had fallen further in the patients given enfuvirtide than they had in patients who just took the optimised regimen. There were less than 50 copies of HIV RNA/mL of plasma in 12% of the patients given enfuvirtide compared with 5% of the control group. The CD4 cell count increased in both groups, but the rise was significantly greater in the enfuvirtide group.[2]

A similar randomised trial in the Americas also found that a regimen containing enfuvirtide had greater efficacy than the same regimen without enfuvirtide. The 328 patients who injected enfuvirtide had greater decreases in viral RNA and greater increases in CD4 count than the 167 patients who took the optimised regimen. After 24 weeks 20% of the enfuvirtide group had less than 50 copies of HIV RNA/mL compared with 7% of the control group.[3]

Injection site reactions were the commonest adverse reactions to enfuvirtide in the clinical trials. Patients may develop painful itchy nodules at the injection site. Although patients are told to rotate the injection sites they may develop a reaction in more than one place. Approximately 3% of patients withdrew from the trials because of injection site reactions.

In addition to injection site reactions, adverse events tended to be slightly more frequent when enfuvirtide was added to the treatment regimen. Adverse reactions which occurred more frequently with enfuvirtide included peripheral neuropathy, pneumonia and depression. As enfuvirtide is a protein, patients can develop hypersensitivity reactions to its injection. More than 70% of patients treated with enfuvirtide had an adverse event

(other than an injection site reaction) resulting in the withdrawal of approximately 8% from the clinical trials.[2]

The clinical trials are ongoing and preliminary results suggest the effect of enfuvirtide is sustained for 48 weeks. However, the measures of efficacy are surrogate end-points so it will take longer to find out if enfuvirtide improves the clinical outcomes for patients. It is unclear when treatment should be stopped in patients who do not initially respond to enfuvirtide. We also do not know if significant resistance will develop later.

While enfuvirtide is an advance, its use will have to be rationed. There are many steps in the manufacturing process and this may limit the supply of the drug. Until supplies increase enfuvirtide will be an expensive treatment[4] (more than $20 000 for a year's treatment).

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Gadobenate dimeglumine

MultiHance (Bracco)

529 mg/mL in 5 mL, 10 mL, 15 mL and 20 mL vials

Approved indication: magnetic resonance imaging

Magnetic resonance imaging (MRI) can be enhanced by contrast agents. Gadobenate is a gadolinium-based compound that can be used as a contrast agent when imaging the liver or central nervous system.

Patients are given an intravenous dose in proportion to their body weight. Higher doses are used when imaging the central nervous system. Gadobenate is distributed in the plasma and extracellular space and will highlight areas where the blood-brain barrier has broken down. Most of the dose is excreted in the urine within 24 hours.

In a clinical trial involving 205 patients, with suspected lesions in the central nervous system, enhancement with gadobenate or gadodiamide produced similar quality images.[1] A comparison with gadopentetate, in patients with suspected liver tumours, found that gadobenate may have an advantage in delayed imaging.[2] While these studies assessed the diagnostic information provided by enhanced MRI, they do not say if the imaging made any difference to the patients' treatments.

The adverse effects of gadobenate include hypertension, tachycardia, injection site reactions, nausea and vomiting. Resuscitation equipment is required as patients may have an anaphylactic reaction to gadobenate.

References †

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Treprostinil sodium

Remodulin (Orphan)

20 mL vials containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL

Approved indication: pulmonary arterial hypertension

Australian Medicines Handbook section 6.7.3

Pulmonary arterial hypertension is a rare condition and there has been criticism that Australian patients have not had access to effective therapy.[1] The approval of treprostinil will increase the options for patients with severe pulmonary arterial hypertension (bosentan and epoprostenol are already available), but hospitals will have to grapple with its cost.

Treprostinil is an analogue of prostacyclin, the natural substance which causes vasodilatation and inhibits platelet aggregation. The haemodynamic effects of treprostinil include reduced pulmonary and systemic vascular resistance.

The drug is given by continuous subcutaneous infusion. Infusion rates are adjusted over several weeks to achieve a balance between improved symptoms and adverse effects. Most of the dose is metabolised in the liver and then excreted in the urine. The half-life is 2–4 hours.

A double-blind trial compared treprostinil to placebo in 470 patients with pulmonary artery hypertension (New York Heart Association (NYHA) functional class II–IV). After 12 weeks there were haemodynamic improvements and a dose-related increase in exercise capacity in the treprostinil group.[2]

Approximately 8% of the participants discontinued treprostinil because of pain at the infusion site. This problem affected 85% of the patients.[2] In addition to problems related to the infusion system, common adverse events include diarrhoea, pain in the jaw, flushing and oedema. As treprostinil inhibits platelets, bleeding, such as gastrointestinal haemorrhage[2], can occur.

Although dyspnoea improved during treatment with treprostinil, the increase in exercise capacity was small. At the start of the study the patients could walk 326 metres in six minutes. The median increase after treatment was 10 metres. Sicker patients tend to improve the most so treprostinil is only approved for patients in the NYHA III–IV functional class.

While it is unknown if treprostinil will have a similar effect on

survival as epoprostenol, it has the advantage of not requiring intravenous infusion. It is possible to change patients from epoprostenol to treprostinil, but this has only been reported in patients with life-threatening complications of intravenous treatment.[3] Treprostinil has not been compared with bosentan, an oral endothelin receptor antagonist, which is considerably cheaper.

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NEW COMBINATIONS

Combined diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated polio vaccine

Infanrix penta (GlaxoSmithKline)

0.5 mL in pre-filled syringe

Combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio, and *Haemophilus influenzae* type b vaccine

Infanrix hexa (GlaxoSmithKline)

0.5 mL in pre-filled syringe, with a vial containing 10 microgram *Haemophilus influenzae* type b vaccine

Approved indication: immunisation

Australian Medicines Handbook section 20.1

The development of new vaccines has increased the potential to prevent childhood illnesses. The expanded range of vaccines has, however, created the difficulty of children needing multiple injections at one time. Multivalent vaccines may help to overcome this problem.

These two products have been approved for primary immunisation at two, four and six months of age. They both contain the same antigens as the currently marketed Infanrix HepB, but also contain inactivated strains of polio virus. To prepare a hexavalent vaccination, the suspension of five vaccines is injected into a vial containing a pellet of haemophilus vaccine. The vaccines are then mixed until the pellet is dissolved and the resulting suspension is then drawn up for injection.

Three injections of the pentavalent vaccine, two months apart, produce an antibody response in more than 99% of babies. This response is as good as that seen when the vaccines are given separately. There is a similar response to the hexavalent vaccine, apart from a 96% response rate to the *Haemophilus influenzae* type b component.

Although the multivalent vaccines induce an immune response, limited information is available about their effectiveness at preventing infections. Their efficacy is considered to reflect that of their components. For example, the diphtheria, tetanus and acellular pertussis component is said to have an efficacy of 84% in protecting against whooping cough. Although the two products have been approved for use as boosters at 18 months, the current Australian Standard Vaccination Schedule does not include booster doses at that age.[1]

As with all vaccines, the health professional giving the intramuscular injection should be ready to deal with an anaphylactic reaction. Adverse reactions to these multivalent vaccines resemble those of their components. The most common reactions are pain at the injection site and irritability. Approximately 20% of children will develop fever.

The National Immunisation Program does not fund all the vaccines in the Schedule and the vaccines used vary between States.[1] While these multivalent vaccines may help to simplify primary immunisation, protecting children against other diseases will still require multiple injections at 12 months of age.

Reference

1. National Health and Medical Research Council. The Australian Immunisation Handbook. 8th ed. Canberra: Department of Health and Ageing; 2003. http://www.immunise.health.gov.au/handbook.htm [cited 2004 Nov 8]

Combined diphtheria, tetanus, acellular pertussis and inactivated polio vaccine

Infanrix IPV (GlaxoSmithKline)

0.5 mL in pre-filled syringe

This vaccine is similar to the above products, but contains fewer antigens. While it can be used for primary immunisation against diphtheria, tetanus, pertussis and polio, its components fit in with the recommended vaccines for four-year-old children.

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* At the time the comment was prepared, information about this drug was available on the web site of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

NEW FORMULATION

Esomeprazole

Nexium IV (AstraZeneca)

vials containing 42.5 mg for reconstitution

NEW STRENGTHS

Cephazolin sodium

Cefazolin Sandoz (Sandoz)

2 g powder for injection

Rasburicase rys

Fasturtec (Sanofi-Synthelabo)

glass vials containing 7.5 mg powder

Trandolapril

Gopten (Abbott)

4 mg capsules

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