have been helpful to include the role of cardiopulmonary resuscitation (CPR) and how it differs in hypothermia, near drowning and electrical injury compared to the standard cardiac arrest situations.

While the chapter on burns is excellent, anaphylaxis is probably too detailed and makes the book look unbalanced given the inadequate coverage of some of the other environmental topics.

The section on altitude illness is so short as to be almost useless. It does not correctly describe the diagnostic criteria for acute mountain sickness, and confusingly, and perhaps dangerously, lumps this common and benign condition together with two less common and deadly ones. The section on prevention is overly brief and contains recommendations for ascent rates that do not comply with internationally accepted standards.

The information on diving medicine and heat-related illness are so short they could only be interpreted by clinicians who understand the topic.

The chapter on hypothermia is again so short that it lacks clarity and accuracy. It misses out critical management issues such as clinical assessment, gentle handling of patients and the role of CPR. The treatment algorithm is too simplified.

This book should cover common wilderness topics such as motion sickness, carbon monoxide poisoning, evacuation and long-term patient care, non-freezing cold injury, frostbite and avalanche rescue medicine. The focus should be as much on prevention as it is on treatment in the emergency situation.

My recommendation for the prospective purchaser is to read the book for its excellent toxicology and toxinology sections. If you want something to cover 'wilderness' topics, I suggest Auerbach's Field Guide to Wilderness Medicine, or the new Oxford Handbook of Expedition Medicine.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and 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.

Maraviroc

Celsentri (Pfizer)

150 mg and 300 mg film-coated tablets

Approved indication: HIV infection

Australian Medicines Handbook section 5.4

Highly active antiretroviral therapy has improved survival for patients infected by HIV, but long-term toxicity and the development of viral resistance are problematic. There is still a need to develop new drugs to treat people with clinically advanced disease which is resistant to several classes of antiretroviral drugs. The entry of HIV into a patient's cells is one target of research and has led to the development of fusion inhibitors such as enfuvirtide (see 'HIV fusion inhibitors: a review', Aust Prescr 2008;31:66–9).

Maraviroc blocks the entry of HIV into cells, but it is not a fusion inhibitor. It acts on human chemokine co-receptor 5 (CCR5) which is found on the cell membrane. Some strains of HIV (CCR5-tropic HIV-1) enter the cell after interacting with this receptor. By selectively binding to the receptor, maraviroc prevents HIV from penetrating the cell surface. This ultimately results in reduced viral replication.

The approval of maraviroc was based on the interim results of two clinical trials involving a total of 635 patients. These patients were infected with CCR5-tropic HIV-1 and had more than 5000 copies of viral RNA/mL despite previous treatment with at least one drug from at least three different classes of antiretroviral drug. A group of 209 patients were randomised to take a regimen of three to six antiretroviral drugs, while 426 added maraviroc 300 mg twice daily to this regimen. After 24 weeks the viral RNA in 23% of the patients taking the 'optimised background regimen' was less than 50 copies/mL. In the group which added maraviroc 45% had less than 50 copies/mL. The increase in the concentration of CD4 lymphocytes was 57 cells/mm^3 with the regimen alone and 106 cells/mm^3 when maraviroc was added.

When these trials were published they reported on outcomes at 48 weeks, having randomised 1075 patients. Viral RNA had fallen to less than 50 copies/mL in 17% of the patients taking the optimised regimen. The same outcome had been reached by 46% of the patients taking maraviroc twice daily and by 43% of patients using a once-daily regimen. CD_4 lymphocytes increased by 61 cells/mm^3 in the control group, by 124 cells/mm^3 with twice-daily maraviroc and by 116 cells/mm^3 with once-daily maraviroc.[1,2]

Adding maraviroc to the treatment of patients taking multiple other drugs does not greatly affect the number of adverse reactions. Nausea, diarrhoea and headache are common. Adverse events which occurred more frequently when maraviroc was added to treatment include paraesthesia, muscle

aches, cough, fever, infections and rashes. Liver enzymes were more likely to increase in patients taking maraviroc and in the USA the drug has a black box warning about hepatotoxicity. There is little information about the safety of the drug in patients with liver disease, especially those who are infected with hepatitis B or C. It is uncertain if the cardiovascular events reported in patients taking maraviroc were related to the drug.

The absorption of maraviroc is variable, possibly because of saturation of the P-glycoprotein transporter. Although absorption can be reduced by a high fat meal, there are no restrictions on taking maraviroc with food. As maraviroc is mainly metabolised by cytochrome P450 3A4, there are many potential drug interactions. A lower dose of maraviroc is recommended if the patient is prescribed an inhibitor of this enzyme such as clarithromycin, itraconazole and the protease inhibitors (except tipranavir/ritonavir and fosamprenavir/ritonavir). A higher dose is recommended if the patient is taking an enzyme inducer such as rifampicin, efavirenz and carbamazepine. Patients should not take St John's wort as it is likely to decrease concentrations of maraviroc. The usual twice-daily dose has a half-life of 16 hours with most of the metabolites being excreted in the faeces.

Maraviroc is being studied in previously untreated patients, but its role in therapy depends on whether the patient is infected with CCR5-tropic HIV-1. CCR5-tropic HIV-1 predominates early in the infection, but viral forms emerge which can use another co-receptor to enter the cell. The use of maraviroc is therefore limited to patients only infected with CCR5-tropic virus. It can take several weeks to test for CCR5-tropic HIV-1, so testing may be a barrier to treatment. The effectiveness of maraviroc will also be reduced if the virus develops a reduced sensitivity to the drug. Like other antiretroviral drugs approved on surrogate end points, maraviroc will require more research to determine its optimal use in combination regimens.

T T T manufacturer provided clinical evaluation

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Romiplostim

Nplate (Amgen)

vials containing 375 microgram and 625 microgram for reconstitution

Approved indication: idiopathic thrombocytopenic purpura

Australian Medicines Handbook Appendix A

One of the causes of thrombocytopenia is idiopathic thrombocytopenic purpura. As the platelets are destroyed by antiplatelet autoantibodies the condition is also known as chronic immune thrombocytopenic purpura. Other causes of thrombocytopenia should be excluded before making the diagnosis.

If the platelet count is low enough to require treatment, corticosteroids are usually prescribed first. Patients who do not respond may be given immunoglobulins. Severe thrombocytopenia can be an indication for splenectomy.

A new approach to managing idiopathic thrombocytopenic purpura is to boost platelet production rather than trying to limit platelet destruction. Romiplostim is a genetically engineered protein which binds to the thrombopoietin receptor even though its structure differs from that of human thrombopoietin. Activation of the receptor increases platelet production.

Romiplostim is given by subcutaneous injection. As the volume is small, a syringe with 0.01 mL gradations should be used. The serum concentration peaks after a median of 14 hours and the median half-life is 3.5 days.

A dose-ranging study gave romiplostim to 24 patients with previously treated immune thrombocytopenic purpura. Depending on the platelet count a second injection was given after at least 14 days. In four of the 12 patients given 3, 6 or 10 microgram/kg of romiplostim the platelet count rose to at least twice the baseline count. Lower doses were not effective.[1] In another phase of this trial 21 patients were given romiplostim (1, 3 or 6 microgram/kg) or a placebo injection containing the excipients of the formulation every week for six weeks. Seven of the eight patients given 1 microgram/kg and three of the eight given 3 microgram/kg achieved the target concentration for platelets. (The 6 microgram/kg dose was dropped from the trial due to an exaggerated increase in platelets.) Adverse events which were more frequent with romiplostim than its excipients were headache and blistering of the oral mucosa.[1]

Using the information from the dose-ranging studies, two parallel trials were designed. Starting with 1 microgram/kg weekly the dose of romiplostim was adjusted to achieve a target platelet count of 50–200 x 10^9/L. One trial enrolled 62 patients and the other enrolled 63 patients following splenectomy. Both trials were placebo-controlled and lasted for six months. Within three weeks half the patients given romiplostim had reached the target. During at least six of the last eight weeks of treatment, 49% of the patients given romiplostim, but only 2% of the placebo group, were in the target range. This durable response was seen in 61% of the non-splenectomised patients and 38% of the splenectomised patients. On average, in patients given romiplostim, the platelet count was above the target for 15.2 weeks in the non-splenectomised group and 12.3 weeks in the splenectomised group. They needed less rescue therapy than patients in the placebo group who only achieved the target for a mean of 0.8 weeks.[2]

Adverse events which were more frequent with romiplostim

than with placebo included headache, epistaxis, arthralgia, myalgia, dizziness, insomnia and abdominal pain.[2] As platelet counts rise there could be an increased risk of thrombosis. An increase in the amount of reticulin in the bone marrow can cause morphological changes in blood cells. Peripheral blood films, as well as platelet counts, should be checked during treatment.

Romiplostim is not a cure for immune thrombocytopenic purpura, the platelet count will fall again after treatment is discontinued. As patients are therefore likely to require repeated treatments, establishing the long-term efficacy and safety will be important. The data are limited, but neutralising antibodies have not yet emerged as a major problem. At present the use of romiplostim will be limited to patients who have had an inadequate response to splenectomy, and those who have not had a splenectomy but cannot tolerate or have not responded to corticosteroids and immunoglobulins.

T T T manufacturer provided clinical evaluation

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

* At the time the comment was prepared, information about this drug was available on the website 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 website of the European Medicines Agency (www.emea.eu).

Answers to self-test questions

1. False
2. True
3. False
4. False
5. True
6. False

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