We should consider if using a combination product helps us to prescribe according to accepted guidelines. Paradoxically, an innovation which at first sight seems to simplify prescribing will perhaps make it more complex.

Conflict of interest: none declared

E-mail: rfwm@unimelb.edu.au

REFERENCES

1. Wright EC. Non-compliance – or how many aunts has Matilda? Lancet 1993;342:909-13.
2. Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Clin Ther 1984;6:592-9.

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 Board 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 Board is prepared to do this. Before new drugs are prescribed, the Board 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.

Dexmedetomidine

Precedex (Abbott)

2 mL ampoules containing 100 microgram/mL

Approved indication: sedation

Australian Medicines Handbook Section 2.2

For several years it has been known that the antihypertensive drug clonidine can reduce the required dose of anaesthetic drugs. It does this by stimulating alpha$_2$ adrenoceptors. Dexmedetomidine also acts as an agonist at these receptors. This action has analgesic effects and, possibly because of an effect on the locus ceruleus, also causes sedation.

Dexmedetomidine has been approved for the sedation of intubated post-surgical patients during treatment in intensive care. It has been compared with placebo for this indication in a British study. Patients who were given dexmedetomidine required 80% less midazolam for sedation and 50% less morphine for analgesia.[1] A study comparing dexmedetomidine with propofol found that both drugs adequately sedated the patients. Those given dexmedetomidine required significantly less morphine for analgesia. Dexmedetomidine has an advantage because it causes little respiratory depression, so patients can be extubated without having to wait for their respiratory function to recover.

As dexmedetomidine is given by infusion, it must be diluted before use. A loading dose is given over 10 minutes followed by a maintenance infusion which is adjusted according to the clinical response. The infusion should not exceed 24 hours.

Dexmedetomidine has a half-life of two hours. It is almost completely metabolised with most of the metabolites being excreted in the urine. Dose reductions may be needed for patients with renal or hepatic impairment. Although cytochrome P450 2A6 is involved in the metabolism clinically significant interactions are thought to be unlikely.

Dexmedetomidine does interact with anaesthetic drugs, opioids and sedatives so it should only be used in intensive care. Patients require monitoring of their electrocardiogram, oxygen saturation and blood pressure.

Hypotension is the most common adverse reaction, occurring in 22% of patients, however some patients will become hypertensive. Dexmedetomidine can also cause bradycardia. Patients who are elderly, or who have diabetes or heart failure, have an increased risk of these adverse effects because of changes in their autonomic nervous systems. Lower doses are recommended for the elderly.

Dexmedetomidine has been approved on the evidence gathered from fewer than 600 patients. It may take more clinical experience to determine whether its benefits are outweighed by the adverse reactions.

REFERENCE

1. Venn RM, Bradshaw CJ, Spencer R, Brealey D, Caudwell E, Naughton C, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 1999;54:1136-42.

Imatinib mesylate

Glivec (Novartis)

50 mg and 100 mg capsules

Approved indication: chronic myeloid leukaemia

Australian Medicines Handbook Section 14.3.9

Most patients with chronic myeloid leukaemia have a translocation of chromosomes 9 and 22. The abnormal chromosome, known as the Philadelphia chromosome, results in the production of an abnormal tyrosine kinase. This enzyme contributes to the production of malignant cells.

Imatinib aims to inhibit the abnormal tyrosine kinase. This action stops cell proliferation and can induce apoptosis of tumour cells.

The drug is well absorbed so it can be given by mouth. It has a half-life of 18 hours and is mainly cleared by metabolism. This metabolism involves cytochrome P450 3A4 so there is a potential for interactions with inhibitors of this enzyme such as grapefruit juice, erythromycin and ketoconazole. Although there have been no studies, drugs such as phenytoin, carbamazepine, dexamethasone and St John's wort may reduce the concentrations of imatinib by inducing P450 3A4. Imatinib has other potential interactions because it also inhibits P450 2D6 and 2C9.

In a pilot study 58 patients with chronic myeloid leukemia who were in blast crisis, were treated with daily doses between

300 mg and 1 g. There was a response in 14 of the 20 patients with a lymphoid blast crisis or acute lymphoblastic leukaemia. In the 38 patients with myeloid blast crisis 21 responded.[1]

Another study treated 83 patients with chronic myeloid leukaemia who had not responded to interferon alfa. All the patients who took 140 mg or more had at least a 50% fall in their white blood cell count.[2]

These early trials were followed by larger studies. In a study of 532 people with chronic myeloid leukaemia who had been unsuccessfully treated with interferon there was a complete haematological response in 88% of the patients. (Their white cell counts fell below 10 x 10^9/L.) In 15% of patients there was a confirmed cytogenetic response as bone marrow biopsy showed no cells with the Philadelphia chromosome. A study of 235 patients in the accelerated phase of the disease showed that 400 mg or 600 mg imatinib produced a complete haematological response in 28% and a confirmed complete cytogenic response in 4%. In patients with myeloid blast crisis there was a complete haematological response in 4% and a confirmed complete cytogenic response in 1%.

During clinical trials up to 68% of patients reported nausea and many vomited. Fluid retention occurred in up to 68% but could often be managed with diuretics. Regular blood counts are required as imatinib is associated with anaemia, neutropenia and thrombocytopenia. Haemorrhage occurred in 13% of the patients who failed interferon therapy and in 48% of those with a myeloid blast crisis. Particular caution is needed if the patient is also taking warfarin. One patient died of acute liver failure which could have been related to an interaction with paracetamol. High doses of paracetamol should therefore be avoided.

Most patients have been followed up for less than six months so there are no long-term safety data about imatinib. There is also a possibility that drug resistance could develop. Further research is needed as it is not yet known whether or not the improvements in laboratory results will lead to better clinical outcomes for the patients.

REFERENCES

1. Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001;344:1038-42.
2. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 2001;344:1031-7.

Levobupivacaine hydrochloride

Chirocaine (Abbott)

10 mL ampoules containing 2.5 mg/mL, 5 mg/mL and 7.5 mg/mL

Approved indication: anaesthesia

Australian Medicines Handbook Section 2.1

Bupivacaine is an amide-type local anaesthetic. Although it blocks neurotransmission, its membrane stabilising action also affects the myocardium. This can cause fatal cardiotoxicity. As bupivacaine is widely used in surgery and obstetrics, attempts have been made to develop a safer long-acting local anaesthetic.

The bupivacaine molecule is a racemic compound. Levobupivacaine is the S-enantiomer of bupivacaine and is thought to have less cardiotoxic potential than the R-enantiomer. The pharmacokinetic parameters of levobupivacaine are similar to those of bupivacaine.

Levobupivacaine has been studied in surgical anaesthesia and for pain management. It can be used for local infiltration, epidural, intrathecal and peripheral nerve blocks. For epidural analgesia it can be given with fentanyl, morphine or clonidine. Double-blind comparisons of levobupivacaine and bupivacaine show that their anaesthetic effects are similar.

The adverse effects of the two drugs are also similar. They are influenced by how the drugs are administered, for example hypotension often occurs during epidural anaesthesia. Nausea and vomiting also occur commonly with both drugs.

To reduce adverse effects the smallest dose and concentration should be used. The 7.5 mg/mL concentration should not be used in children or in obstetrics. Like bupivacaine intravascular injection must be avoided, and levobupivacaine is contraindicated for intravenous regional anaesthesia (Bier's block) because of cardiotoxicity. It is also contraindicated as a paracervical block. Test doses with a short-acting local anaesthetic can be used before using levobupivacaine for a complete nerve block. Although animal studies suggest a benefit, it remains to be proven whether levobupivacaine has significantly less toxicity than bupivacaine.

Trastuzumab

Herceptin (Roche)

vials containing 150 mg lyophilised powder

Approved indication: breast cancer

Australian Medicines Handbook Section 14.1

In up to 30% of patients with breast cancer there is an overexpression of the HER2 gene. This oncogene codes for a receptor to epidermal growth factor. Trastuzumab is a monoclonal antibody which can block this receptor. This inhibits the growth of breast cancer cells.

Trastuzumab is a humanised murine antibody produced by recombinant technology. It is given as a slow intravenous infusion. The first loading dose is given over 90 minutes. If this is well tolerated, subsequent weekly infusions can be given over 30 minutes. These infusions are repeated until the cancer progresses.

The half-life of trastuzumab is approximately six days, but a steady state is not reached for 16-32 weeks. As trastuzumab has non-linear pharmocokinetics its clearance decreases as the dose increases. Serum concentrations are also increased if the drug is given with paclitaxel.

Trastuzumab has been studied as monotherapy for women with metastatic tumours that overexpress HER2. The 222 women in this study had failed to respond to chemotherapy, but 15% showed some response to trastuzumab.

The drug has also been used in combination with chemotherapy for metastatic breast cancer. In terms of the median time before the disease progressed, trastuzumab had significant advantages. Trastuzumab with paclitaxel delayed progression more than paclitaxel alone, and with an anthracycline and cyclophosphamide it delayed progression more than that combination alone. Overall, adding trastuzumab to chemotherapy increased the median time to disease progression by 61%.

Trastuzumab is a protein, so patients can develop hypersensitivity reactions. Serious reactions have occurred during the infusions and many other patients will experience fevers or chills. There is a risk of cardiotoxicity, and approximately 9% of patients treated with trastuzumab will develop heart failure. This risk may be increased in patients treated with anthracyclines so, for combination regimens, only the taxanes can be used with trastuzumab. Common adverse reactions include nausea, vomiting and diarrhoea.

Trastuzumab appears to improve the survival of women with metastatic breast cancer who have overexpression of the HER2 oncogene, but not all women will benefit. Only a small number (8/222) of women had a complete response to monotherapy. In that study, the median time to tumour progression was only three months. When trastuzumab is given with paclitaxel the median time to progression is seven months. Although this increases one year survival from 62% to 73%, the difference is not statistically significant.

Correction

Buprenorphine (Aust Prescr 2001;24:71)

There was an error in the gazettal notice, issued by the Therapeutic Goods Administration, regarding the strengths of buprenorphine sublingual tablets. The available strengths are 0.4 mg, 2 mg and 8 mg, not 2 mg, 4 mg and 8 mg.

Answers to self-test questions

1. True
2. True
3. True
4. True
5. False
6. False
7. True
8. False
9. False
10. True

Australian Prescriber mailing list

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also distributed free of charge, in bulk, to medical, dental and pharmacy students through their training institutions in Australia. To be placed on the mailing list, contact the Australian Prescriber Mailing Service.

Postal: Australian Prescriber Mailing Service
GPO Box 1909
CANBERRA ACT 2601
AUSTRALIA

Telephone: (02) 6241 6044 Fax: (02) 6241 4633

NAME: .....

ADDRESS: .....

.....

.....

.....

PROFESSION: .....

(general practitioner, resident, psychiatrist, surgeon, dentist, pharmacist, etc.)

The full text of *Australian Prescriber* is available on the internet, free of charge, at www.australianprescriber.com

Tick ☑ whichever of the following apply:

I have access to the *Australian Prescriber* web site on the internet ☐ Yes ☐ No

☐ Place me on the mailing list

☐ Delete me from the mailing list

My reference number is .....

☐ Change my address

My reference number is .....

☐ Send me all the available back issues (from Vol. 22 No. 6, 1999)

☐ Send me the following back issue/s

.....

Editorial office

For general correspondence such as letters to the Editor, please contact the Editor.

Telephone: (02) 6289 7038

Facsimile: (02) 6289 8641

Postal: The Editor
Australian Prescriber
PO Box 100
WODEN ACT 2606
AUSTRALIA

E-mail: info@australianprescriber.com

Web site: www.australianprescriber.com