Australian Prescriber

VOLUME 27 | NUMBER 2 | AN INDEPENDENT REVIEW | APRIL 2004

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Editorial

Trouble with tramadol

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Key words: analgesia, drug interactions, serotonin.

(Aust Prescr 2004;27:26–7)

Since tramadol was marketed in Australia in late 1998 its use has increased dramatically.[1] While there is a large amount of information supporting tramadol's effectiveness for pain, there is an increasingly large body of evidence from post-marketing surveillance showing there are problems. In 1999 there were 19 reports of adverse events, while in 2003 there were 286 reports. As of March 2004 the Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received 726 reports of adverse events associated with tramadol, detailing 1922 reactions. In 453 of the reports, tramadol was the sole suspected drug. These reactions suggest that the decision to prescribe tramadol should be carefully considered.

Tramadol is a centrally acting analgesic. Structurally it is not an opiate, but it exhibits some opioid characteristics. Like opioids it binds to μ receptors, although very weakly (binding affinity is 10 times less than codeine and 6000 times less than morphine).[2] Like codeine, tramadol is metabolised via the CYP2D6 isoenzyme of cytochrome P450 to an active metabolite which binds to μ receptors. Patients who metabolise drugs poorly via CYP2D6 (about 7% of Caucasians) may get less benefit from tramadol (and codeine) due to reduced formation of the active metabolite. Tramadol is also metabolised by CYP3A4 so its activity is reduced by drugs which induce CYP3A4.[3]

In this issue…

Scientific advances have led to the development of biological treatments for inflammatory diseases. Geoff McColl assesses how the inhibition of tumour necrosis factor alpha may help patients with severe rheumatoid arthritis.

While technology can separate out the enantiomers from racemate drugs, Andrew Somogyi and colleagues question if some of these chiral switches are a new marketing strategy for the pharmaceutical industry.

Despite such advances the discovery of new antibiotics has slowed down. John Ferguson tells us how to make the best use of those we have.

While old drugs are often still the best treatment, this may not be the case with pethidine. Richard Watts reveals why pethidine is not an ideal drug for treating labour pain.

The analgesic effects of tramadol are not completely reversed by the opioid antagonist naloxone and some patients who do not respond to codeine do respond to tramadol. This suggests that tramadol has additional mechanisms of action. Tramadol inhibits reuptake of serotonin and noradrenaline and this probably contributes to its analgesic effects.

There is no doubt that tramadol is an effective analgesic for moderate, and in some cases, severe pain.[4] In comparative studies in postoperative and post-trauma pain, tramadol 100 mg intramuscularly or intravenously was equivalent to 5–10 mg of morphine. However, in severe pain associated with either surgery or cancer, morphine was more effective than tramadol and remains the drug of choice. In acute and chronic non-malignant pain, oral tramadol 100 mg is comparable to a combination of paracetamol and codeine (1000 mg/60 mg). There have been few direct comparisons of tramadol with non-steroidal anti-inflammatory drugs, but efficacy appears to be similar.

When choosing between equally effective analgesics, relative safety is important. In the case of tramadol, adverse effects are common and sometimes serious. Tramadol binds weakly to opioid receptors, so at normal doses constipation and respiratory depression occur less frequently than with opioids. However, these effects can, and do, occur at higher doses. Tramadol is metabolised in the liver and excreted by the kidneys, so doses should be adjusted in patients with impaired liver or kidney function, and in the elderly.[5]

Other opioid-like effects occur commonly at normal doses, including nausea, vomiting, dizziness and confusion. Titrating the dose slowly may improve tolerability, but this may be impractical in acute pain. A major problem is dizziness which can contribute to falls in at-risk patients. Dizziness appears in 13% of the reports received by ADRAC.

Seizures have been reported with tramadol at normal doses. ADRAC has received 66 reports involving convulsions and in 27 tramadol was the sole suspected drug. Tramadol should be avoided in patients with epilepsy and used cautiously in patients taking medications which lower the threshold for seizures, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), major tranquillisers, bupropion and opioids. Other serious adverse effects include hallucinations, hypertension and hypersensitivity reactions.

Many interactions with tramadol have been identified.[1,4,5] Some involve changes in metabolism. For example, carbamazepine reduces the analgesic effect of tramadol by increasing its metabolism (presumably via CYP3A4). Drugs which inhibit CYP2D6 activity (such as some SSRIs, quinidine, phenothiazines, some protease inhibitors) will inhibit conversion to the active metabolite.

Interactions may involve enhanced drug activity at receptor sites. A severe serotonin syndrome may occur when tramadol is combined with other drugs which also increase serotonin activity.[6] Such drugs include SSRIs, moclobemide and other monoamine oxidase inhibitors, tricyclic antidepressants, sibutramine, St John's wort, lithium and pethidine.[1,7] ADRAC has received 35 reports of serotonin syndrome in association with tramadol, usually in combination with other serotonergic drugs.

In some cases the mechanism of interaction is unclear. For example, tramadol may increase the effects of warfarin.[5] The patient's INR should therefore be carefully monitored.

The potential for abuse and dependence with tramadol is low. However, there have been case reports of dependence and withdrawal after long-term use.[8] ADRAC has received 24 reports of a withdrawal syndrome with tramadol. It is important to monitor patients on long-term tramadol and to avoid abrupt cessation after long-term use.

The decision to prescribe tramadol should not be a trivial one. Tramadol has a place in pain management for selected patients who have not responded to simple analgesics such as paracetamol or aspirin and in whom NSAIDs are contraindicated. For most patients, a combination of paracetamol and codeine will be equally effective and possibly better tolerated than tramadol. In order to minimise adverse effects, patient factors should be carefully considered and the patient's medication history must be carefully reviewed.

Patients on tramadol should be regularly monitored, particularly in the early stages of therapy. Patients with chronic pain should be monitored closely during dose titration, especially where there is dose escalation. Adverse drug reactions with tramadol are common and patients should be given guidance about appropriate action should such reactions occur. In particular, the potential for serious drug-drug interactions should not be underestimated.

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Conflict of interest: none declared

Editorial note:

During the preparation of the editorial there was a suggestion that the popularity of tramadol may be related to the availability of repeat prescriptions on the Pharmaceutical Benefits Scheme (PBS). The Editorial Executive Committee therefore invited the Pharmaceutical Benefits Advisory Committee (PBAC) to comment.

Diana MacDonell, Secretary of the PBAC, comments:

Tramadol capsules 50 mg are listed for two indications on the PBS. One indication is treatment of acute pain conditions where aspirin and/or paracetamol alone are inappropriate or have failed. The PBAC considered that this medication is appropriate for short-term use only, so the maximum quantity is 20 with no repeats in order to encourage appropriate use. The restriction includes a NOTE advising that no applications for increased maximum quantities and/or repeats will be authorised.

The second indication is for dosage **titration** in chronic pain where aspirin and/or paracetamol alone are inappropriate or have failed. For this indication two repeats may be prescribed, however no application for increased maximum quantities and/or repeats will be authorised. This is the only listing for tramadol which allows for repeats to be written without seeking approval from the Health Insurance Commission (HIC), and is specifically to facilitate dosage titration when initiating therapy with tramadol for chronic pain.

The sustained release formulation of tramadol in strengths of 100 mg, 150 mg and 200 mg is listed for pain where aspirin and/or paracetamol alone are inappropriate or have failed. The maximum quantity available on the PBS for this formulation is 20 tablets with no repeats. This listing is consistent with the listing of codeine phosphate (30 mg) with paracetamol (500 mg). Increased quantities and repeats for both tramadol sustained-release tablets, and codeine phosphate with paracetamol will only be granted if the doctor obtains approval from the HIC for such an authority, which is generally limited to one month's therapy. Authorities for increased maximum quantities and/or repeats will be granted only for severe disabling pain not responding to non-narcotic analgesics.

Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

New drug comment – escitalopram

Editor, – I refer to comments regarding escitalopram ('New drugs' Aust Prescr 2003;26:146–51). Only one study that investigated the efficacy of escitalopram in the treatment of major depression[1] was cited in the article, when four other studies were available at the time of writing.[2,3,4,5] The review concludes that escitalopram is a generic strategy.

Regulatory bodies advocate that companies must recognise the existence of chirality, that they should attempt to separate enantiomers, that the contribution of individual stereoisomers to the activity of interest should be assessed and that a rational decision regarding what stereoisomer to market should be made.[6]

The technology to separate the enantiomers of citalopram on a commercial scale has only recently been developed.

Preclinical studies have demonstrated that the antidepressant effect of citalopram resides primarily with the S-enantiomer.[7] Escitalopram alone affects serotonin levels more effectively than escitalopram in combination with the R-enantiomer.[8] The R-enantiomer decreases the association of the S-enantiomer with the human serotonin transporter via an allosteric mechanism.[9] The R-enantiomer thus inhibits the active S-enantiomer.

A pooled analysis[4] provided a sample size adequate for statistical comparisons between escitalopram and citalopram to be made. The results suggest that escitalopram may be superior to citalopram in terms of speed of onset and magnitude of clinical effects.

A meta-analysis[10] has shown that escitalopram-treated patients have significantly higher response rates and an increased mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at weeks one and eight when compared with citalopram. This superiority was more apparent with severely depressed patients.

Pharmacoeconomic analyses have found escitalopram has cost-effectiveness and cost-utility advantages over some other SSRIs and venlafaxine.[11]

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Editorial comment:

Lundbeck was invited to supply *Australian Prescriber* with information about escitalopram during the preparation of the new drug comment. The company informed the Editor that it would not release information because it was confidential. However, following publication of the new drug comment the company has supplied a dossier of data, including the previously confidential information. The Editorial Executive Committee welcomes the change of position by the company and hopes it will be an example other companies will follow.

The additional information does not provide strong evidence that escitalopram has a clear clinical advantage over citalopram. Only two (references 3 and 5) of the four other studies included both drugs in humans. Reference 2 compares escitalopram with placebo, and reference 4 is a pooled analysis of other studies. Reference 5 was a combined study of patients and Polish rats, but it compared each drug with placebo rather than with each other. While reference 3 shows that significantly more patients were in remission after eight weeks of escitalopram than after citalopram (52% versus 43%), neither treatment was significantly better than placebo. The mean change in the 60 point Montgomery-Asberg Depression Rating Scale (MADRS) was 15 points with escitalopram, 13.6 points with citalopram and 12 points with placebo.

It is not entirely clear which three studies were included in the pooled analysis (reference 4), but they are probably included in the company-sponsored meta-analysis (reference 10). The meta-analysis includes references 1, 3, an unpublished study and a conference abstract. While the unpublished study tended to favour citalopram, the meta-analysis showed a higher response rate with escitalopram (55.5% versus 50.8%). The mean change in the MADRS after eight weeks was approximately one point greater with escitalopram than with citalopram (1.02, confidence interval 0.09–1.95). None of the studies showed that patients responded significantly faster to escitalopram although the meta-analysis found an estimated difference of 0.63 (confidence interval 0.08–1.17) in the mean change in MADRS from week one of treatment. The clinical relevance of this difference is debatable.

The Pharmaceutical Benefits Advisory Committee has also concluded that the data do not demonstrate that escitalopram has superior efficacy to citalopram.

New drug comment – pimecrolimus

Editor, – The review of pimecrolimus (Elidel) in the 'New drugs' section (Aust Prescr 2003;26:146–51) states that children may be exposed to 'risks of immunosuppression'. Contrary to this view, clinical signs of systemic immunosuppression were not seen in the long-term paediatric studies.[1,2] Some systemic adverse events were more common in the pimecrolimus group, but these were not significant when the time on study drug was taken into account. Pharmacokinetic studies demonstrated that blood concentrations of pimecrolimus following dermal application were below the limits of detection in the majority of paediatric patients, thus minimising the likelihood of a systemic effect.

Contrary to the review pimecrolimus did not enhance the carcinogenicity of UV light in animal models (see TGA-approved product information). The lymphoma and thyroid adenomas mentioned by the reviewer were observed in animal studies only following oral administration of pimecrolimus, in which systemic exposure was much higher than that observed following clinical use of pimecrolimus cream. To date, clinical trial and postmarketing surveillance data do not indicate an increase in the risk of malignancy. Nevertheless Novartis recommends that patients avoid exposing skin areas treated with pimecrolimus to sunlight.

Incorporating pimecrolimus into the management of atopic dermatitis was shown to improve long-term disease control and reduce the number of flares when compared with reactive use of topical corticosteroids.[1,2] Pimecrolimus has not been associated with skin atrophy and is approved for use on all skin areas including the face, neck and intertriginous areas.

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2. Wahn U, Bos JD, Goodfield M, Caputo R, Papp K, Manjra A, et al. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics 2002;110:e2.

Editorial comment:

It is reassuring to learn that postmarketing surveillance data have not yet shown evidence of malignancy in patients treated with pimecrolimus. However, unlike the Australian product information, the US product information does report an increase in the incidence of tumours in animals following dermal application of pimecrolimus.

While pimecrolimus may not enhance the carcinogenicity of UV light, the topical cream base enhances the development of skin tumours induced by UV radiation. Although the company advises patients to avoid sunlight, this may pose practical problems for patients applying pimecrolimus to the face or neck.

Although blood concentrations are low after topical application, absorption does occur. References 1 and 2 above did adjust for the duration of follow-up, but still showed a higher frequency of systemic symptoms, such as cough and fever, in children treated with pimecrolimus.

Until more data are available, the Editorial Executive Committee still believes that pimecrolimus is not a first-line treatment and caution is needed, particularly when prescribing to infants. Neither the USA nor the UK have approved pimecrolimus for children under the age of two years.

Oximetry

Editor, – I enjoyed the review of oximetry by I. Young (Aust Prescr 2003;26:132–5), but was distressed to see the myth that 'nail polish must be removed' perpetuated in both the article and the self-test questions. An Australian woman can spend up to $1000 each year on nail care and decoration. To have to remove that polish or enamel is both inconvenient and expensive.

A study of painted and unpainted nails, in the same people, tested 10 nail colours and found no significant differences in the SpO_2 measured in the painted and unpainted fingers.[1]

It has been recommended that, since some nail polishes may reduce estimates of SpO_2 by up to 6%, the probe should be rotated through 90° and mounted transversely in patients with nail polish or long nails.[2] Personal observation in long endoscopy lists has shown no significant differences in saturations measured in the conventional way and measured transversely across the finger, in males or females.

We should abolish the myth of the necessity of nail polish removal once and for all and save nursing time.

John Paull
Consultant Anaesthetist
Launceston, Tas.

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Clinical Associate Professor I. Young, the author of the article, comments:

I was aware of the paper that suggests transverse mounting of the probe where nail polish is a problem and, of course, not all polish will cause a significant interference with the signal. My article does state that only strong superficial pigments are likely to be a problem.

I became aware of the Brand paper too late in the editorial process to change the article. The people in this study were normoxic individuals and some interference was found with strong blue and green pigments *in vitro*. However, I entirely accept Dr Paull's argument that it is not necessary to remove nail polish and regret that one of the questions attached to the article has erroneously emphasised this procedure.

Traditional Chinese medicines

Editor, – The authors of 'The quality and safety of traditional Chinese medicines' (Aust Prescr 2003;26:128–30) recommend the establishment of a quality testing system for Chinese herbs and their derivatives, in order to minimise mislabelling and identify undeclared components. This is based on the claims that the 'chemistry of herbal medicines is the foundation of their pharmacology', and that 'for most Chinese medicines the active components responsible for their pharmacological activities and clinical applications are not well defined'. The authors also point to the Chinese Medicine Registration Act in Victoria as an example of statutory regulation which will encourage the safe use of traditional Chinese medicines.

These recommendations are unexceptionable. However, these recommendations contain an irony, or a threat, depending on whether you subscribe to Western or Chinese medical systems. What is proposed is the application of Western scientific methods of analysis to Chinese medicines, in order to classify them as safe. In other words, the Chinese medical system, in order to survive in the dominant scientific culture, must subject itself to that culture's rules. This means that it cannot survive as a distinct and autonomous paradigm.

Mechanisms designed to ensure that Chinese medicines and practice (and any other traditional systems) continue to be recognised and respected, will ultimately ensure their demise.

Malcolm Parker
Associate Professor of Medical Ethics
School of Medicine
University of Queensland

Dr George Li, Dr Colin Duke and Professor Basil Roufogalis, the authors of the article, comment:

The letter raised the issue of the philosophy and position of complementary medicine. There are integrated and plural approaches. The article is in favour of an integrative approach. The recommendations are consistent with the recent report of the Expert Committee on Complementary Medicines.[1]

We appreciate the concern about the possible overzealous application of modern scientific principles to the analysis of traditional medicines which have a different philosophical basis. In this article we addressed the issue of quality and safety of Chinese medicine, and we believe that the evaluation of safety of any device or therapeutic agent overrides cultural considerations. We agree that the assessment of safety of Chinese herbal medicines is complex, as they are made up

of multiple components and used by practitioners in specific ways. Nevertheless, Chinese medicines contain chemical components that have specific biological actions requiring knowledge of the quality and nature of the ingredients.

The recommendations in our article do not address other aspects of Chinese medicine, whose principles can be maintained subject to appropriate evidence-based review. The recent report has recommended that governments introduce legislation to regulate practitioners of traditional Chinese medicine and dispensers of Chinese herbs.[1] This development recognises the use and importance of traditional medicine systems in our society while requiring practitioners to be appropriately trained and accredited. The integrative approach to health care should aim to further develop the traditional system and bring it into the mainstream health care system. It should certainly not try to eliminate a traditional system that has been shown to be safe and effective.

Reference

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BCG vaccination in Australia

Editor, – In their articles on BCG vaccination (Aust Prescr 2003;26:144–6), neither Professor Simpson nor Air Vice-Marshal Short mentioned the potential for tuberculosis control offered by modern tuberculosis-specific tests that are unaffected by BCG vaccination. T-cell mediated immune responses to the tuberculosis-specific proteins ESAT-6 and CFP-10 (proteins not present in BCG or environmental mycobacteria) have been shown to be effective in diagnosing tuberculosis infection in BCG-vaccinated individuals.[1,2]

Unfortunately, despite intense interest in the literature, the use of tuberculosis-specific antigens in diagnostics has to date been limited by the complexity of the methodologies required to measure T-cell responses. Most methods require T-cell purification, counting, and culture, which are expensive and not suited for reproducible, robust diagnosis. However, the whole blood test, QuantiFERON-TB Gold, has now been released in Australia, after extensive testing overseas found it to have high specificity and sensitivity.

The Australian Defence Force may also note the US Centers for Disease Control endorses QuantiFERON-TB testing in the military.[3] QuantiFERON testing detects significantly more active, infectious tuberculosis cases than Mantoux testing.[4] The elimination of the confounding factors of BCG vaccination and sensitisation to non-tuberculous mycobacteria makes the test an even more valuable diagnostic tool.

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(Cellestis are manufacturers of QuantiFERON products)

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Professor G. Simpson, the author of the article, comments:

I did not discuss some of the newer tests for the diagnosis of latent tuberculous infection as the focus of the article was BCG. The tuberculin skin test (TST) or Mantoux test was mentioned as it is the test specified in current protocols concerned with BCG administration. Dr Radford is correct that the TST is imperfect and there is no doubt that sooner or later more sophisticated tests will replace it. Over the past 110 years however, it has proved remarkably robust and we do have vast amounts of data on outcomes related to TST results. These longitudinal data are not available for the newer tests.

The newer tests (QuantiFERON-TB Gold and ELISPOT) rely on detecting interferon gamma production by T-cells responding to antigens which are found in M tuberculosis, but not in BCG. This theoretically will enable us to remove the confounding effect of prior BCG vaccination from testing for subsequent tuberculosis infection. This is of course irrelevant in the context of pre-BCG vaccination testing. So far there is more published information on ELISPOT than QuantiFERON-TB Gold. In the best study so far[1] in a tuberculosis outbreak in the UK the ELISPOT and Heaf test (a form of TST) gave concordant results in 89% of those tested, suggesting that there is limited room for improved diagnostic accuracy with the newer tests. Nevertheless these are exciting

developments in tuberculosis diagnosis and further studies including more longitudinal studies are likely to sound the death knell for the oldest diagnostic test in medicine.

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Editor, – I noted with interest the photo illustrating the article 'BCG vaccine in Australia' (Aust Prescr 2003;26:144–6). What has happened to universal infection control precautions – surely the person administering the injection should have been wearing gloves?

Anna McNulty
Director
Sydney Sexual Health Centre

Drug-induced hyponatraemia

Editor, – The useful review of drug-induced hyponatraemia (Aust Prescr 2003;26:114–7), states that 'blood glucose concentrations above 20 mmol/L can spuriously reduce the serum sodium concentration when measured by flame photometry'. This mistakenly implies that hyperglycaemia produces method-dependent pseudohyponatraemia of the type seen with marked hypertriglyceridaemia.

The hyponatraemia of marked hyperglycaemia is dilutional, from osmotic movement of water from the intracellular space, and is independent of method.[1] The measured serum sodium concentration is analytically valid, but needs to be corrected before relating the value to the normal reference interval. A useful correction, derived from a formula originally given in metric units, is to add a third to a half of the glucose excess in mmol/L to the measured serum sodium concentration.[2]

Apparent hyponatraemia is a reassuring finding in severely hyperglycaemic dehydrated patients, as the serum sodium concentration, when corrected as above, is often close to normal. An apparently normal serum sodium concentration without correction implies hypernatraemia and indicates a water deficit much larger than the salt deficit. Severe hypernatraemia can then be anticipated during resuscitation with isotonic sodium chloride, especially if hyperglycaemia is rapidly corrected.

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Editor, – I found the article on hyponatraemia (Aust Prescr 2003;26:114–7) interesting. I have had several elderly patients who have developed severe hyponatraemia while on tramadol which has been corrected on its cessation. Tramadol is thought to inhibit reuptake of serotonin which causes increased serotonin levels and presumably causes hyponatraemia due to a similar mechanism to the selective serotonin reuptake inhibitors. Tramadol was not included in Table 3 'Drugs commonly associated with hyponatraemia' and it is not listed in the product information as an adverse effect. I would appreciate the authors' comments.

Robin Hunter
Rehabilitation Physician
Brighton, Vic.

Dr S. Fourlanos and Dr P. Greenberg, the authors of the article, comment:

Professor Stockigt correctly indicates a factual error in our paper. We agree with him that the hyponatraemia associated with marked hyperglycaemia is dilutional, not method-dependent.

We note Dr Hunter's comment with interest. We were unaware of any association between tramadol and hyponatraemia, however the Adverse Drug Reactions Advisory Committee has received 12 reports.

Bisphosphonates and avascular necrosis of the jaws

Editor, – We wish to draw readers' attention to a potential drug-related cause of painful bone exposure in the maxilla complicating the healing of dental extractions. We have recently had four such cases in our unit all of whom were unresponsive to local medical and surgical treatments. All these patients were taking bisphosphonates; three were receiving pamidronate and one was receiving alendronate. This group of drugs act primarily through osteoclastic inhibition of bone resorption and are commonly prescribed in Australia to treat a variety of conditions including Paget's disease, hypercalcaemia of malignancy and osteoporosis.

On review of the literature we located a recent letter to the Journal of Oral and Maxillofacial Surgery which highlighted a growing epidemic of bisphosphonate-induced avascular necrosis of the jaws.[1] The particular bisphosphonates implicated in the series of 36 patients are the potent nitrogen-containing bisphosphonates that are

not metabolised, namely pamidronate and zoledronate. Interestingly, alendronate is also a potent nitrogen-containing bisphosphonate that is not metabolised. Consequently, we support the proposal of a link between avascular necrosis of the jaws and certain bisphosphonates currently prescribed in Australia. We draw this to the attention of practitioners prescribing these medications as a significant adverse effect.

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Reference

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Promotion of over-the-counter medicines

Editor, – I concur with Agnes Vitry ('And next: a flask of wine for Daddy?' Aust Prescr 2003;26:99–102). How is it possible that a drug company is allowed in Australia to promote drugs with free giveaways? I believe in most States pharmacists are not legally entitled to promote or advertise such medications.

The selection of an over-the-counter drug should be a therapeutic one, taking into consideration efficacy, adverse effects, safety, quality and quantity of drug information and cost. Free giveaways adversely influence such selections.

Although the evidence for many over-the-counter lines in Australia can be minimal, we nevertheless have a culture and tradition of usage. So even if evidence is scarce on the therapeutics of a drug, what little we have in addition to traditional usage, should play a far more important role then free giveaways.

Furthermore pharmacists should see this as another argument for drug companies to be allowed to promote such drugs in supermarkets, allowing unrestricted access to the public. For if the choice of a drug is dependent more on giveaways rather than therapeutics there is no reason to restrict its access to pharmacies. It is one thing to promote sunscreen with giveaways, it is quite another to do so with restricted over-the-counter products.

Derek Grubb
Pharmacist
Australind, WA

Paediatric formulations

Editor, – The editorial 'Why are children still therapeutic orphans?' (Aust Prescr 2003;26:122–6) rightly says '… even if a drug has good evidence of paediatric efficacy and safety, it may be unavailable in formulations … that are suitable for children.' This may be true in developed countries, but in developing countries like India the situation is the other way round. We have many uncalled for paediatric formulations and combinations that probably do more harm than good.

Take for example the paediatric formulations and combinations of paracetamol, used for musculoskeletal disorders. There are:

- ten formulations of paracetamol (including syrup, suspension and dispersible tablets)
- three formulations containing paracetamol and ibuprofen
- one formulation containing paracetamol and ibuprofen with simethicone
- one formulation containing paracetamol and ibuprofen with magnesium trisilicate
- two formulations containing paracetamol and metoclopramide
- one formulation containing paracetamol and domperidone
- five formulations containing paracetamol and nimesulid.

In addition, there are many more paediatric formulations containing fixed dose combinations of paracetamol available to treat disorders of the respiratory system.

Wishvas Rane
Pune
India

Withdrawal of useful drugs

Editor, – What can be done when a well-known and frequently recommended drug just fades out of sight because the manufacturers won't make it any more? One's suspicions run riot, including that it is too cheap to make and to sell, and the profit margin is therefore too small. Maybe they want to sell something similar but more profitable. Patients' needs and the needs of the Australian community in general seem to be of no consequence!

Donald B. Reid
General practitioner
Bridgetown, WA

Does pethidine still have a place in the management of labour pain?

Richard W. Watts, Rural General Practitioner, Port Lincoln, South Australia

Summary

Pethidine can provide short-term relief of acute pain, but it is not effective for everyone. During labour, intramuscular or intravenous pethidine sedates women, but may not give them adequate analgesia. Pethidine and its active metabolite, norpethidine, can have adverse effects on the neonate as well as the mother, especially if repeated doses are given during labour. There is little evidence to show that other drugs have greater efficacy than pethidine, so epidural analgesia may be a more effective option.

Key words: analgesia, breastfeeding, epidural.

(Aust Prescr 2004;27:34–5)

Introduction

Many women prefer to experience birth actively and as naturally as possible. Their preferences for analgesia should be discussed and reviewed regularly. If required, adequate analgesia during labour is beneficial to the mother, has a positive influence on the course of labour and improves neonatal outcome. The ideal obstetric analgesic should provide potent analgesic efficacy with minimal maternal and neonatal adverse effects.

Pethidine was first introduced in Germany in 1939 and was first used in labour in 1940. Since then pethidine has been the most widely used systemically administered opioid for obstetric analgesia[1], perhaps because it is cheap and easily given by midwives. While pethidine relieves acute pain for 2–4 hours[2], there are concerns about its efficacy in labour. There is also the potential for maternal and neonatal adverse effects from pethidine and its active metabolite norpethidine.

Efficacy of pethidine in labour

Early studies reporting that pethidine had good analgesic effects in labour were unfortunately flawed because efficacy was evaluated by an independent observer rather than the patient. If the patients were interviewed it was 24 hours post-delivery.[3]

A double-blind randomised controlled trial compared intravenous pethidine with placebo in 84 women during labour. Pethidine provided effective pain relief in only 23.8% of patients compared to 7% of those given placebo. Although this difference is significant ($p < 0.05$), there was no difference between the median or mean visual analogue pain scores in the pethidine and placebo groups. Pethidine significantly increased the sedation scores, dizziness, nausea and vomiting.[4]

Comparison with other analgesics

In a randomised controlled trial involving 20 patients in labour, pethidine (up to 1.5 mg/kg) and morphine (up to 0.15 mg/kg) given intravenously produced no significant change in pain scores over time with three doses. Following treatment with opioids 15 of the patients requested an epidural. Nausea was more common with pethidine (6/10) than with morphine (1/10). Patients receiving pethidine were calmer and more euphoric, but both drugs caused similar significant sedation (mean sedation scores 8/10 after three doses). The patients were therefore all significantly sedated and fell asleep during labour, but were awakened by pain during contractions. The researchers concluded that labour pain was not sensitive to systemically administered pethidine or morphine and that it was unethical to treat requests for pain relief by giving sedation.[5]

Pethidine has also been compared with intravenous fentanyl[6], remifentanil[7] and tramadol in randomised controlled trials. Fentanyl given as an intermittent intravenous infusion was equianalgesic to pethidine, but caused less nausea, vomiting and sedation. Remifentanil given as patient-controlled analgesia produced significantly lower pain scores than pethidine. However, the study was terminated early due to low Apgar scores in the pethidine group. In one study tramadol 100 mg intramuscularly had no greater efficacy than pethidine 75 mg.[8] Tramadol has its own safety issues.

A Cochrane review of the available studies has concluded that there is not enough evidence to evaluate the comparative efficacy and safety of the various opioids used for analgesia in labour.[9] Despite antenatal ambivalence about a specific analgesic choice, 65% of nulliparous women in one Australian tertiary unit chose epidural analgesia. Nearly 60% of women given intramuscular opioid 'crossed over' to epidural analgesia, confirming the inadequacy of systemically administered opioids.[10]

Pharmacology

There are pharmacokinetic reasons why systemically administered opioids are ineffective in controlling the pain of labour. Following injection into the gluteal muscle, plasma concentrations of pethidine are significantly lower than after intravenous administration or injection into the deltoid muscle. This suggests that drug absorption from the gluteal muscles

is impaired in pregnant women.[11] Another study of women in labour compared intravenous, intramuscular and epidural administration. Epidural absorption of pethidine was rapid with a plasma concentration similar to intravenous administration. However, the analgesia provided by the epidural route was far superior to that of intravenous and intramuscular administration.[12]

This suggests that for pethidine to be effective in labour its concentration must be sufficient at central opioid receptors. This view is supported by an experimental animal model of noxious distension of the cervix which induces reflex abdominal muscle contraction. Morphine produced a dose-dependent inhibition of this reflex activity, which was reversed by naltrexone, but not by methylnaltrexone, suggesting a central site of inhibition.[13]

Pethidine given intramuscularly or intravenously does not appear to achieve concentrations that are sufficient to inhibit the visceral pain of noxious cervical stimuli. However, the concentration is high enough to produce significant maternal and neonatal adverse effects.

Norpethidine and adverse effects

Norpethidine is the active metabolite of pethidine. It accumulates in both the mother and fetus with a half-life of 20.5 hours and is thought to be responsible for adverse neonatal effects[14] including respiratory depression. Newborns exposed to pethidine have significantly impaired normal infant behaviours such as hand and mouth movements, nipple touching before suckling, and licking movements. Half of the infants exposed to pethidine fail to breastfeed and cry more in the neonatal period.[15] In addition to the maternal sedating effects of pethidine, there is also the theoretical risk of maternal delayed gastric emptying, aspiration and respiratory depression. Norpethidine can also induce seizures.

Conclusion

Pethidine administered systemically has little place in the management of labour pain because it is minimally effective, has significant adverse effects for mother and baby, and does little more than sedate the patient. There is limited evidence supporting the use of any systemically administered analgesic in labour; epidural analgesia is a better option.

Acknowledgement

I would like to thank Associate Professor Michael Paech, University of Western Australia, for his help in preparing this paper.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false

(answers on page 51)

1. Analgesia is effective in 60% of women given intravenous pethidine.
2. The active metabolite of pethidine, norpethidine, does not cross the placenta.

Diabetes and periodontitis

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Summary

Chronic gingivitis and periodontitis are common inflammatory conditions of the periodontal tissues. Given the 'right' concurrence of risk factors, a person with periodontitis can experience significant destruction of tooth-supporting bone, ultimately resulting in tooth loss. Poorly controlled diabetes is an important risk factor for periodontitis, and gingivitis and periodontitis are sometimes the first sign that a patient has diabetes. As severe periodontitis can lead to the loss of teeth, it is important that patients with diabetes practise good oral hygiene and have regular dental check-ups so that problems can be detected quickly.

Key words: gingivitis, dental implications.

(Aust Prescr 2004;27:36–8)

Introduction

In chronic periodontitis, the tooth supporting structures (alveolar bone and the periodontal ligament) are destroyed. The disease has a multifactorial origin. Complexes of commensal oral anaerobic bacteria and perhaps viruses are thought to interact with risk factors, such as smoking, diabetes and depression, to create the conditions which make a person susceptible to periodontitis. The patient's immuno-inflammatory response to the bacteria causes the tissue destruction which occurs in chronic periodontitis. Less than 5% of Australians are susceptible to the severe periodontitis which results in tooth loss, although up to 10% experience moderate amounts of periodontitis-related bone loss.

It is useful to distinguish chronic gingivitis from periodontitis. Chronic gingivitis is the very common inflammatory reaction occurring in the gingival tissues in response to the accumulation of dental plaque. It usually precedes the development of periodontitis, but chronic gingivitis does not inevitably progress to periodontitis. The clinical appearance of gingivitis may be modified by systemic factors such as poorly controlled diabetes, which can significantly accentuate the gingival tissues' response to dental plaque (Fig. 1).

The relationship between diabetes, gingivitis and periodontitis

Although periodontitis is a recognised complication of diabetes, people with well-controlled diabetes who have good oral hygiene are not at increased risk of periodontitis. However, their susceptibility to periodontitis is significantly increased when their diabetes is poorly controlled, particularly if they also smoke.

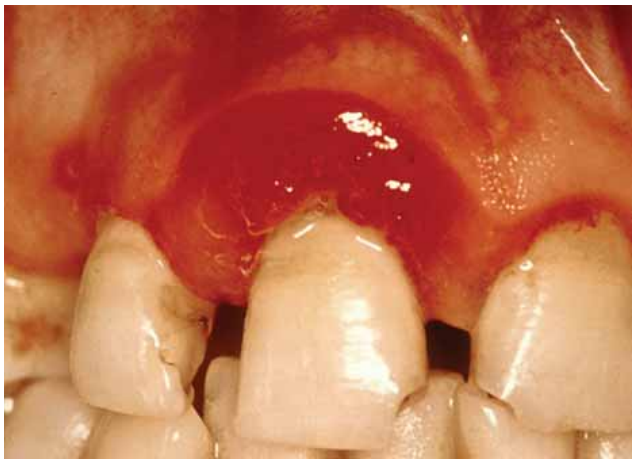
Recent epidemiologic evidence shows that the prevalence of diabetes in patients with periodontitis is significantly greater (by two times) than in people without periodontitis.[1] Given that diabetes may be present for a number of years before it is diagnosed, and that the prevalence of diabetes is increasing in the Australian community, dentists may be the first health professionals to detect a patient's diabetes. The gingival and periodontal signs which may alert the clinician that the patient has previously undiagnosed diabetes or that the patient's diabetes is poorly controlled, include:

- persistence of gingival inflammation after standard periodontal treatment (thorough supra- and subgingival scaling and cleaning, oral hygiene instruction)
- severe gingival inflammatory response to plaque and proliferation of gingival tissues at the gingival margin (Fig. 1)

Fig. 1

Severe gingival inflammatory reaction to dental plaque

This 55-year-old patient has recently diagnosed type 2 diabetes. The gingival tissue is friable, oedematous and prone to bleeding on tooth brushing.



- continuing alveolar bone loss despite periodontal treatment (Fig. 2)
- severe, aggressive periodontitis in people 20–45 years of age (deep periodontal pocketing, increased tooth mobility and tooth migration, causing teeth to over-erupt or spaces to open between teeth, and radiographic evidence of advanced bone loss)
- simultaneous formation of multiple periodontal abscesses (Fig. 3).[2]

Fig. 2

Alveolar bone loss

This orthopantomograph of a 54-year-old patient with poorly controlled diabetes shows extensive alveolar bone loss involving most teeth. The destruction of bone has been rapid even though the patient has been undergoing periodontal therapy.

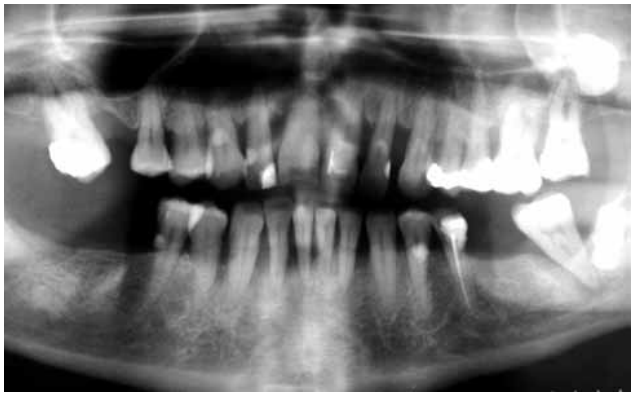
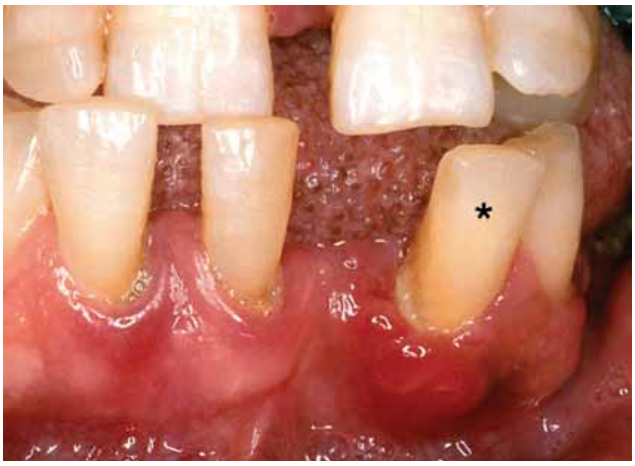


Fig. 3

Periodontal abscess formation

This 56-year-old patient has poorly controlled type 2 diabetes. The lower left lateral incisor (*) is very mobile and has migrated from its usual location in the arch. The tooth has lost more than two-thirds of its supporting bone because of periodontitis.



How diabetes increases susceptibility to periodontitis

Advanced glycation end products deposited in the tissues as a result of hyperglycaemia can alter the phenotype of macrophages and other cells via a specific cell-surface receptor. Macrophages are key cells in the pathogenesis of periodontitis through their ability to produce a large array of cytokines. They also influence the inflammatory response, the metabolism of fibroblasts and lymphocytes and stimulate bone resorption via prostaglandin E_2. It is thought that the advanced glycation end products transform the macrophages into cells with a destructive phenotype, producing pro-inflammatory cytokines in an uncontrolled fashion.[3]

Neutrophils are the primary defence cells of the periodontium. The reduced neutrophil function observed in patients with diabetes is therefore another mechanism increasing the susceptibility to periodontitis.

Is there a relationship between periodontitis and the ability to control diabetes?

While periodontitis is a recognised complication of poorly controlled diabetes, it has been proposed that severe periodontitis may make the metabolic control of diabetes more difficult. The process may be mediated through the systemic release of inflammatory cytokines (e.g. TNF-α) from periodontitis lesions, and chronic, low-level systemic exposure to Gram negative organisms. Although early studies have been poorly designed, one of these suggested that when antibiotics were added to standard periodontal treatment (debridement of the teeth and oral hygiene improvement), diabetic control improved significantly for a period of three months.[2]

What can the patient do?

People with diabetes need to practise high standards of daily oral hygiene, including brushing and flossing. The use of interdental brushes (which are like small bottle brushes) is indicated where there has been some recession of the gingivae. Adjunctive use of a chlorhexidine mouthwash (0.12%) or chlorhexidine gel (0.2%) twice daily (used independently of toothpaste so that the chlorhexidine is not inactivated) may be useful in controlling the more severe forms of gingivitis. Patients should consult with their dentist or periodontist regarding the recommended duration of use of chlorhexidine. Dental care, which is specifically aimed at monitoring the health of the periodontal tissues and providing the necessary treatment, is needed at six-month intervals.

Medical practitioners who suspect a patient has diabetes-related gingivitis or periodontitis should ensure that an early referral is made to a dentist. Dentists in turn need to refer advanced or suspect cases to a periodontist.

Conclusion

Medical and dental practitioners need to be aware of the interrelationship between poorly controlled or undiagnosed diabetes mellitus and chronic gingivitis and periodontitis. This is particularly important because of the rising prevalence of diabetes in the Australian community.

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Conflict of interest: none declared

Photographs courtesy of the author

Self-test questions

The following statements are either true or false (answers on page 51)

3. Periodontitis may be the first presentation of diabetes.
4. Gingivitis precedes periodontitis.

Introducing the Adverse Medicine Events Line 1300 134 237

Traditionally, only health professionals have reported adverse drug reactions to the Adverse Drug Reactions Advisory Committee (ADRAC). However, recent studies have shown that when consumers report adverse drug reactions, the reports are received more quickly, about a broader range of reactions and give a better account of the event. In addition, adverse reactions from complementary medicines are more likely to be reported by consumers.

Consumer reporting of adverse drug reactions has become a reality in Australia with the launch of a new telephone hotline called the Adverse Medicine Events (AME) Line. Operated by clinical pharmacists from Mater Health Services in Brisbane, the AME Line is a telephone service through which consumers can seek information about or report adverse events associated with medicines, including adverse drug reactions, errors and so-called 'near misses'.

The service, which is an initiative of the Australian Council for Safety and Quality in Health Care was launched in October 2003. It will operate from 9am to 6pm, Monday to Friday for an initial period of 18 months. Objectives of the AME Line are to:

- create a system for consumers to report adverse experiences with medicines
- promote openness and accuracy regarding adverse medicine events
- identify trends in adverse medicine events to know when, where and how things go wrong
- ultimately integrate the information into health systems, to improve safety and quality.

The pharmacists operating the AME Line can provide information or answer questions regarding medication-related adverse effects and ensure that adverse drug reaction reports satisfying specific criteria are submitted to ADRAC. Individuals are not named in these reports, but rather safety and quality issues within the system are identified. Medication errors and 'near misses' are reported to the Australian Council for Safety and Quality in Health Care. De-identified data will be collected and fed back to health professionals to assist in changing systems to help prevent the recurrence of these adverse events.

Health professionals are encouraged to refer consumers to the AME Line, for information, advice and reporting of adverse medicine events. Further information about the line is available at: www.safetyandquality.org.au or by contacting Geraldine Moses or Treasure McGuire on (07) 3840 8087.

Antibiotic prescribing: how can emergence of antibiotic resistance be delayed?

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Summary

The discovery of new antibiotic drugs has slowed significantly and widespread use of current antibiotics has resulted in the emergence of many multi-resistant bacterial pathogens. In order to preserve the activity of currently available antibiotics for as long as possible, care should be taken to only prescribe them when an infection is serious and is likely to respond significantly to treatment. Judicious prescribing will reduce the selective pressure on bacteria and thereby slow down the emergence of resistance. In the future, prevention through immunisation and reducing the spread of infection (infection control) will assume greater importance as a way of sidestepping the interplay of antibiotic use and bacterial resistance. It is particularly important to avoid empirical use of antibiotics for most patients with upper respiratory infections.

Key words: drug utilisation.

(Aust Prescr 2004;27:39–42)

Introduction

Antibiotic use remains the primary factor in the emergence and spread of antibiotic resistant organisms. The importance of minimising unnecessary exposure to antibiotics among humans and animals[1] has been rightly emphasised by many authors. There is increasing evidence that directly associates antibiotic use with the emergence of resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus, resistant Gram negative bacilli and *Clostridium difficile*. The recent widespread emergence of serious disease caused by strains of MRSA acquired in the community adds further urgency to the need to reduce antibiotic selective pressure.

Many studies have shown that more judicious use of antibiotics can reduce resistance, independent of traditional infection control measures.[2,3,4,5] However, the situation is complex as resistance, once selected, may not go away after withdrawal of the selective pressure. While there may be a higher metabolic cost for resistant bacteria to maintain the additional genetic material associated with resistance, many strains are able to compensate for this through further mutational change or deletion of non-essential DNA. Combinations of virulence factors and antibiotic resistance genes may make the pathogen better able to spread, colonise and invade a vulnerable patient.

Prevention of cross infection in all healthcare situations through adherence to infection control measures such as hand hygiene is a crucial part of infectious disease control. These measures provide a potent way of reducing the need to use antibiotics for treatment.

Principles of antibiotic prescribing

Antibiotics are prescribed for three reasons:

- prophylaxis – where administration is designed to prevent serious infection in a defined at-risk situation
- empiric therapy – where a clinical syndrome that may be due to infection is managed before evidence confirming the presence of infection or its cause is available
- directed therapy – where antibiotics are aimed at micro-organisms which have been confirmed as the cause of an infection.

For each type of therapy, there are principles that aim to minimise the use of antibiotics and also ameliorate the selection of antibiotic resistance (see Box 1).[6]

Box 1

Principles of appropriate antibiotic use [6]

Evidence-based indications

Microbiology should guide therapy wherever possible

Narrowest spectrum required

Dosage and duration appropriate to the site, type and severity of infection

Check up-to-date guidelines

Antibiotic prophylaxis

Prophylaxis is used for medical (for example, preventing relapses of rheumatic fever or the spread of meningococcal infection) and surgical purposes (prevention of wound infection). Recommendations to use antibiotic prophylaxis for a particular type of surgical operation are made after consideration of:

- the incidence of surgical wound infection
- the usual impact of this infection

- the demonstrated effectiveness of antibiotic prophylaxis in preventing these infections (randomised trial evidence).

Reducing bacterial resistance selection by antibiotic prophylaxis

Exposure to antibiotic surgical prophylaxis is often the initial selective pressure placed upon a patient's bacterial flora on entry to hospital. The flora is modified in such a way as to facilitate colonisation (and potential ensuing infection) with more resistant hospital bacteria. In order to minimise this adverse impact and to maximise effectiveness of antibiotic prophylaxis, narrow spectrum drugs should be used for the shortest time possible (Table 1).

Empiric therapy

Patients often present with symptoms that may be caused by infection. A decision then has to be made about the likely cause of infection and whether it needs drug treatment. On occasions empiric therapy is also used to prevent complications arising from a minor infection.

Are antibiotics indicated?

The decision to use antibiotics in a particular clinical situation is complex. It balances the natural history of the disease or syndrome, the potential seriousness of its outcomes, evidence that antibiotics affect these outcomes and the potential adverse effects of antibiotic therapy. We now recognise that antibiotics are a precious resource, crucial to the management of many potentially fatal infections (such as meningitis). In order to actively safeguard future antibiotic effectiveness in these diseases we must reduce our reliance on antibiotics for mild or self-limiting conditions in hospitals and the community.

Hospital

Difficulties often arise in intensive care units where clinical features are frequently non-specific. For instance, although antibiotics are usually given for lung consolidation in severely ill patients, it is estimated that fewer than 50% of these patients actually have an infective cause for the consolidation.[7]

Community

Most antibiotics are prescribed for patients with upper respiratory infection (acute otitis media, pharyngitis, sinusitis) and acute bronchitis. These conditions are most often caused by viruses and are of self-limited duration. Randomised trials show antibiotics have limited or no impact. The antibiotic guidelines published by Therapeutic Guidelines[6] place increasing emphasis on effective (non-antibiotic) symptom management, preventative measures such as immunisation and where possible, evidence-based selection of subsets of patients that are most likely to benefit from antibiotic therapy. For example, in acute otitis media, children presenting with systemic symptoms such as high fever or vomiting are more likely, than children without these symptoms, to benefit from antibiotic therapy.[8,9] The treatment of otitis media with antibiotics cannot be justified on the grounds of preventing mastoiditis as trial data show that this complication is rare in developed countries (1 per 1000 or less).[10]

Choice of antibiotic

If an antibiotic is indicated, a drug should be chosen that will limit the development of bacterial resistance (Table 2). The choice of drug is influenced by the likely pathogens and local resistance patterns.

Duration of empiric therapy

In hospital, the patient should be reassessed after 24–48 hours of empiric antibiotic therapy to decide whether infection is unlikely (cease therapy) or whether a firm diagnosis can be made (modify therapy as appropriate (see also Table 2)). In community practice, as a general rule, the minimum duration of treatment recommended in Therapeutic Guidelines: Antibiotic[6] should be prescribed.

Table 1

Reducing bacterial resistance selection in surgical prophylaxis with antibiotics

Principles	Common pitfalls
Use surgical prophylaxis only where there is a strong evidence-based indication	There is little current evidence to support use in inguinal hernia repair where prosthetic material is not inserted
Select the antibiotic with the narrowest antibacterial spectrum required	Using a 'third generation' cephalosporin for surgical prophylaxis: their broad spectrum makes them potent selectors for *C. difficile*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus. Additionally, some of these drugs may not have sufficient activity against *Staphylococcus aureus.*
Time the first dose to ensure sufficient drug concentrations at the operative site at the time of incision through to time of closure	Delay in initial dose significantly reduces the prophylactic effect Failure to repeat the dosing of a short-acting drug during a long operation
Minimise postoperative doses of prophylaxis	Dosing until surgical drains are removed (This results in no additive reduction in infection. It makes superinfection with antibiotic resistant bacteria more likely.)

Table 2

Reducing bacterial resistance selection in empiric treatment with antibiotics

Principles	Common pitfalls
Assess patients carefully before therapy	Incorrect diagnosis made: e.g. acute otitis media: detection of middle ear fluid is often inaccurate and leads to diagnostic error
Treat infection, not contamination	Antibiotics directed at a blood culture skin contaminant
Treat infection, not colonisation	Antibiotics directed at: ■ urinary isolates in an asymptomatic patient, whatever the cell count or urinalysis findings ■ Gram negative wound isolates from chronic leg or foot ulcers
Aim empiric therapy at the likely pathogens with knowledge of local susceptibility patterns: ■ take appropriate cultures ■ use appropriate drug(s), dose and route ■ refer to Therapeutic Guidelines: Antibiotic and/or local clinical guidelines	Sepsis syndrome: inadequate number or no blood cultures taken Severe pneumonia: tests for viral infection not performed
Avoid overuse of vancomycin (glycopeptides) to reduce emergence of vancomycin resistance in staphylococci and enterococci[11]	Continued empiric use of vancomycin for presumed infections in patients whose cultures are negative for beta-lactam-resistant Gram positive micro-organisms
In hospital, assess patient after 24–48 hours of empiric therapy and decide: ■ bacterial infection unlikely – cease antibiotics ■ microbiological evidence available – change to directed therapy	Insufficient microbiology tests before therapy (e.g. viral studies in a patient with severe community-acquired pneumonia) Microbiological culture results not reviewed Patients left on antibiotics in the absence of a specific diagnosis

Directed therapy

When the cause of an infection is confirmed, antibiotic therapy is aimed at those micro-organisms. The confirmation may come from clinical or pathological information. Microbiological confirmation is preferred as it gives the greatest assurance that the correct antibiotic drug has been chosen. The involvement of a specific pathogen may be implied by evidence from microscopy, culture or direct detection through nucleic acid amplification (for example, polymerase chain reaction testing for meningococci in blood or cerebrospinal fluid).

Therapeutic Guidelines: Antibiotic[6] provides evidence-based recommendations for directed therapy for common infections. Correct selection of the antibiotic drug, its dosage and route are crucial to minimising the emergence of resistance during therapy. For instance, the common practice of prescribing prolonged (more than 10 days) monotherapy with oral ciprofloxacin for *Pseudomonas aeruginosa* respiratory infection usually leads to stable high level ciprofloxacin resistance in this organism. Another common pitfall is the use of oral monotherapy with rifampicin, fusidic acid or ciprofloxacin for infections due to MRSA, as resistance usually emerges during treatment. In both these circumstances, more resistant bacteria are created that frequently cause therapeutic difficulty in the patient or indeed another person who acquires the resistant strain from the treated patient.

Duration of treatment

Appropriate minimum durations of antibiotic therapy have only been investigated for a few infectious diseases. These include bacterial endocarditis, bone and joint disease and meningitis. Unfortunately, duration of therapy for some common sites of infection such as the lung is not well studied. In these situations, the decision to cease therapy is usually based on clinical criteria. Where possible, minimising the duration of therapy is a key way to reduce emergence of resistance.

Improving antibiotic prescribing

The human impact of antibiotic resistance is significant and increasing. Health professionals have a responsibility to use antibiotics in a manner that reduces the emergence of resistance (see Box 2).

The general practice programs operated by the National Prescribing Service (NPS) provide advice on appropriate antibiotic prescribing through:

- one-to-one educational visits by NPS facilitators
- practice case discussion meetings
- actual case data collection and analysis
- newsletters, patient information brochures and other resources.

Box 2

What can I do to reduce resistance?

- Know the key antibiotic issues for each key disease state (refer to Therapeutic Guidelines: Antibiotic and local guidelines) and follow evidence-based guidelines wherever possible[6,12]
- Educate patients about antibiotics, their potential adverse effects and the recommendations to avoid use in self-limiting illness such as upper respiratory infection
- Be aware of local patterns of antibiotic resistance and how they are changing (your local pathology service should provide this)
- Audit use of antibiotics in specific clinical situations (National Prescribing Service (NPS), hospital drug usage evaluation)

In hospital practice, improving antibiotic prescribing is a complex challenge to infectious diseases, microbiology and pharmacy services.[13] Additional elements of successful hospital programs include:

- regular monitoring of antibiotic usage and drug usage evaluation with feedback to prescribers[14]
- active involvement of clinicians in the development and dissemination of consensus, evidence-based guidelines for antibiotic use
- clinical decision support systems and other aids such as treatment cards or hand-held computerised guidelines
- use of infectious disease consultancy services for advice in the management of complex cases
- improvements in the use of diagnostic technology and microbiology to provide more specific diagnosis of infective syndromes
- formulary control of certain broad spectrum drugs so as to reduce indiscriminate use.

Conclusion

Antibiotics are valuable therapeutic agents. Their widespread use has resulted in the emergence of many multi-resistant bacterial pathogens in hospitals and the community. In order to preserve the action of existing antibiotics, their use for prophylaxis, empiric or directed therapy should be reserved for situations where there is good evidence to support use and/or the consequences of infection are serious. It is increasingly important to avoid empiric antibiotic use for most patients with upper respiratory infections and pursue symptomatic treatment.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 51)

5. Using broad spectrum antibiotics reduces bacterial resistance.
6. A two-week course of ciprofloxacin often results in the development of resistance in *Pseudomonas aeruginosa*.

Tumour necrosis factor alpha inhibitors for the treatment of adult rheumatoid arthritis

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Summary

The management of patients with rheumatoid arthritis now focuses on both the relief of symptoms and the prevention of joint damage. When conventional therapies fail, adalimumab, etanercept and infliximab, inhibitors of the pro-inflammatory cytokine tumour necrosis factor alpha, can be considered. Evidence from randomised controlled studies suggests that many patients who do not respond to conventional therapy improve with adalimumab, etanercept or infliximab, particularly when these drugs are combined with methotrexate. Infusion and injection site reactions occur in some patients and the risks of infection are increased, particularly early in the treatment course. Long-term risks such as an increased risk of malignancy are currently being evaluated.

Key words: adalimumab, etanercept, infliximab.

(Aust Prescr 2004;27:43–6)

Introduction

The last decade has seen a substantial shift in the management of rheumatoid arthritis. It has moved from symptom control with the empirical use of drugs borrowed from other specialties, to 'designer' therapies, based on the known pathogenesis of rheumatoid arthritis, which alleviate symptoms and retard joint destruction. Three examples of these new therapies are adalimumab, etanercept and infliximab. These drugs inhibit the action of a key pro-inflammatory cytokine – tumour necrosis factor alpha (TNF-α).

Cytokines in the pathogenesis of rheumatoid arthritis

Rheumatoid arthritis is a systemic inflammatory disease that results in the normally bland single cell layer of synovial fibroblasts in the joint transforming into an inflammatory maelstrom that may cause bone and cartilage destruction. The specific cause of rheumatoid arthritis remains obscure, but it is most likely a combination of a genetic predisposition, an environmental trigger and possibly a random immunological event.

Once an inflammatory process begins, the mechanisms that perpetuate and amplify it are much better understood and seem to involve an ongoing imbalance between pro- and anti-inflammatory factors. Central to this process are cytokines, particularly TNF-α.

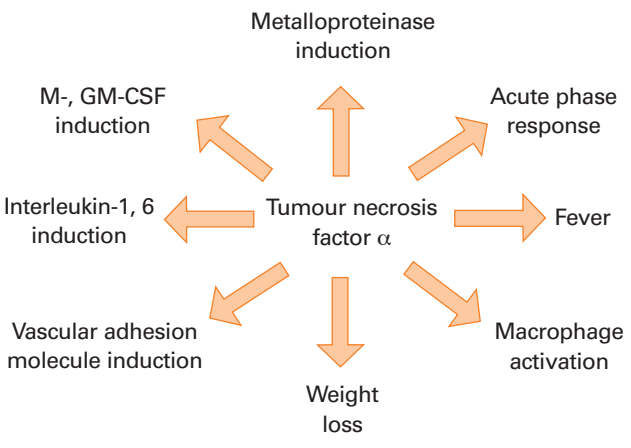
TNF-α is a pleiotropic pro-inflammatory cytokine with many actions that are central to the pathogenesis of rheumatoid arthritis (Fig. 1). Along with interleukin 1, another important pro-inflammatory cytokine, TNF-α has therefore been a target for biological therapy in rheumatoid arthritis.

Pharmacology of TNF-α inhibition

TNF-α is predominantly produced by monocytes and activated macrophages and its activity may be potentially inhibited at a variety of sites. These include strategies that inhibit the production or release of TNF-α from the cell, neutralise TNF-α on the cell surface or in the soluble phase or block the TNF-α receptor or its downstream signal transduction pathway. Currently, clinical trials are examining the efficacy and toxicity of many of these strategies. Research is most advanced for strategies that neutralise TNF-α on the cell surface or in the soluble phase.

Fig. 1

Actions of tumour necrosis factor α



Infliximab was the first anti-TNF-α drug to be tested in rheumatoid arthritis. It is a recombinant chimeric monoclonal antibody composed of a human antibody backbone with a mouse idiotype (the region that binds TNF-α). Infliximab is given by intravenous infusion.

Adalimumab is an anti-TNF-α monoclonal antibody that is similar to infliximab, but with a more humanised molecule. It is given by subcutaneous injection every other week.

Etanercept is also a recombinant protein composed of an immunoglobulin backbone and two p75 TNF-α soluble receptors. It is given as a twice-weekly subcutaneous injection.

Efficacy of TNF-α inhibitors

Symptom-modifying effects

In recent times the symptomatic outcome measures for rheumatoid arthritis trials have been standardised. Most studies have used the American College of Rheumatology (ACR) response criteria or the disease activity score (DAS).[1] The ACR response criteria are a composite outcome measure composed of the number of swollen and tender joints, the ESR or C-reactive protein and the patient's and physician's global assessments of the activity of the arthritis. These scores can help when comparing the different trials. Three levels are calculated for the ACR response criteria:

- ACR20 – a 20% improvement in disease measures, considered to be the minimum response perceptible by the patient
- ACR50 – a 50% improvement, considered by the patient to be a significant decrease in their arthritis severity
- ACR70 – a 70% improvement, considered to be a highly significant decrease in their arthritis severity.

Infliximab

The efficacy and toxicity of infliximab for the treatment of patients with rheumatoid arthritis was assessed in the large multicentre Anti-Tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study.[2,3] This study enrolled 428 patients with rheumatoid arthritis that was active (defined as the presence of six or more swollen and tender joints, raised acute phase markers and/or early morning stiffness of more than 45 minutes) despite at least three months of oral or parenteral methotrexate at a weekly dose of at least 12.5 mg. Patients were randomised to continue their current methotrexate dose and receive either placebo intravenous infusions or one of four schedules of intravenous infliximab (3 mg/kg four or eight weekly, 10 mg/kg four or eight weekly).

The results of the ATTRACT study (Table 1) show that about 50% of the patients receiving infliximab at a dose of 3 mg/kg every eight weeks (the dose approved by the Australian Pharmaceutical Benefits Advisory Committee) achieve an ACR20 response and about 25% achieve the more clinically significant ACR50. The response is sustained over the 54 weeks of treatment.

Table 1

Clinical outcomes from the randomised controlled studies evaluating the efficacy of tumour necrosis factor inhibitors in patients with rheumatoid arthritis

Author	TNF inhibitor (dose)	ACR20 (%)	ACR50 (%)	ACR70 (%)	Comments
Maini et al (1999)[2]	Infliximab (3 mg/kg 8 weekly, intravenously) with methotrexate	50	27	7	ATTRACT study results at week 30
	Methotrexate alone	20	5	0	
Lipsky et al (2000)[3]	Infliximab (3 mg/kg 8 weekly, intravenously) with methotrexate	42	21	10	ATTRACT study results at week 54
	Methotrexate alone	17	8	2	
Moreland et al (1999)[4]	Etanercept (25 mg twice weekly, subcutaneously) no methotrexate	59	40	9	Results of a placebo-controlled study at six months
	Placebo	11	5	–	
Weinblatt et al (1999)[5]	Etanercept (25 mg twice weekly, subcutaneously) with methotrexate	71	39	15	Results at 24 weeks
	Methotrexate alone	27	3	0	
Bathon et al (2000)[6]	Etanercept (25 mg twice weekly, subcutaneously)	72	49	25	Results at 12 months in a group of early, methotrexate naïve, patients
	Methotrexate alone	65	41	2	
Weinblatt et al (2003)[7]	Adalimumab (40 mg every second week, subcutaneously) with methotrexate	67	55	27	ARMADA results at 24 weeks
	Methotrexate alone	14	8	5	

Etanercept

The efficacy of etanercept has been evaluated in three randomised controlled studies. One study randomised 234 patients, whose rheumatoid arthritis had responded inadequately to at least one disease-modifying drug, to receive either placebo injections or etanercept 10 mg or 25 mg subcutaneously twice-weekly for six months. Although methotrexate was not used in this study, the ACR20 and ACR50 responses (Table 1) were similar to the responses to infliximab.[4]

In a more clinically relevant study, 89 rheumatoid arthritis patients with active disease, despite at least six months of methotrexate at doses of 15–25 mg weekly, were randomised to add either placebo injections or twice-weekly etanercept 25 mg for 24 weeks. Although this study was shorter, the ACR20 and ACR70 responses were higher, presumably because of the concomitant use of methotrexate.[5]

The third etanercept study included 632 patients who had suffered rheumatoid arthritis for less than three years, but who had active disease with evidence of bone erosions on X-ray and were rheumatoid factor positive. The patients were randomised to start either methotrexate and placebo injections or placebo tablets and etanercept 10 mg or 25 mg for 12 months. Patients receiving 25 mg of etanercept twice weekly improved more rapidly than the patients taking weekly methotrexate, but by the end of the study the clinical parameters of the two groups were not statistically different.[6]

Adalimumab

The efficacy of adalimumab was evaluated in the ARMADA study in which 271 patients with active rheumatoid arthritis were randomised to receive either 20 mg, 40 mg or 80 mg of adalimumab or placebo injections subcutaneously every second week for 24 weeks.[7] The participants remained on methotrexate treatment. The results were similar to those of treatment with infliximab and etanercept (Table 1).

Disease-modifying effects

To evaluate the effects of treatment on the progression of rheumatoid arthritis, X-rays of the hands and feet are taken and scored using the modified Sharp method. This scores the severity of the erosions and the narrowing of the joint space of predefined joints.[8] However, the changes in the Sharp score are a surrogate marker for end-points such as joint replacement surgery. Changes in the modified Sharp score occur slowly and therefore only the longer ATTRACT[2] and etanercept[6] studies have evaluated the disease-modifying ability of the TNF-α inhibitors.

In the ATTRACT study the mean change in the modified Sharp score at 54 weeks was an increase (worsening) of 7.0 in the methotrexate alone group and an increase of 1.3 in the group treated with weekly methotrexate and infliximab 3 mg/kg every eight weeks. In the etanercept study the mean increase in the modified Sharp score at 12 months was 1.0 in the group receiving etanercept 25 mg alone and 1.59 in the group receiving methotrexate alone. The TNF-α inhibitors are, therefore, currently the most significant inhibitors of radiologically-measured joint damage. However, it remains to be proven that a smaller increase in a surrogate outcome results in better functional outcomes.

Toxicity of TNF-α inhibitors

When evaluating the safety of a new drug all sources of information are considered including the randomised and open label studies and post-marketing surveillance. As infliximab and etanercept are powerful immunosuppressive drugs, particular scrutiny needs to be focused on the incidence of infection and malignancy.

Concerns regarding the activation of demyelinating conditions after the use of TNF-α inhibitors have recently been reported. At this stage it would seem prudent to avoid using TNF-α inhibitors in patients with multiple sclerosis and similar conditions.

Infliximab

In the ATTRACT study there was no difference in the incidence of adverse and serious adverse events or deaths when the methotrexate alone and infliximab-treated patients were compared. Despite this observation, the authors reported marginal numerical increases in the incidence of upper respiratory tract infections, sinusitis and pharyngitis in the infliximab group. Malignancy was reported in five of the infliximab-treated patients, but it is difficult to conclude if these cancers were related to the drug. Infusion reactions occurred in about 20% of the patients given infliximab, but were often mild and required minimal treatment. Recurrent infusion reactions were managed with prophylactic antihistamines, hydrocortisone and/or a slower infusion rate. Antibodies to double stranded DNA (ds-DNA) were significantly more frequent in the infliximab-treated patients, but only one patient developed a rash suggestive of systemic lupus erythematosus (SLE).

In patients treated with infliximab for Crohn's disease, infusion reactions and antibodies to infliximab have reduced the efficacy of the treatment.[9] The same study, however, found that co-administration of other immunosuppressant medications reduced the frequency of these phenomena and therefore improved efficacy. It is therefore a requirement that when infliximab is used in the treatment of rheumatoid arthritis patients it must be given with methotrexate.

The reactivation of tuberculosis was recently reported in 70 patients treated with infliximab for rheumatoid arthritis, Crohn's disease and a variety of other autoimmune conditions.[10] In the majority of cases the tuberculosis developed after three or fewer infusions and 40 of the 70 patients had extra-pulmonary disease. As a result, guidelines to prevent tuberculosis have

recently been promulgated. It is currently recommended that a chest X-ray and Mantoux test be performed before patients start a TNF-α inhibitor. The reported frequency of other opportunistic infections has not increased.

Etanercept

In the studies of etanercept, the commonest adverse effects attributable to the drug were injection site reactions, occurring in 37–49% of the patients. The frequency of these reactions reduced during each of the studies and their occurrence did not decrease the efficacy of the drug. The frequency of ds-DNA antibodies was increased, but clinical SLE did not develop in any of these patients. Antibodies to etanercept were uncommon. Infections were not increased in the etanercept-treated patients, but it is reasonable to assume that tuberculosis might be reactivated by etanercept so caution should be exercised.

Adalimumab

In the studies evaluating adalimumab the adverse event profile was similar to that of etanercept and infliximab. It would be anticipated that much of the toxicity reported for the anti-TNF drugs would be related to the TNF inhibitor effect rather than drug-specific effects, with the possible exception of infusion reactions with infliximab.

Other diseases and biological agents

The inhibitors of TNF-α (including adalimumab, etanercept and infliximab) are currently being evaluated in other forms of inflammatory arthritis including ankylosing spondylitis and psoriatic arthritis. Results of these studies are extremely promising, particularly the improvements in axial disease.

A variety of other drugs are being developed to inhibit the action of TNF-α, some of which may be orally bioactive. Inhibitors of other key pro-inflammatory cytokines, including interleukin 1, are also being evaluated. Anakinra, which antagonises interleukin 1α and 1β, has recently been approved for use in Australia. Some research is examining the effects of combining cytokine inhibitors. All of these studies suggest incremental improvement in the outcomes for patients with severe rheumatoid arthritis. The question for the future is the price we are willing to pay for these incremental improvements.

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Further reading

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Associate Professor McColl is a member of the Schering Plough Infliximab Advisory Board in Australia, and is an investigator in studies evaluating the toxicity and efficacy of infliximab and adalimumab.

Self-test questions

The following statements are either true or false (answers on page 51)

7. To avoid immunosuppression, patients with rheumatoid arthritis should stop methotrexate before starting infliximab.
8. Inhibitors of tumour necrosis factor alpha may reactivate tuberculosis.

Inside the isomers: the tale of chiral switches

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Summary

Chiral drugs are made up of molecules with the same chemical structure, but different three-dimensional arrangements. Modern manufacturing has enabled the development of products containing a single molecular arrangement. The development of these single enantiomers from chiral drugs is known as chiral switching. Enantiomers of the same drug can have different pharmacodynamic and pharmacokinetic properties. This may translate into potential health benefits, such as an improved safety margin, if one of the enantiomers has more favourable therapeutic and pharmacokinetic characteristics. However, some chiral switching has resulted in unpredicted toxicity and the withdrawal of the enantiomer from the market or a halt in its development. Drug companies are increasingly using chiral switching as a marketing strategy, but before prescribers switch to single enantiomer drugs they should look for evidence from well-conducted clinical trials that shows the chiral switch is cost-effective and improves the outcomes for patients rather than patents.

Key words: enantiomers, drug industry, pharmacokinetics, adverse effects.

(Aust Prescr 2004;27:47–9)

Introduction

Have you ever tried putting your left shoe on your right foot or your right glove on your left hand? Unless you intend to destroy the function of this apparel, you know you will not succeed. Your left and right hands and feet are non-superimposable mirror images of one another. Chemicals including drugs can behave in a similar way. Many drugs consist of a mixture of left- and right-handed molecules (enantiomers), but there is an increasing trend for the pharmaceutical industry to develop and market products containing only the left- or right-handed molecule.[1] While many of these single enantiomer drugs (such as sertraline and salmeterol) are new chemical entities, others have been developed from currently marketed drugs which are a mixture of different enantiomers (racemates). For example, esomeprazole is an enantiomer of the racemate omeprazole. The term chiral switching has been coined to describe the development of single enantiomers from old racemate drugs.

Enantiomer:	one of a pair of stereoisomers that are non-superimposable mirror images of one another and therefore have a different 3-dimensional configuration
Isomers:	compounds with the same molecular formula but with different 3-dimensional configuration
Racemate:	a mixture of two enantiomers, usually in one-to-one ratio

Definitions and chemistry

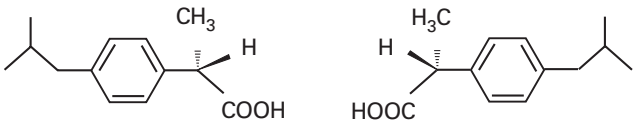
If a drug has a centre of asymmetry (usually a carbon atom with four different substituents), then it can exist as two non-superimposable left-handed and right-handed mirror images, also known as enantiomers. A racemate is a mixture of equal amounts of these two enantiomers. Many drugs are marketed as racemates. They are said to be chiral drugs (from the Greek word for hand, *cheir*).

There are different methods for naming enantiomers. The definitive way is to use the prefix (R)- (right hand) and (S)- (left hand). Other prefixes are (+) and (–) or D and L. An example is ibuprofen (Fig. 1) which, as marketed in Australia, contains an equal amount of (R)-ibuprofen and (S)-ibuprofen.

Enantiomers have identical physical and chemical properties such as molecular weight, solubility and melting point. The only difference is their three-dimensional spatial configuration.

Fig. 1

Ibuprofen is a racemic mixture of two non-superimposable mirror image enantiomers, (+)-(S)-ibuprofen and (–)-(R)-ibuprofen. The majority of the effects of racemic ibuprofen are elicited by (+)-(S)-ibuprofen.



(+)-(S)-ibuprofen (–)-(R)-ibuprofen

Most drugs obtained from nature are chiral, but in nature only the biologically active enantiomer is synthesised. For example, the poppy plant *Papaver somniferum* only synthesises the pain relieving (–)-(5R,6S,9R,13S,14R)-morphine. As morphine has a demanding chemical structure with five asymmetric centres, the technical difficulties and costs associated with chemically manufacturing large amounts for therapeutic use are such that it is more economically viable for companies to extract the morphine for the world market from poppies, rather than to artificially synthesise it. However, for many other chiral drugs, synthesis of the individual enantiomers is now economically feasible.

Pharmacodynamic differences between enantiomers

The interactions in the body between a drug and the proteins which elicit therapeutic or adverse effects and eliminate the drug require a specific three-dimensional configuration of drug and protein.

Since enantiomers have different three-dimensional configurations, the pharmacodynamics and pharmacokinetics of the two enantiomers which make up a racemic drug can be quite different. The differences often depend on whether the centre of asymmetry of the drug is in close proximity to the points of attachment to the protein. For example:

- (S)-ibuprofen is over 100-fold more potent an inhibitor of cyclo-oxygenase I than (R)-ibuprofen
- (R)-methadone has a 20-fold higher affinity for the μ opioid receptor than (S)-methadone
- (S)-citalopram is over 100-fold more potent an inhibitor of the serotonin reuptake transporter than (R)-citalopram.

The so-called inactive enantiomer (one that has much less affinity for the drug's target site) is not necessarily an inert substance with no effects *in vivo*. For example, the cardiotoxicity of bupivacaine is mainly associated with the (R)-enantiomer, the psychomimetic effects of ketamine are more associated with the (R)-enantiomer, and (S)-baclofen antagonises the effects of (R)-baclofen. The beneficial effects of a drug can therefore reside in one enantiomer, with its paired enantiomer having:

- no activity
- some activity
- antagonist activity against the active enantiomer
- completely separate beneficial or adverse activity from the active enantiomer.

Pharmacokinetic differences between enantiomers

As the distribution and elimination of drugs from the body also involves their interaction with proteins, then the pharmacokinetics of enantiomers can also be different. For example:

- the bioavailability of (R)-verapamil is more than double that of (S)-verapamil due to reduced hepatic first-pass metabolism
- the volume of distribution of (R)-methadone is double that of (S)-methadone due to lower plasma binding and increased tissue binding
- the clearance of (R)-fluoxetine is about four times greater than (S)-fluoxetine due to a higher rate of enzyme metabolism
- the renal clearance of (R)-pindolol is 25% less than (S)-pindolol due to reduced renal tubular secretion.

These differences in clearance and volume of distribution translate into differences in half-life. For example the half-life of (S)-fluoxetine is one quarter that of (R)-fluoxetine. In addition, these pharmacokinetic properties can be modified in a stereoselective manner by disease, genetics, ethnicity, age and other drugs. Finally, the enantiomers of some drugs such as warfarin can be metabolised by different enzymes.

Rationale for marketing chiral specific drugs

There are several possible health benefits to chiral switching. They include:

- an improved safety margin (therapeutic index) through increased receptor selectivity and potency, and reduced adverse effects
- a longer or shorter duration of action due to pharmacokinetic considerations (e.g. half-life) resulting in a more appropriate dosing frequency
- decreased interindividual variability in response commonly due to polymorphic metabolism
- decreased potential for drug-drug interactions.

As some racemic drugs were patented without separate patents for each enantiomer, some companies have seized the opportunity to develop and market or license single enantiomers of marketed chiral drugs (for example an American company now markets (R)-salbutamol). Another commercially driven reason for chiral switches is the impending expiry of the patents of some 'blockbuster' racemic drugs. The manufacturers have developed and marketed the single enantiomer with a view to extending the patent franchise and protecting themselves from competitors who produce generic copies of the racemate.[2]

Obtaining marketing approval for a chiral switch usually requires relatively few new studies to be conducted if the racemate is already marketed. The single enantiomer can be ready for launch before the patent for the racemate expires and before the marketing of any generics (which tend to substantially drive down the cost of the racemate).

Pros and cons of recent chiral switches

Many single enantiomer chiral switches have recently received marketing approval in Australia or are likely to be submitted for approval. These include single enantiomers of omeprazole, bupivacaine, citalopram, ofloxacin, salbutamol, ketamine, methylphenidate, cetirizine and oxybutinin. In most cases, the manufacturer has claimed specific advantages over the racemate, particularly decreased incidences and severity of adverse effects. These claims need to be confirmed in clinical trials with sufficient power to show any clinically significant advantages.

In some cases, chiral switching has been of no benefit. For example, the clinical development of (R)-fluoxetine for depression (based on a more acceptable half-life and less propensity for significant drug-drug interactions) was stopped because of a small but statistically significant prolongation of the QT interval with high doses. Dilevalol was thought to have advantages over labetalol, but was removed from the Japanese market because of hepatotoxicity.

Esomeprazole

A recent addition to the Pharmaceutical Benefits Scheme is esomeprazole, the (S)-enantiomer of omeprazole. All proton pump inhibitors exist as two inactive enantiomers (prodrugs) that are converted to active moieties which equally inactivate the H^+/K^+-ATPase pump. Both enantiomers of omeprazole are equipotent, however, their metabolism is different. (R)-omeprazole is mainly metabolised by the polymorphic CYP2C19 enzyme. There is a 7.5-fold difference in the systemic exposure to (R)-omeprazole in patients who are poor metabolisers compared to extensive metabolisers. With (S)-omeprazole this difference is reduced to about three-fold so it was argued that use of esomeprazole would be associated with less interindividual variability in efficacy. However, there are few data to support this theoretical advantage[3], especially when only 3% of the Caucasian population are poor metabolisers. There may be a benefit in the Asian population where the incidence of poor metabolisers is about 20%. A rationale for chiral switching to esomeprazole might therefore be based on ethnic differences in metabolism.

Escitalopram

The selective serotonin reuptake inhibitor activity of citalopram and its active metabolites resides mainly in the (S)-enantiomer. This enantiomer and its metabolites are eliminated slightly faster from the body than the (R)-enantiomer and its metabolites. In overdose, there is a concern about the potential for sudden death, possibly related to QT prolongation due to a secondary metabolite formed from (R)-citalopram. (S)-citalopram (escitalopram) was therefore developed with the aim of a better harm:benefit ratio compared to (R)-citalopram. However, this potential clinical advantage remains to be clinically proven.

Conclusion

Drug development is becoming longer and more complex, while marketing is increasingly competitive. Differences between single enantiomers and racemates are likely to become the focus for aggressive promotion of the 'new' entity. Regulatory authorities and independent sources of drug information (Australian Medicines Handbook, *Australian Prescriber*, Therapeutic Guidelines, National Prescribing Service) need to be provided with good evidence, from well-conducted clinical trials and appropriate pharmacoeconomic studies, that chiral switches have advantages for the prescriber and the consumer. The future will see not only more chiral switches but metabolite switches and metabolite-chiral switches providing fertile ground for patent lawyers and clinical pharmacologists.

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Further reading

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The authors have received funding for their research in this field from the National Health and Medical Research Council, and the US National Institutes of Health/National Institute on Drug Abuse.

Self-test questions

The following statements are either true or false
(answers on page 51)

9. The enantiomers which make up a racemate may not have identical biological effects.
10. Some enantiomers have no clinically significant advantages over the racemate they are part of.

Book review

Therapeutic Guidelines: Psychotropic. Version 5. Melbourne: Therapeutic Guidelines Limited; 2003. 338 pages. Price: $33, students $25.30, plus postage

Ian Wilson, Senior Lecturer, Department of General Practice, University of Adelaide, Adelaide

It is an interesting experience to be asked to review a book that you have used previously. I have used earlier versions of this small book as a reference to look up specific details. I have now read this version in detail and am impressed with the depth and extent of coverage.

Any book discussing psychotropic medication has to determine how it will include non-pharmacological treatments that form such an important part of the treatment of mental health problems. Therapeutic Guidelines: Psychotropic takes the straightforward approach of indicating the importance of psychotherapy, but does not try to become a textbook of all possible treatment modalities. This works very well.

As an urban general practitioner with a special interest in mental health problems, I know and respect the sections on the use of antidepressant and anti-anxiety medications. Detailed reading of these sections produced some new elements of knowledge, such as the potential of nefazodone to cause hepatic damage. The sections on atypical antipsychotic medication impressed me. This is an area where general practitioners are being asked to take a more active role.

The section on behavioural emergencies was new to me and I not only found it very educational, but was left wishing it had been available when I was in rural practice.

The index works well and enabled me to check prescribing for a number of difficult patients. The only area of deficiency in this book is the lack of a section dealing with the complex comorbidities seen in general practice. It is the patients on multiple psychotropic medications, who also abuse alcohol or drugs and are pregnant, that tax the practitioner and any textbook.

This book should be in the library of, and used by, any doctor who prescribes psychotropic medication. It would also be valuable to medical students and non-medical staff involved in treating patients with mental health problems.

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 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.

Insulin glargine

Lantus (Aventis Pharma)

100 IU/mL in 3 mL cartridges, and 5 mL and 10 mL vials

Approved indication: diabetes mellitus

Australian Medicines Handbook section 10.1.1

Insulin glargine is a recombinant insulin. Its chemical structure differs from human insulin by three amino acids. The molecule is completely soluble at pH4, but after injection it becomes less soluble. Microprecipitates form, and these allow a slow continuous release of insulin. These properties make a daily injection of insulin glargine suitable for providing a patient's basal insulin requirements.

In clinical trials insulin glargine had similar effects to NPH human insulin, but in some studies fewer patients experienced symptomatic hypoglycaemia. These trials were relatively short, so the long-term effectiveness of insulin glargine is currently unknown.

Patients may find insulin glargine more painful to inject because of its acidity. It should not be mixed with other insulins.

An analysis by the National Institute for Clinical Excellence in the UK concluded that while insulin glargine is an option for type 1 diabetes, it is not recommended for routine use in people with type 2 diabetes who require insulin.[1]

Reference

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NEW FORMULATION

Azithromycin

Zithromax IV (Pfizer)

500 mg powder for solution for infusion in 10 mL glass vial

NEW STRENGTHS

Lercanidipine

Zanidip (Solvay)

20 mg tablets

Perindopril erbumine

Coversyl (Servier)

8 mg tablets

NEW PROPRIETARY BRANDS

Influenza vaccine

Fluad (Chiron Vaccines)

0.5 mL in pre-filled syringe

Leuprorelin acetate

Eligard (Mayne Pharma)

7.5 mg, 22.5 mg and 30 mg single use injection kit

Methylphenidate

Concerta (Janssen-Cilag)

18 mg, 36 mg and 54 mg extended-release tablets

Answers to self-test questions

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

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Australian Prescriber is indexed by the Iowa Drug Information Service, the Australasian Medical Index and EMBASE/Excerpta Medica.

Typesetting
Barnes Desktopping and Design

Printed in Australia by
National Capital Printing
22 Pirie Street, Fyshwick, ACT 2609

Published by the
National Prescribing Service

NPS
National Prescribing Service Limited

INTERNATIONAL SOCIETY OF DRUG BULLETINS

Print Post Approved PP349181/00151 • ISSN 0312-8008