Editorial

Trouble with tramadol

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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]

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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.