# Dental notes

## Managing acute pain in patients with an opioid abuse or dependence disorder

*Prepared by Dr M McCullough of the Australian Dental Association*

The use of illicit drugs, in particular heroin, can have profound effects on the dentition, causing rampant caries, advanced periodontal disease and exacerbation of mucosal diseases. In surveys of injecting drug users, up to 70%, reporting concern about the state of their mouths, described problems such as 'teeth snapping off', 'teeth falling apart', gum disease and trauma. Methadone and methamphetamines are perceived by some injecting drug users to 'eat away their teeth'.[1] This may be partly related to the effect these drugs have on salivary flow, dietary changes and the concomitant long-term lack of oral hygiene.

Dentists can therefore be confronted with patients presenting with acute dental pain who are either currently dependent or are recovering from their dependency. It is essential that our attitudes, and those of our staff, do not become barriers to Effective management of these patients' pain. Self-reporting of the degree of dental pain must be accepted on face value, as the experience of pain is totally subjective in nature and these patients' pain thresholds may have been significantly affected by long-term drug use. This can result in diagnostic dilemmas with the reported pain appearing out of proportion to the clinical signs.

Most dental pain can be treated clinically with effective local anaesthesia, interventional dental treatment and in the immediate post-treatment phase, by maximising the use of non-opioid analgesia such as paracetamol and non-steroidal anti-inflammatory drugs. If a patient has extreme pain which does not respond appropriately to dental treatment and short-term, non-opioid analgesia, it would be wise to consult with the patient's medical practitioner.

### Reference


1. Reid G, Crofts N, Hocking J. Needs analysis for primary health care among the street drug using community in Footscray. Melbourne: The Centre for Harm Reduction, Macfarlane Burnet Centre for Medical Research; 2000.


# New drugs

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

## Anti-thymocyte globulin

Thymoglobuline (Genzyme)

vials containing 25 mg freeze-dried powder

Approved indication: renal transplant rejection and aplastic anaemia

Australian Medicines Handbook section 14.5.3

Anti-thymocyte globulin is indicated for the prophylaxis of renal graft rejection as well as the treatment of steroid-resistant renal transplant rejection. Kidney transplantation is the treatment of choice for most patients with end-stage renal disease. However, 15–35% of transplant recipients will experience one episode of acute rejection in the first year. Giving antibody to deplete thymocytes (T cells) is one way to suppress the immune system to prevent or reverse graft rejection.

Anti-thymocyte globulin is a polyclonal antibody against human T cells. It is a gamma immunoglobulin produced by immunising rabbits. As well as depleting T cells in the circulation, anti-thymocyte globulin is also thought to reduce T cell proliferation, homing and cytotoxic effects within the body. Depletion of T cells occurs within a day of starting intravenous treatment.

This immunoglobulin has been compared to other treatments in renal transplant patients who are also receiving other immunosuppressant drugs. In a randomised trial of 72 patients, anti-thymocyte globulin was more effective at preventing acute rejection during the first year after transplantation than a similar polyclonal antibody derived from horses (4% vs 25% patients had acute rejection).[1] Five years after surgery, patient survival was similar for both treatments, but graft survival was significantly better in patients treated with anti-thymocyte globulin (77%) compared to those treated with the horse antibody (54%).[2]

The rabbit polyclonal has also been compared to basiliximab (an antibody directed towards the interleukin-2 receptor) for the prevention of acute rejection in 278 renal transplant patients.

Although there was a lower incidence of biopsy-proven acute rejection with anti-thymocyte globulin compared to basiliximab (16% vs 26% of patients), approximately half of the patients in both groups had acute rejection, delayed graft function, graft loss or had died after one year.[3]

In another trial, the rabbit antibody was found to be as effective as a horse antibody at reversing acute rejection episodes (return of serum creatinine to baseline levels). After one year, there was no significant difference in overall graft survival between the two treatments (83% vs 75% of patients). Response to treatment depended on the severity of the initial rejection episode.[4]

Anti-thymocyte globulin is also indicated for refractory or relapsing aplastic anaemia. This is an autoimmune disease resulting from the destruction of pluripotent stem cells in the bone marrow. Depletion of these stem cells reduces the number of red and white blood cells and platelets. Anti-thymocyte globulin is thought to benefit these patients by preventing activation and clonal expansion of cytotoxic T cells which are involved in mediating the disease.

The approval of anti-thymocyte globulin for the treatment of aplastic anaemia is based on an uncontrolled trial of 30 adults and children who had not responded to a course of immunosuppressive therapy (which included a horse anti-lymphocyte antibody). These patients were given a second course of treatment consisting of rabbit anti-thymocyte globulin for 1–5 days plus cyclosporin for 1–180 days and in addition most received granulocyte colony stimulating factor for 1–90 days. After a median of 95 days, 23 of the 30 patients had responded to treatment, which was defined as transfusion not required for at least one month. (Women were less likely to respond than men.) After two and a half years, 93% of the patients were still alive. One patient had died early during treatment from sepsis.[5]

Following intravenous administration of this drug, fever, chills, dyspnoea, nausea, diarrhoea, changes in blood pressure, malaise, rash and headache consistent with cytokine release syndrome have been reported. Anaphylaxis has also occurred. Reducing the infusion rate may help to reduce the incidence and severity of these adverse events. Premedication with paracetamol, corticosteroids and/or antihistamines is also recommended. This antibody is contraindicated in patients with hypersensitivity to rabbit proteins.

Leucopenia and thrombocytopenia are common with anti-thymocyte globulin treatment but can be reversed by decreasing the dose. White blood cell and platelet counts should be monitored. Not surprisingly, infections or reactivation of infections (such as cytomegalovirus) are very common so careful patient monitoring and appropriate prophylaxis are recommended. Immunisation with live vaccines should be avoided. In one of the trials, 19% of patients developed acne.[1]

Some patients have developed cancer, in particular lymphoma and post-transplant lymphoproliferative disease, after receiving anti-thymocyte globulin as part of their immunosuppression therapy.

Around two-thirds of renal transplant patients developed anti-rabbit antibodies to the anti-thymocyte globulin. It is not clear if these antibodies would affect the efficacy of this drug if it is used again. Monitoring the patient's T cell count to ensure depletion is recommended for all patients receiving treatment.

This polyclonal antibody seems to be effective in preventing or reversing rejection in renal transplant patients when given with other drugs to induce immunosuppression. Patients with aplastic anaemia may also benefit from this drug. However, because of the profound depletion in T cells, patients must be monitored closely for serious adverse events.

T T T manufacturer provided clinical evaluation

## References


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## Galsulfase

Naglazyme (Cedarglen Investments)

glass vials containing 5 mg/5 mL

Approved indication: mucopolysaccharidosis VI

Australian Medicines Handbook Appendix A

Mucopolysaccharidosis VI is one of the lysosomal storage diseases. It is also known as Maroteaux-Lamy syndrome. As there is an inherited deficiency of the enzyme acetylgalactosamine sulfatase, the degradation of dermatan sulfate is reduced. This substrate accumulates in the lysosomes resulting in deformities, organ damage and growth retardation. Hydrocephalus can develop, but mental development is usually normal. The condition may progress slowly or rapidly. Bone marrow transplant helps a few patients, but has a high mortality and morbidity.

Galsulfase is a recombinant form of acetylgalactosamine sulfatase, produced using Chinese hamster ovarian cells. The solution has to be infused intravenously over at least four hours. Although the half-life of galsulfase is less than 30 minutes, it only needs to be infused once a week.

As mucopolysaccharidosis VI is a very rare disease the main trial of galsulfase only included 39 patients. They were given a weekly infusion of the enzyme or a placebo for 24 weeks. Although the patients were randomised, there was a significant baseline difference between the groups. Before treatment the mean distance patients in the galsulfase group could walk in 12 minutes was 227 metres, whereas the placebo group could cover 381 metres. At the end of the trial the patients given galsulfase could walk 336 metres, while those in the placebo group could walk 399 metres. The mean change in the enzyme group (109 metres) was significantly greater than in the placebo group (26 metres). The mean number of stairs patients could climb in three minutes increased from 19 to 27 with galsulfase and from 31 to 33 with placebo.[1]

Common adverse events during treatment with galsulfase are fever, headache, arthralgia, abdominal pain, ear pain, diarrhoea and vomiting. There can be severe adverse reactions to the infusion, with urticaria, bronchospasm, respiratory distress and apnoea. Although patients should be given antihistamines before each treatment, this will not prevent all the infusion reactions. These reactions can occur for the first time after many weeks of infusions, so resuscitation equipment must always be available during treatment. Nearly all patients develop antibodies to galsulfase, but these do not predict the severity of the infusion reactions.

The assessment of galsulfase was complicated by the imbalance between the groups in the clinical trial.[1] Re-analysis of the data by regulatory authorities was needed to confirm the efficacy of the enzyme. There is also evidence, from a 24-week extension of the trial, that patients who switch to galsulfase from placebo will increase the distance they can walk in 12 minutes (mean increase 66 metres). This extension was 'open label' so there is some uncertainty about the benefit. Galsulfase had no significant effect on joint pain and stiffness, but the trial was not powered to show a difference.[1] In view of these uncertainties and the unknown long-term effect of anti-galsulfase antibodies on clinical outcomes, patients given galsulfase should be in a clinical surveillance program.

T manufacturer provided only the product information

## Reference *†


1. Harmatz P, Giugliani R, Schwartz I, Guffon N, Teles EL, Sa Miranda MC, et al; the MPS VI Phase 3 Study Group. Enzyme replacement therapy for mucopolysaccharidosis VI: a phase 3, randomized, double-blind, placebo-controlled, multinational study of recombinant human N-acetylgalactosamine 4-sulfatase (recombinant human arylsulfatase B or rhASB) and follow-on, open-label extension study. J Pediatr 2006;148:533-9.


## Panitumumab

Vectibix (Amgen)

vials containing 20 mg/mL in 5 mL, 10 mL or 20 mL volume

Approved indication: metastatic colorectal carcinoma

Australian Medicines Handbook section 14.2.1

Panitumumab is a humanised monoclonal antibody for the treatment of metastatic colorectal carcinomas expressing the epidermal growth factor receptor. It is indicated for patients whose tumours have progressed after fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.

This antibody prevents the growth of tumour cells and causes cell death by binding to the epidermal growth factor receptor and competitively inhibiting autophosphorylation induced by various ligands such as epidermal growth factor and transforming growth factor-alpha. Antibody binding also decreases the production of interleukin-8 and vascular endothelial growth factor.

Panitumumab is given as an intravenous infusion. The pharmacokinetics of this drug vary depending on the dose, with clearance decreasing at higher doses. Steady state is reached after three doses of 6 mg/kg once a fortnight. The mean half-life during this dosing interval is approximately 7.5 days.

In an open-label phase III trial of 463 patients with progressive metastatic colorectal cancer, panitumumab with best supportive care was compared to best supportive care alone. Patients were given panitumumab until their disease progressed or they died. Although the median progression-free survival time with panitumumab was similar to the control (8 vs 7.3 weeks), the mean progression-free survival for panitumumab was 5 weeks longer (13.8 vs 8.5 weeks). There was no difference in overall survival between the groups.[1]

The efficacy of panitumumab seems to be confined to a subset of patients with tumours expressing the wild-type (non-mutated) KRAS gene (Kirsten rat sarcoma-2 virus oncogene). Following further analysis of the phase III trial, the median progression-free survival was 12.3 weeks in patients with wild-type KRAS and 7.4 weeks in those with mutant KRAS, after receiving panitumumab. There was no difference in overall survival between the groups.[2] In total, 43% of patients in the trial were found to have KRAS mutations so this is an important factor to consider when selecting patients for panitumumab therapy.

Although panitumumab benefits some patients, it causes considerably more adverse events than supportive care alone. Skin-related toxicity is the most common adverse effect, affecting over 90% of patients. Erythema, acneiform dermatitis, pruritus, skin exfoliation, paronychia, rash and skin fissures have been reported.[1] (The likely cause of these reactions is inhibition of epidermal growth factor receptor in the basal layers of the skin.) Eye-related toxicities and stomatitis have also been observed with this drug. Patients should be monitored for inflammatory and infectious conditions associated with skin

toxicity. Sunlight can exacerbate skin reactions so protection from the sun is recommended.

Health professionals should be aware that panitumumab has been associated with an increased risk of venous thromboembolic events. In the phase III trial, 12 of 231 patients had a thromboembolic event.[1] One case of pulmonary embolism with panitumumab was fatal and two were life-threatening.

Almost 40% of patients who received panitumumab developed hypomagnesaemia, 5% of which were serious, so patients should be regularly monitored during and for eight weeks after completion of therapy. Gastrointestinal problems were more common with panitumumab than with the control treatment.[1]

So far, adding panitumumab to chemotherapy does not appear to give clear benefits. Severe diarrhoea was reported by 58% of patients who received panitumumab in combination with fluorouracil, leucovorin and irinotecan. As diarrhoea can exacerbate electrolyte depletion, this combination of drugs should be avoided. In another trial, adding panitumumab to oxaliplatin- and irinotecan-based chemotherapy and bevacizumab resulted in increased toxicity without improving efficacy.

Although the benefits seem marginal, panitumumab does offer another option for patients who have not responded to standard chemotherapy. It is not known how panitumumab compares with cetuximab, another inhibitor of the epidermal growth factor receptor, for the treatment of colorectal cancer.

Before starting treatment it is important to first ascertain that the patient's tumour is expressing epidermal growth factor receptor. Expression of the wild-type KRAS gene may improve a patient's response to panitumumab. However, these findings are still preliminary and need to be confirmed in further studies.

T manufacturer provided only the product information

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

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

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.emea.europa.eu).

## Answers to self-test questions

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

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