The role of opioids in cancer pain

Columba Quigley

Columba Quigley, as a specialist in palliative medicine, works in a hospital based support team. She also works with a community based palliative care team and in a hospice, where patients are admitted for terminal care, respite, and control of symptoms. Pain occurs often in patients with cancer, particularly those with advanced disease. In addition, pain is one of the most feared symptoms in people with a diagnosis of cancer. Using analgesics (particularly opioids) appropriately effectively controls cancer pain in most patients

This article is based on a module that is available on the BMJ Learning website (www.bmjlearning.com). Access to the site is free but registration is required

Cancer Centre, Hammersmith Hospital, London W12 0HZ
Columba Quigley *consultant in palliative medicine*
cquigley@hhnt.nhs.uk

BMJ 2005;331:825–9

Introduction

Pain is a subjective experience, influenced by physical, psychological, social, and spiritual factors. The concept of total pain acknowledges the importance of all these dimensions and that good pain relief is unlikely without attention to each aspect.

Pain and cancer are not synonymous: at least two thirds of patients experience pain at some time during the course of their illness, and most will need opioid analgesics.[1]

Summary points

Most patients with advanced cancer experience pain

Treatment of cancer pain is based on the WHO analgesic ladder

Morphine is generally accepted to be the drug of choice for managing moderate and severe cancer pain

Morphine's position is being challenged by the introduction of other opioids such as hydromorphone and oxycodone

Transdermal opioids such as fentanyl and buprenorphine are best reserved for patients who have stable opioid requirements

All doctors should be familiar with the basic rules of the WHO analgesic ladder and should use only those drugs with which they are familiar

How should we manage cancer pain?

The aims of managing cancer pain are to[2]:

- Achieve a level of pain control that is acceptable to the patient
- Assess pain and evaluate the effectiveness of management promptly
- Be aware of the components of total pain
- Relieve pain at night, at rest, and on movement
- Provide patients and their carers with up to date information on using pain relieving drugs
- Support and encourage carers.

World Health Organization analgesic ladder

Most cancer related pain can be managed effectively using orally administered analgesics. Current pharmacotherapy is based on the WHO concept of an analgesic ladder.[3] This involves a stepwise approach to the use of analgesic drugs. The ladder suggests that clinicians should start with a non-opioid and if pain is not controlled progress to a weak opioid and then to a strong opioid.

The WHO analgesic ladder, which has been extensively validated,[4 5] is a framework of principles and allows flexibility in the choice of analgesics. It is one part of a comprehensive strategy for managing cancer pain. Analgesic pharmacotherapy is used in an integrated way with disease modifying treatment and non-drug measures.

Some types of pain, such as neuropathic pain, may be less responsive to opioids than other types of pain, such as nociceptive or soft tissue pain.

Twycross and Wilcock stated that for effective pain control, analgesics should be given "by the mouth, by the clock, by the ladder."[6] In addition, patients should be given:

- The right analgesic at the right dose and at the right time

Clinical tip

Patients with cancer often see several doctors and may receive opioids from more than one clinician. To avoid this happening it is good practice for one person to take the lead role in prescribing

- The analgesic by the most appropriate route (the oral route is preferable)
- The maximum dose before moving up to the next step.

Clinicians should also:

- Consider coanalgesics at any time
- Manage side effects of analgesia.

If a patient's pain is not controlled on step 1 or 2, then the clinician should climb to the next step.

Step 3: Opioids for moderate to severe pain

Morphine is the drug of choice for managing moderate to severe cancer pain. No drug has been shown to have greater analgesic efficacy. Morphine is also the most cost effective analgesic.

Oral morphine

The oral route is the simplest and most acceptable for administering morphine.

Dose titration

Consider the following points when titrating the dose of oral morphine:

- Titrate the dose against the effect. Give the next dose before the effect of the previous one has worn off
- The starting dose is determined by previous analgesic requirements; patients moving from a step 2 analgesic will usually start with 5 mg morphine every four hours. Lower doses may be needed in elderly people and those with renal impairment
- Prescribe every four hours. A longer dosing interval may be needed for people with renal impairment
- During dose titration using the four hourly standard release morphine, use the full four hourly dose as needed as a "rescue" for breakthrough pain.[7] Reassess pain control regularly. If pain is not controlled, increase the dose by 30-50%—for example, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, and 30 mg every four hours
- Increase the rescue dose at the same time and to the same level in line with the regular four hourly dose. Rescue treatment can be given every hour if necessary.[7] Give a rescue dose before any procedure that is likely to exacerbate pain
- Morphine has no ceiling dose, but be cautious of incremental change at higher doses
- The systemic bioavailability of oral morphine varies between 15% and 60%. This explains why the effective analgesic dose varies widely between patients.[8]

Converting to sustained release morphine

Once the patient's pain has been adequately controlled and a stable dose achieved for 48 hours, convert to a sustained release morphine preparation (for example, MST Continus (Napp; Cambridge, United Kingdom) twice daily). Always prescribe rescue immediate release morphine equivalent to the four hourly dose.

Several modified release formulations of morphine are available. Evidence is lacking that the various 12 hourly oral formulations (tablets, capsules, and liquids) have significantly different potency or duration of effect.[9]

Many once a day formulations are also available. Although some show differences in kinetic profile,[10] there is no evidence that this is clinically significant.[7]

Alternative routes of administration

- If patients are unable to take oral morphine, the preferred alternative route is subcutaneous
- Diamorphine is usually preferred for parenteral administration because it is more soluble than morphine (smaller volumes can be used for injection).[11] Intramuscular opioid injections are not recommended in palliative care. Subcutaneous diamorphine is around three times more potent than oral morphine
- To convert a 24 hour dose of oral morphine to an equivalent dose of subcutaneous diamorphine divide by three—for example, 60 mg MST Continus twice daily is equivalent to 40 mg subcutaneous diamorphine in 24 hours
- Give appropriate breakthrough doses with subcutaneous injection equivalent to a four hourly diamorphine dose
- In a pain emergency or pain crisis, subcutaneous diamorphine may be more appropriate than oral analgesia because of its quicker onset of action
- Transdermal fentanyl may be used as an alternative to oral morphine for patients who require stable opioid doses
- Some patients prefer rectal administration. The bioavailability and duration of effect of rectal morphine is similar to that of oral morphine, and therefore the equianalgesic dose by both routes is the same.[12]

Side effects of morphine

It is important to warn patients about possible side effects. These can occur when taking weak opioids at step 2 of the analgesic ladder as well as when taking strong opioids at step 3.

Nausea and vomiting

Up to two thirds of patients may develop nausea and vomiting when starting morphine, which may last up to seven days.[7] All patients should be offered an antiemetic. Commonly used regimens include[2]:

- Haloperidol 1.5-3 mg at night
- Cyclizine 50 mg every eight hours
- Metoclopramide 10-20 mg every six hours.

Evidence is lacking that any of these regimens is superior to another. Opioid induced nausea is unlikely once the dose is stable; if nausea persists other causes should be investigated.

Constipation

Constipation is predictable and occurs in at least 90% of patients. Most guidelines on the management of opioid related constipation recommend prescribing both softening and stimulating laxatives. Use stimulating laxatives with caution in patients at risk of bowel obstruction. Opioid related constipation is a persistent effect.

Drowsiness

Drowsiness may occur at the start of treatment. It usually resolves within a few days.

Cognitive impairment

Cognitive impairment is minimal for most patients on stable doses of morphine. Tolerance develops over a few days. Ability to drive does not seem to be significantly impaired in alert patients receiving a stable opioid dose.[13]

Dry mouth

To avoid dry mouth, patients should be encouraged to adopt good mouth care and to take regular sips of water, suck boiled sweets, and use sugar free chewing gum.

Urinary retention
Urinary retention is uncommon but may occur with spinal opioids.

Pruritus
As with urinary retention, pruritus is uncommon but may occur with spinal opioids.

Concerns about morphine
Morphine has long been feared by the general public and the medical profession.[14] Underlying this fear is the mistaken belief that the potential for misuse of opioids is linked with their use as analgesics. Unfortunately, concerns about addiction, respiratory depression, and excessive sedation cause healthcare professionals to avoid using opioids or to use them in suboptimal doses. Clinical experience has shown that these fears are largely unfounded and that addiction is not likely if morphine is used to manage pain responsive to opioids in doses titrated to the degree of pain.[11]

Withdrawal symptoms indicate physical dependence and should not be confused with psychological dependence (addiction).

Opioid toxicity
Opioid toxicity can occur:
- When dose escalation is too rapid
- In patients with renal impairment
- If pain is not responsive to opioids
- After therapeutic pain relieving intervention—for example, chemotherapy, radiotherapy, or nerve block.

Warning signs include:
- Pinpoint pupils
- Hallucinations
- Vomiting
- Drowsiness
- Confusion
- Myoclonic jerks
- Micro sleeps.

If toxicity occurs, stop opioid analgesia. The patient may need to miss one or several four hourly doses, then:
- Restart at a reduced dose or
- Convert to an alternative opioid at a lower dose.

Consider using the opioid antagonist naloxone if life threatening respiratory depression occurs. Use with care, however, as it may increase the patient's pain.

Give naloxone as an intravenous injection as follows:
- Dilute ampoule of naloxone 400 μg/ml to 10 ml 0.9% sodium chloride injection
- Administer 0.5 ml (20 μg) every two minutes until the respiratory rate is satisfactory
- Give further boluses if necessary every 30 to 60 minutes because naloxone has a short duration of action.

Respiratory depression is unlikely unless doses much higher than prescribed have been given.

Giving morphine to patients with renal impairment
Take care when prescribing opioid analgesics for people with renal impairment because these patients are extremely sensitive to opioids. Seek specialist advice from the palliative care team.

Remember:
- Do not prescribe sustained release preparations of morphine unless renal function and dose requirements are stable
- Prescribe small doses of immediate release morphine
- The dosing frequency may need to be decreased
- To consider opioid alternatives that are not renally excreted (for example, subcutaneous alfentanil).

No opioid is truly safe in patients with renal impairment, usually because of the accumulation of toxic metabolites. Of the opioids mentioned, alfentanil by subcutaneous injection seems to be the best tolerated opioid in this clinical context.[15]

How effective is the management of cancer pain?

Several studies have validated the effectiveness of the WHO analgesic ladder for the management of cancer pain.[16 17] More than 8000 patients have been included in these reports.

Overall it is estimated that between 71% and 100% of patients achieve adequate analgesia for cancer pain when the WHO ladder is used appropriately. A small proportion of patients (10-30%) do not respond to morphine, however, experiencing a poor analgesic response or intolerable side effects, or both.[18]

At present it is impossible to predict which patients are likely to achieve good analgesia from morphine and which patients are likely to develop side effects. Dose limiting side effects most often involve toxicity of the central nervous system, for example:
- Drowsiness
- Cognitive impairment
- Confusion
- Hallucinations
- Myoclonic jerks.

Switching opioids

An increasing number of alternatives to morphine are available in the United Kingdom. For example:
- Hydromorphone
- Oxycodone
- Transdermal fentanyl patch
- Transdermal buprenorphine patch
- Methadone.

In patients who are intolerant to morphine it is becoming increasingly common to switch to an alternative strong opioid, such as oxycodone or fentanyl. Even with these alternatives, outcomes are often variable and unpredictable. In one prospective study, 20% of patients needed two or more switches to alternative opioids before a satisfactory outcome was achieved.[19]

Hydromorphone and oxycodone
Hydromorphone and oxycodone are available in similar normal release and modified release formulations as morphine. The efficacy and tolerability of morphine and hydromorphone seem similar.[20]

Oxycodone is an effective alternative to morphine.[7] Its side effect profile and analgesic efficacy is similar to that of morphine.[21] Oxycodone has better systemic bioavailability (60-90%) and the equianalgesic dose of oral oxycodone is between one half to two thirds that of oral morphine.[22]

Methadone
Methadone is also a potent opioid analgesic. It is widely available and seems to have similar efficacy and a comparable side effect profile to morphine.[23] However, it

Sample questions

Here is a small sample of the questions that you can find at the end of this module. To see all the questions and to get the answers, go to www.bmjlearning.com/

1. Which one of the following opioids is the safest for patients with renal failure?
   a. Morphine
   b. Oxycodone
   c. Hydromorphone
   d. Alfentanil
2. Once patients are receiving stable doses of morphine, which one of the following opioid related side effects persists?
   a. Constipation
   b. Drowsiness
   c. Nausea
3. What is the duration of action of oral transmucosal fentanyl citrate?
   a. About one hour
   b. About two hours
   c. About four hours
   d. About six hours
4. Which one of the following opioids has the longest half life?
   a. Morphine
   b. Oxycodone
   c. Methadone
5. A 60 year old man was recently diagnosed as having bowel cancer. He has opioid responsive pain but keeps vomiting up oral morphine. His pain is unpredictable and unstable. Which one of the following available options should you advise him to take?
   a. Subcutaneous morphine
   b. Subcutaneous diamorphine
   c. Subcutaneous fentanyl

has complex pharmacokinetics, which varies between people. Also there is a risk of drug accumulation owing to its long half life. Therefore, experienced doctors need to take responsibility for starting and monitoring the prescribing of methadone.[23]

Fentanyl

Fentanyl is a lipid soluble synthetic opioid, which can be delivered in a transdermal controlled systemic delivery formulation for up to 72 hours.[24] Transdermal fentanyl has been shown to be effective for treating cancer pain.[25–27] Although the drug is an effective alternative to oral morphine, it is less flexible and needs to be used with caution in patients with unstable pain.

Because of the unique delivery system of fentanyl, it takes 12-24 hours for serum levels to stabilise after starting the patch or changing the dose.[24] Some evidence shows that transdermal fentanyl may cause less constipation than morphine.[25 28]

The European Association for Palliative Care recommends that transdermal fentanyl is reserved for patients who require stable opioids doses.[7] Opioid toxicity has been reported with inappropriate prescribing of transdermal fentanyl.[29] In addition, owing to limitations in patch size, small increments in dose are not possible. The dose is effectively doubled when increasing from 25 µg/h to 50 µg/h patches, and clinical problems have been reported with this dose increment.[30]

Oral transmucosal fentanyl citrate produces a rapid onset of analgesia in five to 15 minutes, with a duration of action of about two hours. It is a relatively new treatment for breakthrough pain and has been shown to be effective.[31] Expense, however, limits widespread use.

Buprenorphine

Transdermal buprenorphine is licensed for the treatment of moderate to severe cancer pain. It has been shown to be more effective than placebo in a double blind randomised controlled trial.[32] It is not clear how its efficacy compares with that of oral morphine.

Evidence for the effectiveness of switching opioids when managing cancer pain is limited. This was highlighted by a recent systematic review.[33] If a clinician thinks that a patient needs a different opioid they should seek help from the palliative care team.

Opioids and neuropathic pain

The use of opioids for neuropathic pain has been intensely debated, but reports suggest they have a role.[34] In the management of cancer related neuropathic pain, opioids are used in conjunction with adjuvant agents such as antidepressants and anticonvulsants.[35]

The role of non-steroidal anti-inflammatory drugs has been well established in the treatment of mild cancer pain and in association with opioids in the treatment of moderate to severe pain.[36] Non-steroidal anti-inflammatory drugs have been shown to have a relevant opioid sparing effect.[37]

Competing interests: None declared.

1 World Health Organization. *Cancer pain relief. With a guide to opioid availability*. 2nd edn. Geneva: WHO, 1998.
2 National Council for Hospice and Specialist Palliative Care Services. *Guidelines for managing cancer pain in adults*. London: NCHSPCS, 2003.
3 World Health Organization. *Cancer pain relief*. Geneva: WHO, 1986.
4 Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer* 1987;59:851-6.
5 Zech DFJ, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief. A 10-year prospective study. *Pain* 1995;63:65-76.
6 Twycross R, Wilcock A. *Symptom management in advanced cancer*. 3rd edn. Oxford: Radcliffe Medical Press, 2001.
7 Hanks GW, de Conno F, Cherny N, Hanna M, Kalso E, McQuay HJ, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001;84:587-93.
8 Twycross R, Wilcock A, Charlesworth S, Dickman A. *Palliative care formulary*. 2nd edn. Oxford: Radcliffe Medical Press, 2002.
9 Collins SL, Faura CC, Moore A, McQuay HJ. Peak plasma concentrations after oral morphine: a systematic review. *J Pain Symptom Manage* 1998;16:388-402.
10 Gourlay GK, Cherry D, Onley MM, Tordoff SG, Conn DA, Hood GM, et al. Pharmacokinetics and pharmacodynamics of twenty-four hourly Kapanol compared to twelve hourly MS Contin in the treatment of severe cancer pain. *Pain* 1997;69:295-302.
11 Twycross RG. *Pain relief in advanced cancer*. Edinburgh: Churchill Livingstone, 1994:255-74.
12 Ripamonti C, Bruera E. Rectal, buccal and sublingual narcotics for the management of cancer pain. *J Palliat Care* 1991;7:30-5.
13 Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* 1995;346:667-70.
14 Lasagna L. Addicting drugs and medical practice: towards the elaboration of realistic goals and eradication of myths, mirages and half-truths. In: Wilner DM, Kassebaum GG, eds. *Narcotics*. New York: McGraw, 1965:53-66.
15 Van Peer A, Vercauteren M, Noorduin H, Woestenborghs R, Heykants J. Alfentanil kinetics in renal insufficiency. *Eur J Clin Pharmacol* 1986;30:245-7.
16 Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. *JAMA* 1995;274:1870-3.
17 Mercadante S. Pain treatment and outcomes for patients with advanced cancer who receive follow up care at home. *Cancer* 1999;85:1849-58.
18 Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001;19:2542-54.
19 Cherny NJ, Chang V, Frager G, Ingham JM, Tiseo PJ, Popp B, et al. Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer* 1995;76:1283-93.

20 Quigley C, Wiffen P. A systematic review of hydromorphone in acute and chronic pain. *J Pain Symptom Manage* 2003;25:169-78.
21 Hanks GW, Hawkins C. Agreeing a gold standard in the management of cancer pain: the role of opioids. In: Hillier R, Finlay I, Welsh J, Miles A, eds. *UK key advances in clinical practice series 2000. The effective management of cancer pain*. London: Aesculapius Medical Press, 2000;57-75.
22 Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, et al. Randomised double blind crossover trial comparing safety and efficacy of oral controlled release oxycodone with controlled release morphine in patients with cancer pain. *J Clin Oncol* 1998;16:3222-9.
23 Nicholson AB. Methadone for cancer pain. *Cochrane Database Syst Rev* 2004;(2):CD003971.
24 Muijsers RB, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. *Drugs* 2001;61:2289-307.
25 Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained release oral morphine in cancer pain: preference, efficacy and quality of life. *J Pain Symptom Manage* 1997;13:254-61.
26 Donner B, Zenz M, Strumpf M, Raber M. Long-term treatment of cancer pain with transdermal fentanyl. *J Pain Symptom Manage* 1998;15:168-75.
27 Radbruch L, Sabatowski R, Petzke F, Brunsch-Radbruch A, Grond S, Lehmann KA. Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. *Palliat Med* 2001;15:309-21.
28 Megens A, Artois K, Vermeire J, Meert T, Awonters FH. Comparison of the analgesic and intestinal effects of fentanyl and morphine in rats. *J Pain Symptom Manage* 1998;15:253-7.
29 Ross JR, Quigley C. Transdermal fentanyl: informed prescribing is essential. *Eur J Pain* 2003;7:481-3.
30 Mercadante S, Villari P, Ferrera P. Clinical problems with transdermal fentanyl titration from 25 to 50 microg/hr. *J Pain Symptom Manage* 2001;21:448-9.
31 Portenoy RK, Payne R, Coluzzi P, Raschko JW, Lyss A, Busch MA, et al. Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. *Pain* 1999;79:303-12.
32 Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomised, double-blind, placebo-controlled study. *Clin Ther* 2004;26:1808-20.
33 Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev* 2004;(3):CD004847.
34 Raja SN, Haythornthwaite J, Pappagallo M. Opioids versus antidepressants in postherpetic neuralgia: a randomised, placebo-controlled trial. *Neurology* 2002;59:1015-21.
35 Portenoy RK. Adjuvant analgesics in pain management. In: Doyle D, Hanks GWC, MacDonald N, eds. *Oxford textbook of palliative medicine*. Oxford: Oxford University Press, 1993:187-203.
36 Grond S, Zech D, Schug SA, Lynch J, Lehmann KA. The importance of non-opioid analgesics for cancer pain relief according to the guidelines of the World Health Organization. *Int J Clin Pharmacol Res* 1991;11:253-60.
37 Mercadante S, Fulfaro F, Casuccio A. A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects on dose-escalation and a pharmacoeconomic analysis. *Eur J Cancer* 2002;1358-63.

Lesson of the week

Osmotic demyelination syndrome

Rachel Abbott, Eli Silber, Joerg Felber, Enefiok Ekpo

Patients with chronic alcoholism are commonly admitted to hospital and given intravenous fluids as part of the treatment of alcohol withdrawal. These patients are predisposed to chronic severe hyponatraemia because of a variety of mechanisms including psuedohyponatraemia, hypovolaemia, "beer" potomania syndrome, cerebral salt wasting syndrome, and reset osmostat syndrome.[1] If hyponatraemia (serum sodium concentration <136 mmol/l) is present it is important to correct this slowly, at a rate of less than 8 mmol/l/day to minimise the risk of developing osmotic demyelination syndrome, the general term for central pontine and extrapontine myelinolysis.[2]

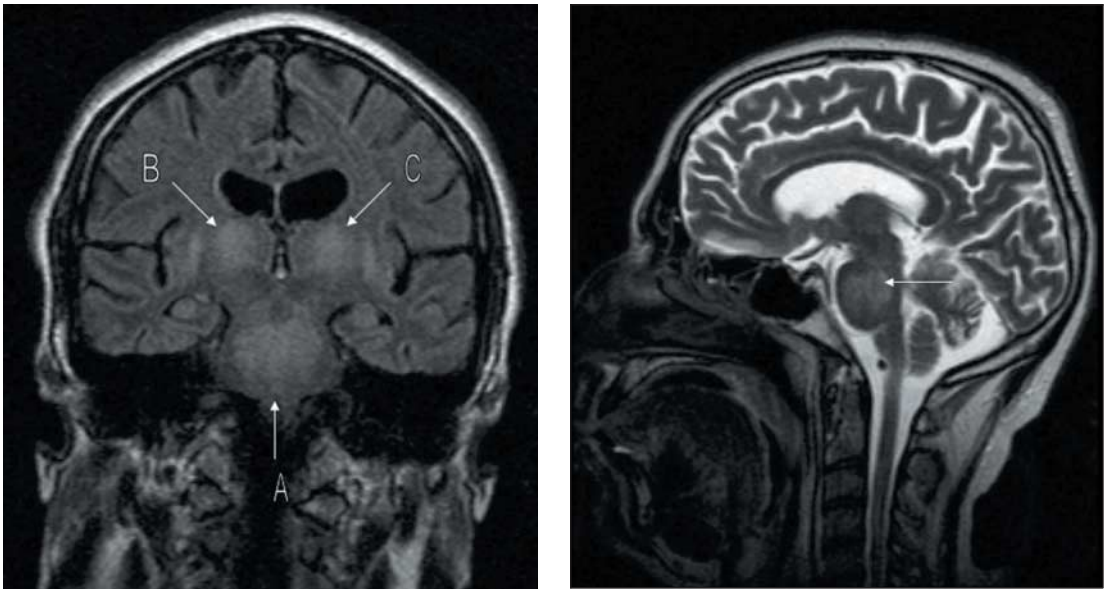
Case report

A 42 year old man with chronic alcoholism presented with confusion. He had no significant medical history and was not taking any regular medications. On the day of admission his serum sodium concentration was 105 mmol/l at 5 pm. His serum was hypo-osmolar at 212 mmol/kg and his urine sodium concentration was

It is important to identify patients at risk from osmotic demyelination syndrome and to correct their hyponatraemia appropriately

Queen Elizabeth Hospital, Woolwich, London SE18 4QH
Rachel Abbott *senior house officer*
Eli Silber *consultant neurologist*
Joerg Felber *senior house officer*
Enefiok Ekpo *care of the elderly consultant*
Correspondence to:
R Abbott
rachel.abbott@nhs.net

BMJ 2005;331:829–30



Magnetic resonance images of patient's brain. Left: FLAIR sequence coronal view showing an altered sequence within the pons (A), thalami, and basal ganglia (B and C). Right: T2-weighted sagittal image through the midline showing extensive T2 hyperintensitivity in the pons (arrow)