Opiate toxicity in patients with renal failure


Published in:
BMJ

Document Version:
Publisher's PDF, also known as Version of record

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investigations, which were planned by NF, NLTC, HJK, AH, PBC; HJK conducted hygiene investigations. NF computerised the data. Analysis and interpretation was conducted by NF and agreed on by all authors. NF wrote the initial draft; and NF and PBC revised it. All authors approved the final manuscript. NF is the guarantor.

Competing interests: None declared.


subsequently made a full recovery, and we advised her against taking further opioid analgesics.

Discussion
The altered pharmacokinetics of opiates in renal failure may result in the accumulation of the parent compound or an active metabolite. Morphine, for example, is metabolised to morphine-3-glucuronide and morphine-6-glucuronide, both of which are renally excreted. Morphine-6-glucuronide, which is more potent than morphine itself, has a half life of about 50 hours in patients with end stage renal failure compared with 3-5 hours in the presence of normal renal function. Pethidine, another commonly prescribed opiate, is converted to the neurotoxic renally excreted metabolite norpethidine. Patients with renal dysfunction are therefore susceptible to opiate toxicity unless doses are reduced or dosing intervals are lengthened appropriately.

The first case illustrates the difficulties in managing postoperative pain in patients with renal disease, including patients who appear to have relatively mild renal dysfunction when assessed by measurement of serum creatinine. We suspected opiate toxicity at an early stage but discounted it because of an inadequate response to naloxone, which had unwittingly been administered subcutaneously. Subsequently, we gave naloxone via an intravenous infusion. We continued this for 48 hours, as the half life of naloxone is much shorter than that of morphine-6-glucuronide in patients with renal failure. Respiratory depression has been reported up to 12 hours after stopping the naloxone infusion. Indeed, we have previously observed life threatening opiate toxicity occurring more than 12 hours after withdrawal of patient controlled analgesia, when the protocol driven monitoring of respiratory function had already been discontinued. Finally, reversal of opiate toxicity coincided with the resolution of acute renal failure, a phenomenon previously described and probably reflecting morphine's haemodynamic effects.

The second case emphasises that life threatening side effects may also result from conventional doses of less potent opioid drugs in patients with chronic kidney disease. Similar effects have been encountered with other weak opiates, including over the counter preparations. Although we do not have definitive evidence of opiate toxicity, because naloxone was not given in this case, strong circumstantial evidence exists. Firstly, the patient's pupils were small despite giving her atropine and adrenaline. Secondly, the patient had recovered sufficiently from her cardiorespiratory arrest to obey commands and yet made no respiratory effort. Finally, there was a rapid improvement in respiratory function after removal of opiate metabolites during haemodialysis.

In conclusion, in patients with renal dysfunction, opiates and their active metabolites may accumulate, resulting in potentially life threatening toxicity. Use of non-opioid drugs should be considered and when opiates are necessary, those that tend not to accumulate in renal disease, such as buprenorphine or alfentanil, may be preferred for mild and more severe pain, respectively. Both medical staff and patients must be aware that patients with renal dysfunction have an increased risk of toxicity due to opiates, including over the counter preparations.

Contributors: BRC, DGF, and CCD conceived the idea for the paper and reviewed the literature. All authors contributed to the preparation of the manuscript. DGF and WEN were responsible for the patient care in cases 1 and 2 respectively, and BRC was involved in the management of both cases. BRC is guarantor. Funding: No additional funding.

Competing interests: None declared.

A memorable patient
Students forever
An elderly woman was admitted under my care after an extensive myocardial infarction. After I had explained her prognosis to the waiting relatives, they asked me to speak to another family member, a retired professor of medicine. When I telephoned him, I was surprised to discover that he was my professor from 20 years ago when I was at medical college. He cautioned me about my unfamiliarity with state of the art tools and modern treatments. But incidents like this teach us that, in their eyes, we may even feel more knowledgeable than our teachers and deride their unfamiliarity with state of the art tools and modern treatments. We tend to become more confident with age and experience. We may even feel more knowledgeable than our teachers and deride their unfamiliarity with state of the art tools and modern treatments. But incidents like this teach us that, in their eyes, we remain students forever.

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(Accepted 8 November 2005)