Opiate toxicity in patients with renal failure


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investigations, which were planned by NF, NLTC, HJK, AH, and expertised by BMJ, BJ, HF, 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.

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Lesson of the week

Opiate toxicity in patients with renal failure

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Opiates and their metabolites are known to accumulate in renal failure, with increased potential for toxicity, the most serious aspect of which is respiratory failure. Despite this knowledge, we continue to see life threatening cases of opiate toxicity in patients with renal failure, two recent examples of which we present below.

Case reports

Case 1

A 68 year old woman with type 2 diabetes, angina, and obesity had an uncomplicated below knee amputation. Baseline creatinine was 133 µmol/l (estimated glomerular filtration rate 36 ml/min). In the first 36 hours after surgery she received 50 mg of morphine and 76 mg of codeine. On the second day she developed oliguria despite intravenous fluid resuscitation, and her serum creatinine rose to 213 µmol/l. She became increasingly drowsy and her respiratory rate fell to 8 breaths/min. Opiate toxicity was suspected after consultation with the on-call nephrologist. She did not respond to 400 µg of naloxone intravenously, which was titrated to maintain her respiratory rate above 12 breaths/min. Her hyperkalaemia was managed conservatively. Within hours her urinary output increased, and in the following days her serum creatinine returned to baseline.

We gave 400 µg of naloxone via a new cannula, and her Glasgow coma scale score improved to 14/15, and her respiratory rate rose to 14 breaths/min. We started a naloxone infusion, which was titrated to maintain her respiratory rate above 12 breaths/min. Her hyperkalaemia was managed conservatively. Within hours her urinary output increased, and in the following days her serum creatinine returned to baseline.

Unrecognised accumulation of opiates in patients with renal failure may be life threatening

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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, he cautioned me about potential life threatening 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.3

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.3,5 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 cardiopulmonary 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 opiate toxicities resulting from 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.3 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.3

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.3 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.3 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.3

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