Opiate toxicity in patients with renal failure


Published in:
BMJ

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

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Published under a Creative Commons Attribution Non Commercial (CC BY-NC 4.0) licence that allows reuse subject only to the use being non-commercial and to the article being fully attributed (http://creativecommons.org/licenses/by-nc/4.0).

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Download date: 15. Feb. 2017
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.


Lesson of the week

Opiate toxicity in patients with renal failure

B R Conway, D G Fogarty, W E Nelson, C C Doherty

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.1 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).2 In the first 36 hours after surgery she received 50 mg of morphine and 76 hours 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 intravenous naloxone, how ever, and therefore she was transferred to the regional renal unit.

On admission she was drowsy and uncommunicative. Observations showed oxygen saturation 91% on 28% inspired oxygen; respiratory rate 6 breaths/min; pulse 50 beats/min, and blood pressure 132/68 mm Hg. Pupils were pinpoint. Initial investigations detected sodium 130 mmol/l, potassium 7.6 mmol/l, urea 28.4 mmol/l, creatinine 320 μmol/l, pH 7.39, Po2 7.9 kPa, and Pco2 5.9 kPa. Electrocardiogram showed no haemodynamically stable. Although she was obeying commands and resisting the endotracheal tube, she made no respiratory effort, therefore we sedated and paralysed her, and transferred her to the intensive care unit. Investigations found 17.4 mmol/l bicarbonate, 9.5 kPa. An electrocardiogram showed a junctional rhythm, rate 50 beats/min, with no ischaemic changes. A chest radiograph was normal.

In the intensive care unit her pupils were noted to be small despite previous atropine and adrenaline administration. It was ascertained that she had been below .

In the intensive care unit her pupils were noted to be small despite previous atropine and adrenaline administration. It was ascertained that she had been previously used to administer naloxone had tissue.
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.1 Pain, another commonly prescribed opiate, is converted to the neurotoxic renally excreted metabolite norphetidine. 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.2 3 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.


(Accepted 8 November 2005)

A memorable patient

Students forever

An elderly woman was admitted under my care after an extensive emergency admission for cardiac arrest and 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.1 Pain, another commonly prescribed opiate, is converted to the neurotoxic renally excreted metabolite norphetidine. 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.2 3 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.


(Accepted 8 November 2005)