A fall from grace: exposing the neurotoxicities of morphine

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Falls in older people, leading to femoral fracture, are common and should normally be uneventful medical emergencies from which we would expect a speedy and safe recovery. In this issue of *British Journal of Pain*, Woodward et al. (2017) describe just such a commonplace event in which, however, a very unusual combination of complications arose.¹ The case is worthy of publication in order to raise awareness of such consequences, and also to ask the question why they occurred.

The case involved an elderly man who fell and sustained a fracture of the neck of femur. He also had a soft-tissue injury to his chest wall, but thoracic imaging showed no fracture there. He underwent routine repair with a cemented arthroplasty and received one dose of intravenous morphine intra-operatively. Following surgery he had paracetamol for 3 days. Then, for persisting pain in his chest wall, he was started on 6-hourly oral morphine solution with extra morphine as required. Over the next 5 days he developed increasing chest wall pain with local hyperalgesia and, concurrently, developed myoclonic jerks of his limbs and neck. Investigations were unhelpful and a neurological consult did not elucidate any causative factors. Diagnoses of opioid-induced hyperalgesia (OIH) and opioid-induced myoclonus (OIM) were made. The therapeutic response was to withdraw the opioid, continue paracetamol and add pregabalin. The abnormal signs abated and the patient was discharged 5 days later.

Three main questions arise from this case, which deserve exploration in order to improve our understanding of post-operative, or any short-term management, of moderate-to-severe pain:

- (1) What mechanisms could underlie the development of OIH and OIM in such a scenario?
- (2) Why did these occur together and after such low doses of oral morphine?
- (3) What are the implications for research and practice?

The case report presents a brief but helpful review of the literature on the occurrence and management of these opioid ‘toxicities’. It is perhaps more honest to call them thus rather than ‘side-effects’ because of their potential seriousness. In recent decades we have become more aware of opioid toxicities – ranging from mild sedation and constipation, which may be inconvenient but tolerable in the context of the need for short-term pain control, to respiratory depression, cardiac arrhythmias and immunosuppression, which are possibly amongst the causes of some of the increasing ‘epidemic’ of opioid deaths, which is described in the USA.²

OIH is ‘a state of nociceptive sensitisation caused by exposure to opioids’.³ There is overwhelming evidence from pre-clinical experiments that animals exposed to both short- and long-term opioids develop the apparently paradoxical state of hyperalgesia (Roeckel et al., 2016). Mechanisms include the interactions of analgesic mu-opioid agonists with not just mu-opioid receptors but also other G-protein coupled receptors (GPCRs) which are ubiquitous on neuronal and other cell membranes; the role of *N*-Methyl-D-aspartate receptor (NMDA) activation and other post-synaptic responses to glutamate neurotransmission which lead to long-term potentiation and wind-up; the emerging role of neuro-immune mechanisms such as toll-like receptor 4 (TLR4) and activation of glial cells. Genetic and gender differences may also play a part both in animal models and in humans.^{3–5}

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And yet, the more we study opioid effects – beneficial and toxic – in the laboratory, the more surprising it is that we do not ‘see’ more evidence of OIH in our patients. In reality, the features of OIH may be present, but they could be masked by the complex changes that follow pain in people, as opposed to lab animals or selected subjects in a trial. For example, in cancer, where opioids are well established, increasing pain and muscular irritability may easily be attributed to neoplastic disease progression and biochemical factors.

But if we open our eyes, ask the right questions and examine our patients carefully, we can pick up signs of OIH and often also the opioid tolerance that can accompany it. Indeed, the paradoxical effects of opioids have been recorded since the 19th century: ‘when dependence on opioids finally becomes an illness of itself, opposite effects like restlessness, sleep disturbance, hyperaesthesia, neuralgia and irritability become manifest’.³ In humans, OIH has most often been recognised after prolonged exposure and usually with high doses.³ In the case presented by Woodward et al. (2016), however, the subject had only a single intra-operative dose of 10 mg morphine followed, after a gap of 3 days, by 5 days of intermittent oral morphine before the toxicities became apparent.¹ The total dose of morphine the patient was exposed to was 130 mg, spread over 10 days.

At the same time as the subject developed OIH, he also started displaying the clinical features of OIM. Compared with OIH, this syndrome has been less well studied and understood. It is seen in humans usually after prolonged exposure and nearly always with higher doses of opioids. Gretton et al. (2013) studied blood levels of morphine and its metabolites M3G and M6G in cancer patients.⁶ They found that myoclonus was associated with ‘extremely high concentrations of plasma morphine and metabolites’.⁶ It is thought that the M3G metabolite, which has no analgesic activity but is neurotoxic, is the cause of myoclonus in such situations. However, neuromuscular toxicity and OIM have been described in patients on other opioids, such as fentanyl which has no known toxic metabolite.

Other drugs also cause myoclonus, notably antidepressants, anti-psychotics, anti-emetics, NSAIDs and fluoroquinolone antibiotics. Kango Gopal et al. (2014)⁷ reported the case of an elderly lady who – similar to the subject in Woodward et al.’s case¹ – sustained a hip fracture after a fall. Post-operatively she was given ciprofloxacin for a hospital-acquired pneumonia and was started on oxycodone sustained release 5 mg twice daily, increasing to 10 mg twice daily.⁷ She developed myoclonus after 6 days of opioids and this persisted after stopping the ciprofloxacin. Eventually the oxycodone was switched to fentanyl and 2 days later the myoclonus abated. It was argued that both oxycodone and ciprofloxacin have the potential to

cause myoclonus, but it was the combination that precipitated it in this patient.

For the concurrent development of both OIH and OIM, other extraneous factors must of course be considered, including the surgery and especially anaesthetic agents used. Both subjects were elderly, but in Woodward et al.’s case,¹ there was no evidence of renal or other organ failure. We can only speculate that for the OIH to develop, there may have been some special local features of the soft tissue injury to the thorax. Regrettably, quantitative sensory testing (QST) of the hyperalgesic area, which might have shed light on the mechanism, was not carried out.

Management of OIH and OIM share a common important feature – the removal of the causative opioid. After a very brief exposure of only a few days it is reasonable, as in the case described by Woodward et al. (2016),¹ to stop the opioid abruptly. After more prolonged opioid dosing, it should be tapered to avoid features of withdrawal (which could include hyperalgesia itself). For OIH, a strategy used commonly in cancer pain management, where opioids can be used for months and at high dose, is to switch from the original opioid to methadone. This agent has several interesting properties, including the ability to act as a NMDA antagonist. In experienced hands, a short course of the potent NMDA antagonist ketamine can be used to bring the previous opioid dose down rapidly.³

As in this case, it is helpful to use non-opioid drugs both to add to the analgesic effect and to be opioid-sparing. The patient was on paracetamol, but pregabalin was added. This drug blocks the calcium channel in neurones that facilitate neurotransmission and may have an especially useful role in OIH. Other interventions that have been described include COX-2 inhibitors, propofol, and alpha-2 receptor agonists such as clonidine.³

The management of OIM – if opioid withdrawal itself or switching to another opioid fail – is not evidence based.⁸ In practice, clinicians often use neuromuscular sedatives such as benzodiazepines. It is interesting to note that the inclusion of midazolam to an opioid infusion is a common intervention at the end of life and may be partly driven by the need to suppress overt or incipient OIM, which may not be recognised as such but attributed to general restlessness in the dying patient.

As recently as 2010, Bannister and Dickenson wrote: ‘Whether or not OIH is a clinical reality is an ongoing debate’.⁹ It is disappointing that in the intervening 6 years, no large-scale prospective randomised trials which include pharmacokinetics, pharmacogenetics and formal QST, have been undertaken to clarify the expression and the proper prevention and management of this entity. Instead, we are still heavily reliant on data from animal models, observational

studies and case reports. Because of the unpredictability of opioid toxicities, we must be mindful that analgesics should be tailored to the individual, and not always driven by protocol.¹⁰ The new report by Woodward et al. (2016) shows that vigilance for both OIH and OIM needs to be maintained, even after short exposure to morphine and with relatively low doses.¹ We desperately need better opioids that may intrinsically protect against these and other troublesome toxicities.

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