

## 'Doctor, my pain is getting worse. Please help me.' Some thoughts on opioid-induced neurotoxicity

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It is usually possible to deal with severe pain in patients with advanced cancer by following basic palliative care principles. Occasionally, however, a patient whose pain had previously been well controlled suddenly starts experiencing pain again.

'Doctor, my pain is getting worse. Please help me.' This is a real challenge for any doctor. Consider the following possible reasons for this change:<sup>1-7</sup>

- The disease has progressed. The appropriate response would be to increase the dose of the analgesics.
- Coping with cancer is challenging. At times the patient's ability to manage is overwhelmed and this distress is expressed in excessive somatic complaints that have no organic basis. Somatisation needs careful exploration rather than more analgesia.<sup>7</sup>
- The patient has developed pharmacological tolerance to the dose of their current analgesics and the dose should be adjusted.<sup>1-3,7</sup>

- The previous reduction in pain has allowed the patient to be more active and the current dose is too low for such additional physical activity. This patient needs a more flexible regimen to allow for incidental activity.<sup>1,2</sup>

Let us imagine that you have explored the patient's emotional state and you decide the increased pain is not due to somatisation. Careful examination reveals no evidence of further disease progression. So you decide that the patient has developed pharmacological tolerance and you increase the dose of the opioid analgesic by 30% as recommended by the palliative care consultant, Dr Mary Smith, whose lecture you attended last week.

The next day, much to your surprise, things have deteriorated. 'Mr Jones is not well today,' says Sr Margaret, 'he has become very drowsy. The night staff reported that he was restless and complaining of strange animals in his room'. As you examine Mr Jones you notice brief, irregular jerking of the muscles of his right arm. There is also twitching of his facial and abdominal muscles. He grimaces even when you touch him lightly. 'You've got to help me, doc. This pain is unbearable.'

What's going on now? You did what the expert advised and now things are worse. Fortunately you have the consultant's emergency number. You call and explain

the situation. 'It's the paradoxical pain of opioid-induced neurotoxicity (OIN) with hyperalgesia,' Dr Smith replies. She goes on to explain that although morphine does not have the limitation of a maximum dose like many other analgesics, sometimes OIN occurs. In some individuals, particularly in the context of mild dehydration or deteriorating renal function, there is a build-up of morphine metabolites, especially morphine-3-glucuronide. These metabolites bind to the  $\mu$  receptors and block the analgesic effect of morphine. In addition they stimulate the nervous system and cause myoclonic jerking, confusion and hallucinations. Sensitivity to light touch, allodynia, is another feature of OIN.<sup>1-7</sup>

'That's fascinating but what do I do now?' you ask, 'Should I give naloxone to reverse the condition?' Dr Smith calmly responds 'No, that would just make things worse as you would precipitate an acute opioid withdrawal syndrome with severe pain and even convulsions.'<sup>7</sup>

'Here is what you can do,' continues Dr Smith:<sup>1-7</sup>

- 'Reduce the morphine by 50% or change to a fentanyl patch. This will allow the kidneys to gradually clear the morphine metabolites without leaving Mr Jones in agony. Another alternative would be to use sublingual buprenorphine every 8 hours. It's a pity we don't have methadone

available here as that also works well in this situation.<sup>1,4</sup>

- 'Encourage adequate hydration. If he cannot drink enough oral fluids, you could give 1 litre of normal saline by subcutaneous infusion (hypodermoclysis) over 24 hours.'<sup>7</sup> This is a simple procedure. Insert a butterfly needle into the subcutaneous tissues on Mr Jones's abdomen and attach the IV solution to it. This is far less troublesome than an IV line and you won't get called out at 2 am to re-site an IV cannula.
- 'If Mr Jones is not already on paracetamol, add 1 gm 6 hourly orally but avoid non-steroidal anti-inflammatory drugs as they may aggravate the condition. If you get desperate, dexamethasone has been recommended in the literature.'<sup>2</sup> Personally I have never found that necessary yet as OIN usually settles down over a day or so.'<sup>6</sup>

The next day Mr Jones is all smiles: he is eating and drinking well. He is looking forward to watching the World Cup rugby final on Saturday. You are pleased that everything has turned out well but there is obviously more to learn about good palliative care and you decide to register for the Diploma in Palliative Medicine at the University of Cape Town with Dr Liz Gwyther.

References available at [www.cmej.org.za](http://www.cmej.org.za)