CASE REPORT

Successful use of pregabalin by the rectal route to treat chronic neuropathic pain in a patient with complete intestinal failure

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SUMMARY

Pregabalin is widely used for treatment of neuropathic pain and is only approved for oral use. This is the first reported case of using pregabalin by the rectal route for treatment in a 70-year-old patient with chronic neuropathic pain and complete intestinal failure. Therapies used in an attempt to manage his chronic pain have included a variety of doses and strengths of opioid preparations and cannabinoids, plus topical and alternative therapies. These were not effective, so it was decided to start a trial of pregabalin administered by the rectal route. Serum levels were measured to assess absorption. Within a few weeks of starting the treatment, the patient had improved pain control and appeared more comfortable and calm.

BACKGROUND

Chronic pain is a big problem in the UK, with prevalence estimated at around 20%.¹ It is exceedingly difficult to effectively relieve chronic neuropathic pain as there are limited treatment options. This case presents a picture of mixed chronic pain and demonstrates the limitations of currently available medical treatments for addressing the neuropathic element of this patient's pain. Treating mixed chronic pain requires trial and error due to the considerable variety of medication responses between patients. National Institute for Health and Care Excellence (NICE) guidelines recommend the use of one of four drugs to manage neuropathic symptoms: pregabalin, gabapentin, amitriptyline or duloxetine.² Only oral preparations of these medications are currently available.

CASE PRESENTATION

A 70-year-old man with a 2-year history of sub-acute bowel obstruction caused by thickened mesentery of uncertain origin presented to secondary care; he had dysphagia and odynophagia potentially caused by parotiditis. He developed sepsis from an aspiration pneumonia 4 days after admission to hospital. He was reviewed by the critical care outreach team and transferred to the intensive care unit (ICU), where he was sedated, ventilated and eventually had a tracheostomy inserted for long-term ventilatory support.

Once taken off sedation medication, the patient was left in pain that had increased in severity compared to his preadmission state. Previously, for pain management for his chronic back pain caused by ankylosing spondylitis and cervical disc

degeneration, he had been taking paracetamol (1 g four times per day), 80 mg two times per day oxycodone MR, plus a 75 µg fentanyl patch. He did not have neuropathic pain symptoms prior to admission.

On review by the acute pain team, the pain was scored at a 2–3/3 (moderate-to-severe pain, with 0 equalling no pain present—table 1 for local routine pain scoring system).

The patient communicated the severity of his pain by writing answers down. He described the pain as 'a sharp, stabbing in both legs and buttocks' of new onset, coexisting with the chronic back pain that he had been admitted with. The patient was not examined by the pain team and so signs such as paraesthesia, allodynia and hyperalgesia were not documented. The pain was initially managed as nociceptive, but the patient continued to report sharp, shooting pain in both legs, which remained relatively unresponsive to opioid therapies, and so was diagnosed with a mixed pain that was difficult to sufficiently address. This diagnosis was based solely on the patient's continuing descriptions of the pain.

Prior to admission, he had been dependent on total parenteral nutrition (TPN) for 2 years and his body mass index was 27 kg/m² (this has decreased to 18.2 throughout his stay in hospital due to recurrent infections and difficulty adjusting to the TPN feed). He was reviewed by the nutritional team daily, as his TPN feed required regular adjustment depending on the presence of infection and levels of serum electrolytes. Previously, he could swallow tablets with thickened fluids, however, he was assessed by the speech and language therapists in ICU, who found him to be unsafe to be allowed swallowing.

The patient remained in hospital for just over 200 days due to an inability to wean from the ventilator. Over this time, he developed numerous infections, mainly ventilation-acquired pneumonias and urinary tract infections, often leading to him becoming very unwell and requiring life-saving antibiotic therapy. He also suffered from a tension pneumothorax, a sacral pressure sore and acute kidney injuries, which recovered with treatment. Non-steroidal anti-inflammatory drug medication was avoided and overall kidney function was good with an average estimated glomerular filtration rate >90 mL/min. The patient consented to the signing of a DNAR (do not attempt resuscitation) and, towards the end of his stay in hospital, he

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Table 1 Pain scoring system used at the Royal Preston Hospital (RPH)

Pain Score	Pain at rest	Pain on movement
0	None	None
1	None	Mild
2	Intermittent	Moderate
3	Continuous	Severe

Reproduced with permission from the acute pain team at RPH.

consented to be not for life-saving antibiotics. He died from a ventilation-acquired pneumonia shortly after day 200.

Other medical problems included oesophageal stricture causing oesophageal dysmotility, congestive cardiac failure (ejection fraction approximately 25%), emphysema (requiring previous ICU admissions), atrial fibrillation and depression (not medically treated). Other medication used throughout the patient's stay in hospital included: a variety of antibiotics, sedation medications, including propofol and alfentanil, benzodiazepines, citalopram, amiodarone, esmolol and other β -blockers for rate control, norepinephrine, hydrocortisone, furosemide, omeprazole, aminophylline, acetazolamide, colomycin and saline nebulisers, metoclopramide and erythromycin. The ankylosing spondylitis was not treated using a biological agent due to the high infection risk that the patient already presented. He also received several units of red blood cells for a normocytic anaemia and a variety of vitamin and electrolyte replacement therapies. There were regular medication reviews by the clinical pharmacist.

TREATMENT

Initially, the acute pain team began with titration of intravenous oxycodone starting at 5–10 mg when required (PRN) in combination with fentanyl patches (up to 75 μ g). However, the patient remained in increasing back and new abdominal pain consistently ranked at 2–3/3. As a result, the fentanyl patches were stopped and a 24 h subcutaneous (SC) infusion of 150 mg of oxycodone was started, with breakthrough SC oxycodone 10–15 mg four-hourly PRN. Lidocaine 5% plasters were tried for direct application to the back, which the patient felt were helpful and used regularly throughout his stay in hospital. One plaster was applied for 12 h, with a 12 h break before applying a new plaster. Owing to the localised nature of this therapy it was used only to target the back pain.

Over the 6 months the patient had spent in ICU, the oxycodone infusion had been titrated up to 200 mg/24 h SC as he had remained in chronic pain. The breakthrough dose of oxycodone was titrated up to 30 mg 2–4 hourly SC over the first 2 months. The patient used, on average, 200 mg of his oxycodone over 24 h, however, his pain always increased if he was suffering with an infection and he would request the maximum doses of his breakthrough analgesia during these periods. He regularly requested a 30–35 mg dose in the evening prior to sleeping, which did not change throughout his time in hospital.

After the first 2 months, the acute pain team decided to trial ketamine to reduce PRN opioid consumption and further control the pain. Fifty mg was added to the oxycodone solution to give SC over 24 h. The plan was to titrate the dose to 200 mg/day by increasing the dose by 25 mg every 24 h. Two days later, the patient became increasingly confused and suffered hallucinations, so the ketamine was immediately stopped.

On further review by the acute pain team, the patient was still ranking his pain as moderate or severe. The patient had now spent 3 months in ICU due to inability to wean from the ventilator. A trial of clonidine was started at 25 μ g SC two times per day to be titrated every 24 h by 25 μ g two times per day until 100 μ g two times per day was reached. This did not effectively manage the pain, so the clonidine was changed to 200 μ g SC over 24 h. This made little difference and therefore the clonidine was eventually stopped. Acupuncture and a transeletrical nerve stimulation machine were tried and the patient felt there was some benefit from these, but not enough to bring his pain score below 2.

After 4 months sativex spray, a *Cannabis sativa* extract, was started at 1 spray two times per day. One spray delivers a dose of 100 μ L. This was increased up to six puffs two times per day over 2 weeks, however, the patient found that he did not like the taste and that it was not greatly helping his pain. It was stopped 2 weeks after starting treatment.

Owing to his inability to swallow and absorb any oral medication, it was difficult to address the neuropathic element of this patient's pain. Despite all the different drugs used, his pain was still poorly controlled. Opioids such as buprenorphine and tramadol, which are more neuropathic pain specific, were not started due to the high opioid dose that the patient was admitted on, of which the morphine equivalent was between 495 and 590 mg/day.³ Tapentadol is only available at Royal Preston Hospital (RPH) in the form of a slow release oral tablet and capsaicin patches (used for localised neuropathic pain) are not available in the RPH formulary. Epidural administration of pain relief was not considered an option due to the presence of pressure ulcers, the history of multiple infections and the practicalities of the procedure. This reduction in options led to the decision to trial pregabalin administered by the rectal route, which was started at 75 mg two times per day. The risks were stated as minimal for no absorption and local irritation, including the potential for a rectal bleed, through effects on the surrounding mucosa. A single patient unlicensed use form was filled in. The plan was to titrate the dose every 7 days to 150 mg two times per day and then to 300 mg two times per day, with measurement of the patient's pregabalin serum levels to assess absorption.

OUTCOME AND FOLLOW-UP

The first serum pregabalin level was sent for, 3 weeks after the pregabalin was started, as the rate of absorption was unknown and therefore it was important to check that there had not been greater than anticipated absorption. The patient was also monitored clinically for any signs of side effects such as increased drowsiness. At this point, the patient was taking 150 mg two times per day and ranking his pain on average at 1/3. When the value was then returned at <1 mg/L (range 2–8 mg/L), the dose was increased to 300 mg two times per day. The second value was then sent for, a week later, and was 2 mg/L. Blood samples were not analysed locally and took 7 days to process.

Over the 10th week of using the pregabalin, the patient was consistently ranking his pain at 0–1/3, the lowest score since his admission to hospital 6 months previously. He had also reduced his use of the PRN oxycodone to an average of 150 mg, from 200 mg, over 24 h. This average, however, had been affected by the patient's increased requirements during times of infection. The decision was taken to increase the pregabalin dose to 300 mg three times per day to further increase therapeutic serum levels and reduce PRN consumption of oxycodone, and was based on the clinical indication, as the patient was not yet

experiencing side effects but gaining benefit from the pregabalin. Levels were sent for 1 week after starting the higher dose and returned at 3 mg/L, showing adequate absorption into the circulation. The blood sample was taken consistently at the same time to avoid any peaks or troughs in serum levels.

The patient stated that he was still in some pain but felt more comfortable than he had for a long time. He also stated that the severity of the shooting and stabbing pains had decreased since starting the medication. Outcome and benefit were measured by the reduction in the patient's perception of his symptoms, the serum levels reaching therapeutic range and the reduction in the patient's requirement for PRN oxycodone.

DISCUSSION

Neuropathic pain is defined as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'.⁴ In this patient, the combination of his ankylosing spondylitis, prolonged immobility and degeneration of his functionality may have been the origin of his pain. NICE guidelines recommend pregabalin as a treatment option for neuropathic pain; it works by acting on the $\alpha 2\text{-}\delta\text{-1}$ subunit of the voltage-dependent calcium channel.^{2 5 6} Pregabalin was chosen to trial first of four recommended by NICE, as it has the advantage of doses only being required twice daily. Although it acts in a similar way to gabapentin, the linear pharmacokinetics mean that the action of pregabalin is easier to predict, which is especially important when using the drug in a novel way.⁷ Pregabalin was chosen over duloxetine despite the patient's background of depression, as duloxetine is available only as a capsule and there was greater experience among the pain team in the use of pregabalin.

Using a drug rectally is a good potential alternative, especially when options are limited. Radbruch *et al* reviewed alternative application options for opioids, including rectal use, and compared these to oral or SC administration. It has been reported that rectal administration of opioids produces more effective pain relief with increased speed of onset and prolonged maintenance of the analgesia.⁸ Searching the literature did not provide any previous cases or studies where pregabalin has been used rectally. However, it was effective for this particular patient as quantitatively shown by the reduction in pain severity scores, reduction in PRN opioid use and the serum levels showing adequate absorption into the circulation. This could be further standardised by using a visual analogue score or numerical rating score for easier comparison of improvement between patients.

Most studies in neuropathic pain have been conducted based on post-herpetic neuralgia and diabetic neuropathy, and these studies have shown that neuropathic pain can often show little response to conventional analgesics such as opioids and non-opioids.^{4 7} Despite this, a recent meta-analysis has shown that opioids should be second-line therapy for some types of neuropathic pain.⁹ Pregabalin has been shown to effectively relieve neuropathic pain as a sole therapy, but has also been shown to relieve pain in combination with opioids in patients with cancer suffering from mixed chronic pain.¹⁰ Indication may alter effectiveness of therapies and, in this patient, pure opioid therapy was not sufficient to control his pain, whereas a mixture of oxycodone, topical lidocaine patches and pregabalin began to bring the pain under control.

Opioids have been shown to have an increased side effect profile compared to pregabalin, including gastrointestinal side effects such as reduced motility and sphincter contraction, which were particularly problematic in such a patient. The

major side effects associated with pregabalin are sedation, dizziness and peripheral oedema; pregabalin should be used with caution in renal insufficiency.^{6 7} In this case, there was the added risk of local mucosal effects; this was discussed with the patient prior to commencing treatment. The patient was also monitored by nursing staff for any occurrence of these local effects or any side effects as the rate of absorption was unknown. As the patient's kidney function was good there was no need to further adjust the dose, however, this may not be the case for other patients.

Other recommendations with regard to managing chronic pain include identifying psychological comorbidities and implementing lifestyle changes such as reducing stress, improving sleep and increasing the amount of exercise undertaken by the patient. This is especially important as randomised control trials have shown that current pharmacological treatment for neuropathic pain may only relieve up to 40–60% of the pain experienced by patients.⁷ In this case, it was difficult to sufficiently address these recommendations. The patient was confined to his bed and spent around 200 days in the ICU, and suffered from ICU psychosis for a period of his admission. This may have contributed to the worsening of his chronic pain, and it certainly affected his psychological well-being. However, pregabalin can reduce anxiety and this may also have benefitted his pain, especially based on his background of depression.¹¹ Thus the patient may have become more accustomed to his pain over time, with or without the cognitive effects of pregabalin, and so began to cope with his pain better leading to a reduction in his pain scores.

Learning points

- ▶ The rectal route for pregabalin can be considered in patients with total gut failure.
- ▶ If using pregabalin in this novel way, serum levels can be measured to assess absorption with samples taken at consistent times to avoid variation.
- ▶ The success of this therapy was measured against a reduction in the patient's perception of his pain and, therefore, in cases such as this, a more standardised grading spectrum such as a visual analogue score or numerical rating score may be more appropriate to measure outcome.
- ▶ The dose of pregabalin may need to be adjusted for a patient with chronic kidney failure or with an acute kidney injury.

Competing interests None declared.

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