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Calcitonin for acute neuropathic pain associated with spinal cord injury

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SUMMARY

Neuropathic pain associated with spinal cord injury is caused by complex neural mechanisms and is often refractory to standard therapy. Salmon calcitonin was an effective treatment for neuropathic symptoms in this case series of three patients with recent spinal cord injury. Salmon calcitonin is already used to help manage pain after limb amputation and also after vertebral fractures and it is perhaps surprising that it has not been trialled previously for spinal cord injury pain. Calcitonin is thought to exert its effect by modulation of the serotonergic system and is generally well tolerated and convenient to administer. This underutilised drug may be a very useful adjuvant for neuropathic pain associated with spinal cord injury.

Key Words: calcitonin, spinal injury, neuropathic pain

Spinal injuries cause profound disability but it is perhaps less well recognised that they are often associated with chronic refractory neuropathic pain. There is no universally effective treatment and even with appropriate combination therapy, symptoms may be only partially relieved. Calcitonin has previously been shown to be effective in the management of acute pain following amputation[1], vertebral fractures and other neuropathic conditions[2,3]. However, there is no evidence in the literature for its use in spinal cord injury pain. Patients with recent spinal cord injury may have severe acute neuropathic symptoms that are resistant to conventional analgesia such as opioids, non-steroidal anti-inflammatory drugs and even drugs with proven efficacy for neuropathic pain. It is relatively common for complex patients to have multiple sites of pain and describe the presence of both nociceptive and neuropathic symptoms when questioned directly. Each pain-site may have a different level of severity. The pain scores in this series reflect both the challenge posed by acute spinal cord injury pain and also represent the inherently subjective nature of pain itself. A multidisciplinary approach is required to address the complex therapeutic challenges that may be posed by each patient, but conventional management still has room for improvement.

CASE HISTORIES

Three patients with recent spinal cord injuries who were suffering from an acute neuropathic pain condition were given calcitonin in addition to their existing appropriate pharmacological therapy. All three patients complained of distressing neuropathic symptoms that were resistant to the conventional drugs that they had already received as well as tricyclic antidepressants. The patients in the series gave their consent to receive 100 international units of salmon calcitonin subcutaneously once daily for three days with antiemetic prophylaxis in the form of either prochlorperazine or metoclopramide. Specific $5HT_3$ antagonists such as ondansetron were avoided because a proposed mechanism of action for calcitonin is via the serotonergic system[4]. Administration of calcitonin via the intravenous route is associated with significant nausea, but when given subcutaneously with anti-emetic prophylaxis it does not appear to be a significant issue. Patients were warned about the possibility of minor side-effects such as temporary diarrhoea.

Numerical pain scores and adverse effects were recorded for the patients in this case series. Where pain scores were assessed, patients were asked to rate their best and worst pain levels on a scale of 0 to 10 (0=no pain and 10=worst pain imaginable). Sedation scores were used to assess a patient's level of sedation from 0 to 3 (Table 1) as an indication of increasing opioid-related central nervous system

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and respiratory depression. The highest level in the preceding 24 hours was recorded. The author also made detailed inquiry into the character of symptoms focusing on the presence of any neuropathic features.

A summary of pain and sedation scores for all patients as well as relevant medications and their doses from three days prior to calcitonin administration until three days after the third dose, is provided in Tables 1 to 3.

Case 1

A 45-year-old man, with a past history of chronic bipolar disorder who was on long-term therapy with sodium valproate at therapeutic dosage, sustained a C5 teardrop fracture in a motorbike accident that was associated with spinal cord compression at the level of C4/5. This resulted in total quadriplegia. At the time of review by the author he complained of a severe ache in his neck that responded to conventional analgesics. However, he also had severe intractable burning pain across his neck and shoulders in a C3-C5 distribution. His analgesic regimen consisted of paracetamol, high doses of oxycodone, a ketamine infusion, nortriptyline and sodium valproate continued at his usual dose. As he was already on a high dose of sodium valproate for severe bipolar disease there was a reluctance to add another anticonvulsant such as gabapentin if another

TABLE 1

Case 1 medication and pain summary from three days prior to three days after completion of calcitonin therapy (100 international units)

Day	-3	-2	-1	0	+1	+2	+3	+4	+5
Pain score									
Best	3	8	8	4	4	5	2	8	8
Worst	10	10	10	10	10	7	8	10	10
Calcitonin, SC				100	100	100			
Oxycodone, PO	40	60	60	105	75	15	2.5	2.5	2.5
Methadone, PO	–	–	–	–	–	10	10	10	10
Ketamine infusion, IV	200	200	200	–	–	–	–	–	–
Nortriptyline, PO	25	50	50	50	50	50	50	50	50
Sodium valproate, PO (usual medication)	1500	1500	1500	1500	1500	1500	1500	1500	1500
Prochlorperazine, SC	–	–	–	12.5	12.5	12.5	–	–	–
Sedation score	0	0	1	0	0	0	0	0	0

Medication dosages are in mg/24 hours or international units for calcitonin. Pain is assessed by a numerical rating score from 0 to 10 with 10 the worst imaginable. Sedation is scored from 0 to 3. (0=awake and alert, 1=mild sedation, easy to rouse, 2=moderate sedation, unable to stay awake but easy to rouse, 3=difficult to rouse). SC=subcutaneously, PO=orally, IV=intravenously.

TABLE 2

Case 2 medication and pain summary

Day	-3	-2	-1	Zero	+1	+2	+3	+4	+5
Pain score									
Best	?	5	7	7	8	?	2	2	6
Worst	10	10	10	10	10	8	8	8	8
Calcitonin, SC	–	–	–	100	100	100	–	–	–
Oxycodone, PO	100	65	125	65	50	30	20	30	30
Methadone, PO	–	–	–	20	20	20	20	20	20
Amitriptyline, PO	50	50	50	50	50	50	50	50	50
Gabapentin, PO	3600	3600	3600	3600	3600	3600	3600	3600	3600
Prochlorperazine, SC	–	–	–	12.5	12.5	12.5	–	–	–
Metoclopramide, IM	–	10	20	20	20	10	–	10	10
Sedation score	0	0	0	0	1	0	0	0	0

Medication dosages are in mg/24 hours or international units for calcitonin. Pain is assessed by a numerical rating score from 0 to 10 with 10 the worst imaginable. Sedation is scored from 0 to 3. (0=awake and alert, 1=mild sedation, easy to rouse, 2=moderate sedation, unable to stay awake but easy to rouse, 3=difficult to rouse). SC=subcutaneously, PO=orally, IM=intramuscularly.

TABLE 3
Case 3 medication and pain

Day	-3	-2	-1	Zero	+1	+2	+3	+4	+5
Pain score									
Best	5	6	1	1	1	?	?	?	0
Worst	9	7	4	4	4	4	2	3	0
Calcitonin, SC	–	–	–	100	100	100	–	–	–
Morphine, IV, PCA	90	130	85	72	16	–	–	–	–
Oxycodone, PO		30	30	30	30	75	60	55	15
Ketamine infusion, IV	48	48	48	48		–	–	–	–
Nortriptyline, PO	25	25	25	50	50	50	50	50	50
Prochlorperazine, SC	–	–	–	12.5	12.5	12.5	–	–	–
Sedation score	1	0	1	1	1	0	0	0	0

Medication dosages are in mg/24 hours or international units for calcitonin. Pain is assessed by a numerical rating score from 0 to 10 with 10 the worst imaginable. Sedation is scored from 0 to 3. (0=awake and alert, 1=mild sedation, easy to rouse, 2=moderate sedation, unable to stay awake but easy to rouse, 3=difficult to rouse). SC=subcutaneously, IV=intravenously, PCA=patient-controlled analgesia, PO=orally.

option was available. The patient agreed to a trial of calcitonin therapy and after three days he reported that the burning pain had decreased significantly and was no longer troublesome. Methadone 10 mg daily was also added to his treatment regimen on the last day of calcitonin injections. Other posture-related pain with a nociceptive quality, however, was still present and this may have accounted for the high pain scores recorded. It is worth noting that the patient reported high pain scores in the days following calcitonin treatment, but requested very little oxycodone analgesia even though it was readily available to him (in contrast to oxycodone consumption prior to and during calcitonin administration). Eight days after calcitonin administration the patient felt that his symptoms had almost completely resolved and all analgesic medications including methadone were discontinued except for paracetamol and nortriptyline. Sodium valproate was continued as before.

Case 2

A 22-year-old morbidly obese man was struck by a car as he walked across a road. He sustained a minimally displaced fracture of C2, fractures of the transverse processes of T1-T3 and a fracture of the vertebral body of T3, which was associated with a paraspinal haematoma. He underwent T1-T5 decompression and stabilisation but still developed almost complete paraplegia. He also had a mid-shaft fracture of his left tibia, which was managed by open reduction and internal fixation. His predominantly nociceptive symptoms had been managed on a satisfactory analgesic regimen for four weeks after his surgery, but then he developed a severe refractory burning pain in his left foot and ankle that was associated with marked hyperalgesia and allodynia. He could not bear even a cotton sheet resting on his foot. At the time of review he was being managed with paracetamol, oxycodone, gabapentin 3600 mg daily and amitriptyline 50 mg daily.

Methadone 20 mg daily was commenced. He also received three days of calcitonin and suffered mild nausea on the first day only (he was the only patient who received a second antiemetic). The pain in his left foot disappeared over this period. The allodynia remained, but its intensity was significantly diminished. Subsequently, he was able to tolerate desensitising physiotherapy to reduce this symptom. Despite having received several weeks of therapy with opioids his dose requirements declined and he was weaned off all opioids over a few weeks. The dosages of gabapentin and amitriptyline were also reduced to 1800 mg and 25 mg respectively and the man was transferred to a rehabilitation centre for further management.

Case 3

A previously fit and well 22-year-old man sustained a burst fracture of T12 in a road traffic accident. A bone fragment and a localised haematoma resulted in cauda equina syndrome including partial paraplegia. He underwent T11 to L1 fusion with T12 laminectomy. He had been managed for several days on paracetamol, high doses of opioids (intravenous patient-controlled analgesia morphine and oral oxycodone) and a ketamine infusion for nociceptive type low back pain. He then developed severe sharp, burning pains radiating down both legs.

These new neuropathic symptoms were reduced by nortriptyline, but not completely controlled, and the patient found the symptoms to be very hard to tolerate. After a three-day course of calcitonin his pain virtually disappeared and one week later he refused all analgesia except for paracetamol and non-steroidal anti-inflammatory drugs.

DISCUSSION

Pain related to spinal cord injury

Spinal cord injury is often associated with severe pain that can be refractory to treatment[5-7]. This pain has been classified into nociceptive features (musculoskeletal and visceral) and neuropathic features (above-level, at-level and below-level)[8]. The neural mechanisms that occur after an injury to the spinal cord are complex and, as yet, poorly understood[6,7]. Multiple neurotransmitters and neural pathways appear to be involved and the balance between glutamine-mediated excitation and glycine- and GABA-mediated inhibition may be altered. Neuroplasticity may result in pathological nociceptive pathways associated with hypersensitivity and spontaneous pain. A reduction of serotonergic tone may also lead to a hyperexcitable state of dorsal horn neurones[5,7].

Perhaps due to the random and heterogeneic nature of the condition itself there are few randomised controlled trials on the management of spinal cord injury pain and most of the ones that have been carried out have reported limited or no benefit[5,6,9]. Therefore the management of patients with spinal cord injury is often extrapolated from therapies that have been effective in other forms of neuropathic pain. Based on the available evidence, Siddall and Middleton[6] developed a comprehensive algorithm for the systematic management of spinal cord injury pain. The management approach has separate arms for nociceptive and neuropathic symptoms and incorporates multiple therapeutic modalities. These include pharmacotherapy, physical therapy, medical and surgical management where appropriate, physical interventions and also cognitive therapy to address psychosocial issues[6].

Calcitonin

Calcitonin is secreted by the thyroid gland and causes a decrease in plasma calcium concentration by the inhibition of bone reabsorption and the promotion of renal excretion as part of calcium homeostasis[2,10]. In humans it is a polypeptide hormone consisting of 32 amino acids, while in other creatures more primitive variations are present[2]. This fact is relevant because other forms of calcitonin, such as salmon calcitonin, may have much greater efficacy for neuropathic symptoms[2,11,12].

The mechanism by which calcitonin reduces pain has not yet been definitively elucidated in humans. There are a number of proposed targets and it may exert its analgesic effects via multiple mechanisms. There is growing evidence in animal models that the principle analgesic effect of calcitonin is mediated by a central effect on the serotonergic system[2,4,13,14]. Indeed, its efficacy is increased by co-administration of serotonergic agonists and decreased by antagonists[13]. In addition, it requires an intact serotonergic system to enable it to provide analgesia[4,14]. Other potential mechanisms of action include the inhibition of prostaglandin and thromboxane synthesis[15] and increasing beta endorphin levels[11]. The latter mechanism could be consistent with the observation that naloxone may cause a small reduction in the analgesic efficacy of calcitonin, although this effect may not be clinically significant[14,16,17]. The analgesic effect of calcitonin is typically rapid and sustained far beyond the anticipated pharmacological duration of action[1,2,11,18,19].

Calcitonin has been shown to be effective for acute phantom limb pain in a randomised controlled trial1 and systematic reviews have found it to be effective for managing acute pain associated with vertebral fractures[2]. There are conflicting results for its efficacy in the management of complex regional pain syndrome[19-22], but this is a notoriously complex and multifactorial condition to manage. Indeed, no single intervention is universally effective and the most effective management is based on aggressive multidisciplinary combined therapy[23]. The optimum dosage, route of administration and duration of calcitonin therapy have also yet to be determined[2].

Patients with spinal cord injury may often have symptoms of deafferentation similar to amputees. Indeed, it is not uncommon for them to experience phantom limbs as separate entities from their paralysed limbs. In addition, these people often have simultaneous vertebral fractures. The apparent lack of information in the literature on the use of calcitonin in spinal injuries may therefore seem surprising.

Adverse effects of calcitonin are consistent with increased serotonergic activity, but they are usually mild and self-limiting[1,2,18]. A pre-emptory explanation of this to the patient along with antiemetic prophylaxis is usually sufficient. 5-HT_3 antagonists such as tropisetron and ondansetron should be avoided as they may reduce the efficacy of analgesia[13]. There are no known drug interactions[2] but the patient's existing medication regimen should be reviewed to ensure

that multiple drugs with serotonergic effects are not being prescribed simultaneously due to the theoretical risk of serotonin toxicity. Lower risk substances include tramadol and low-dose tricyclic antidepressants. Higher risk combinations include selective serotonin reuptake inhibitors and monoamine oxidase inhibitors[24]. These risks may be justified, however, if the potential benefit of calcitonin for managing problematic pain is confirmed in the setting of spinal cord injury.

CONCLUSION

Calcitonin may be a potential therapy for the management of acute neuropathic pain associated with spinal cord injury although it does not appear to be particularly effective for nociceptive symptoms. Calcitonin is well-tolerated, associated with minimal adverse effects and is a convenient and low-cost therapy. A randomised controlled crossover trial would be useful to confirm its efficacy. A comparison of the comparative potencies of subcutaneous and intranasal administration would also be worthwhile.

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