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Intrathecal baclofen overdose mimicking brainstem death during deep brain stimulation surgery for pain

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ABSTRACT

We describe a unique case of intrathecal baclofen overdose mimicking brainstem death, during bilateral anterior cingulate cortex deep brain stimulation (DBS) for pain. A 37-year-old man with chronic regional pain syndrome requiring an intrathecal baclofen pump underwent DBS under general anaesthesia and experienced an intraoperative generalised tonic–clonic seizure on dural opening. Once the operation was completed, the patient was noted to have fixed, dilated pupils bilaterally and was transferred for an emergency computed tomography scan of the head, which did not reveal any acute intracranial pathology. The patient was transferred to the intensive care unit for management of concurrent hypotension, bradycardia and supportive management of his low Glasgow Coma Scale (GCS) score. A trial of atropine to counter the bradycardia was unsuccessful. Intrathecal baclofen toxicity was suspected as a diagnosis of exclusion, necessitating urgent aspiration of the baclofen pump. The patient's GCS score improved after pump aspiration and he was discharged home several days later. It was noted that the intrathecal baclofen pump had been refilled several days previously and the patient had reported intermittent episodes of somnolence. In perioperative patients with intrathecal baclofen pumps in situ, baclofen toxicity should always be considered as a differential in perioperative complications, even if it is considered a rare event.

KEYWORDS
Intrathecal baclofen – DBS – Toxicity – Brainstem death

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Background

We describe a unique case of intrathecal baclofen overdose mimicking brainstem death, during bilateral anterior cingulate cortex deep brain stimulation (DBS) for pain. It highlights that, in perioperative patients with intrathecal baclofen pumps in situ, baclofen toxicity should always be considered as a differential in perioperative complications and managed as such, even if it is considered a rare event.

Case history

A 37-year-old man suffered an occupational crush injury to the left leg in 2011, following which the limb suffered from acute swelling but no identifiable bony fractures. The pain continued despite simple analgesics and developed into chronic regional pain syndrome. On presentation to the neurosurgery clinic in October 2019 the patient's chief complaint was a constant intolerable burning sensation in his left leg and marked hypersensitivity like walking on hot coals.

The patient had previously trialled spinal cord stimulation and had an implanted Flowonics Prometra II baclofen pump. The rate of intrathecal baclofen infusion was 860μg/24h. He had previously undergone spinal cord stimulation from 2011 to 2012 without clinical success. He had also undergone a previous L5 discectomy in 2018. Concurrent medications, listed in Table 1, included gabapentin, amitriptyline, tramadol, mirtazapine, quetiapine and zopiclone.

On clinical examination, there was marked atrophy of the left calf muscles and marked vascular changes. The patient was unable to move his foot due to pain and sensitivity to touch.

The patient received bilateral anterior cingulate cortex DBS for pain with an Abbott Infinity 7 PC device that was connected by 50cm extension leads to 1.5mm spaced directional deep brain electrodes.

The surgery was performed under general anaesthesia with a preoperative stereotactic computed tomography (CT) head scan in a Cosman-Roberts-Wells (CRW) base ring. The patient was noted to be slightly drowsy before surgery and bradycardic (heart rate 50bpm) and hypotensive (blood pressure 70/40mmHg) after induction of general anaesthesia.

The left anterior cingulate cortex was targeted approximately 1cm lateral to the midline, 20mm

Table 1 Patient medications on admission

Medications on admission	Dose
5% Lidocaine patch TT od	5%
Naproxen E/C 500mg BD	500mg
Mefenamic acid 500mg TDS PRN	500mg
Tramadol 50–100mg TDS PRN	50–100mg
Gabapentin 300mg TDS	300mg
Amitriptyline 25mg ON	25mg
Zopiclone 7.5mg OD	7.5mg
Pantoprazole 40mg OD	40mg
Mirtazapine ON	45mg
Quetiapine 50mg OD ON	50mg
Quetiapine	100mg
Nicorette 25mg OM	25mg

posterior to the tip of the frontal horn and just above the corpus callosum, with a gyral entry point near the coronal suture just lateral to the target. The right was similarly targeted. The patient's head was carefully fixed to the operating table and prepped in the usual fashion with double chlorhexidine. A left frontal scalp entry point was marked by methylene blue dye using the drill bit and stereotactic frame, and 5ml of 0.5% bupivacaine and adrenaline was infiltrated into the scalp. A 3cm linear incision was made and scalp haemostasis obtained. The skull entry point was marked with methylene blue dye and a pilot drill used to mark a divot. A Synthes 13mm titanium mini-plate was loosely screwed to the skull. The 2.7mm stereotactic drill was then used to penetrate the skull and dura.

At the point of durotomy, the patient experienced a self-terminating generalised tonic–clonic seizure lasting <1 min. The patient received a loading dose of 1g levetiracetam intravenously. The decision was made to proceed with lead implantation following the self-terminating seizure.

The closed Nashold biopsy needle was slowly passed to target after confirmation of its accuracy on the phantom. The deep brain electrode was then passed to target. The electrode was fixed in position with a silk tie marking its skull entry point and the mini-plate secured over it. Bone wax was used to seal the hole. The process was repeated on the right side of the head with minimal venous bleeding. The whole surgery from skin incision to closure took 40 min.

The patient was found to have fixed dilated pupils on first assessment immediately after the operation was terminated, while still under general anaesthesia. A postoperative CT confirmed appropriate electrode position and accuracy with no haemorrhage or brain swelling. The stereotactic frame was removed and the patient positioned supine with their head in a horseshoe and turned to the right. A pacemaker was inserted through a left subclavicular incision above pectoralis fascia. The extension leads were tunnelled via a left posterior auricular incision. The pacemaker was kept switched off.

After surgery, the patient remained with fixed dilated pupils, bradycardia of 45bpm and hypotension with minimal respiratory effort. He was catheterised and transferred to the intensive care unit (ICU) intubated. A dose of 1.2g of intravenous atropine failed to improve the bradycardia 6h after surgery and so overdose of intrathecal baclofen potentiated by general anaesthesia causing severe brainstem depression was diagnosed. The intrathecal baclofen pump was aspirated and emptied aseptically by the neurosurgeon at midnight as an emergency 8h after surgery. A volume of 15ml was calculated to be remaining in the pump and 15ml of baclofen was aspirated. The patient briefly obeyed commands when he was rolled and he attempted to self-extubate overnight. He was kept comfortably sedated until extubation the next day.

On day 1 after surgery the patient was well with no neurological deficit and reasonable pain control, but still had an unsteady gait, with dilated pupils. The Flowonics Prometra II baclofen pump was interrogated and found not to be malfunctioning. Pupils returned to normal size 2 days later and the patient experienced minimal pain and spasms. The intrathecal pump was refilled with 2mg/ml baclofen on postoperative day 3 and restarted at 430μg/24h (half the previous normal flow rate of 860μg/24h). All normal medicines (gabapentin, amitriptyline, tramadol, mirtazapine, quetiapine and zopiclone nocte) were reintroduced by postoperative day 4. The patient recovered on the ICU until postoperative day 5 when oral baclofen cover 20mg TDS introduced. Hospital discharge after a full recovery was 6 days after the initial operation. This was maintained at follow up 12 months after surgery with satisfactory pain relief with a self-rated 50% reduction in pain. A time course of the procedure and admission course can be found in Figure 1.

The patient gave their written informed consent to publish their case and their identity has been anonymised.

Discussion

Delivery of intrathecal baclofen via a surgically implanted pump is an increasingly utilised method of treating spasticity arising from both spinal and central aetiologies. As a gamma-aminobutyric acid (GABA) agonist, baclofen acts on GABA-B receptors that elicit both pre- and post-synaptic inhibition.[1] The receptors are distributed widely throughout the nervous system, including in the thalamus and cerebellum dorsal horns of the spinal cord, allowing baclofen to produce an inhibition of spasticity. Because of its relative inability to cross the blood–brain barrier despite good oral bioavailability, intrathecal administration of baclofen produces an excellent therapeutic response at a fraction of the equivalent oral dose required.

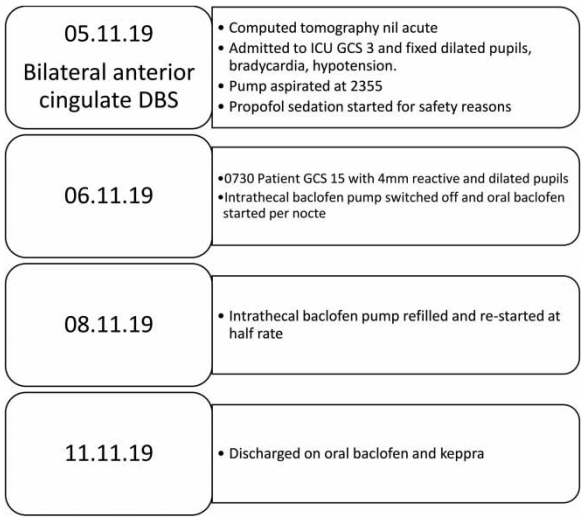

Figure 1 Timeline of procedure and admission

Complications pertaining to intrathecal baclofen administration are related to implantation of the device, failure of the device, withdrawal or toxicity related to baclofen itself.[2] Baclofen overdose mimicking brainstem death has been reported rarely in the literature to date.[3–8] Intrathecal baclofen overdoses in general can be due to pump malfunction, catheter malfunction and incorrect programming. The resultant effects include flaccid paralysis, bradycardia, hypotension, respiratory depression and central nervous system depression, but rarely do they mimic brainstem death following an unrelated surgical procedure. The emergent management of such a complication is widely accepted to involve emergency airway management and intensive care, with simultaneous intrathecal baclofen pump aspiration.[9] The pump can also be interrogated for malfunction at that point and intrathecal administration halted.

It is also vital to concurrently rule out other causes of these symptoms. In this case, the patient had been undergoing an invasive cranial procedure and was found to have fixed, dilated pupils immediately postoperatively. Intracerebral haemorrhage and fulminant cerebral oedema were ruled out with an immediate postoperative CT scan of the brain. Baclofen pump failure was implicated in the case of Tunali *et al*[5] but in our patient subsequent pump interrogation did not reveal any malfunction. Perioperative dosing was found to be correct and appropriate for the patient. It is also worth noting that a decision was made to proceed to lead implantation despite the self-limiting intraoperative seizure, based on a balance of risk and benefit. At the point of seizure initiation only a durotomy had been performed, with no contact with the underlying parenchyma. It was deemed that the seizure would be highly unlikely to be due to an event such as an intracerebral haemorrhage and so the decision was made to proceed to lead implantation. An immediate post-implantation check CT addressed both lead positioning and ruled out an intracranial event.

Following aspiration of the pump and supportive therapy in the ICU, the patient recovered spontaneously and rapidly, negating the need for electroencephalography or further brainstem testing. This was especially true considering an absence of radiological evidence of devastating brain injury and the difficulty of ruling out persistent drug overdose.

It is possible that the some of the patient's other medicines, specifically gabapentin, potentiated the baclofen overdose. Such polypharmacy is common in patients receiving intrathecal pumps and drug interactions should be considered.[10] It is also likely that the concentration of intrathecal baclofen at last preoperative pump refill was higher than usual as the patient in retrospect reported being symptomatic since then, feeling drunk and unsteady.

It is important to note that serum and intrathecal levels of baclofen were not taken due to the patient's prompt neurological recovery and clinical suspicion of baclofen as the causative agent. Baclofen levels are not a routine laboratory measure in the United Kingdom and levels would likely have taken several days to return. Given the relatively short half-life of baclofen of around 2–6 h and the fact that the pump reservoir had been aspirated successfully, a watch-and-wait approach was implemented with supportive care of patient's airway, breathing and circulation. Some reports have advocated the administration of physostigmine in the absence of a known baclofen anatagonist[11] but this is not a currently accepted therapy for intrathecal overdose.[9,12]

Conclusion

In perioperative patients with intrathecal baclofen pumps in situ, baclofen toxicity should always be considered as a differential in perioperative complications, even if it is considered a rare event.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

All of the named authors have made substantial contributions to the conception or design of the work manuscript, revised it critically for important intellectual content; approved the final version to be published and have agreed to be accountable for all aspects of the work. They will ensure that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement

All data generated or analysed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

References

1. Benarroch EE. GABAB receptors. *Neurology* 2012; **78**: 578. http://n.neurology.org/content/78/8/578.abstract
2. Cooper D, Bergman J. Massive baclofen overdose. *Crit Care Resusc: J Australas Acad Crit Care Med* 2000; **2**: 195–197.
3. Sullivan R, Hodgman MJ, Kao L, Tormoehlen LM. Baclofen overdose mimicking brain death. *Clin Toxicol* 2012; **50**: 141–144. https://pubmed.ncbi.nlm.nih.gov/22292975/ (cited 2021 May 12).
4. Romijn JA, Lieshout JJV, Velis DN. Reversible coma due to intrathecal baclofen. *The Lancet* 1986; **328**: 696. https://pubmed.ncbi.nlm.nih.gov/2876176/ (cited 2021 May 12).
5. Tunali Y, Hanimoglu H, Tanriverdi T *et al*. Intrathecal baclofen toxicity and deep coma in minutes. *J Spinal Cord Med* 2006; **29**: 237–239. https://pubmed.ncbi.nlm.nih.gov/16859228/ (cited 2021 May 12).
6. Ostermann ME, Young B, Sibbald WJ, Nicolle MW. Coma mimicking brain death following baclofen overdose. *Intensive Care Med* 2000; **26**: 1144–1146. https://pubmed.ncbi.nlm.nih.gov/11030173/ (cited 2021 May 12).
7. Stroud J, Scattoloni J, Blasingim M, Nafiu OO. Intrathecal baclofen toxicity: An unusual cause of paediatric postoperative coma and respiratory depression. *Eur J Anaesthesiol* 2014; **31**: 334–336. https://journals.lww.com/ejanaesthesiology/Fulltext/2014/06000/Intrathecal_baclofen_toxicity__An_unusual_cause_of.9.aspx
8. Pearson RP, Hoang LK, Roufail J *et al*. Baclofen toxicity mimicking brain death: A case report of a pediatric patient. *Pediatr Emerg Care* 2021; **37**: e141–e146. https://journals.lww.com/pec-online/Fulltext/2021/03000/Baclofen_Toxicity_Mimicking_Brain_Death__A_Case.23.aspx
9. Watve SV, Sivan M, Raza WA, Jamil FF. Management of acute overdose or withdrawal state in intrathecal baclofen therapy. *Spinal Cord* 2012; **50**: 107–111.
10. Murphy L, Wolfer H, Hendrickson RG. Toxicologic confounders of brain death determination: A narrative review. *Neurocrit Care* 2021; **34**: 1072–1089. https://pubmed.ncbi.nlm.nih.gov/33000377
11. Hsieh JC, Penn RD. Intrathecal baclofen in the treatment of adult spasticity. *Neurosurg Focus* 2006; **21**: E5. https://thejns.org/focus/view/journals/neurosurg-focus/21/2/article-pE5.xml
12. Saltuari L, Baumgartner H, Kofler M *et al*. Failure of physostigmine in treatment of acute severe intrathecal baclofen intoxication. *N Engl J Med* 1990; **322**: 1533–1534.