SHORT REPORT

Gabapentin in the management of dysautonomia following severe traumatic brain injury: a case series

Ian J Baguley, Roxana E Heriseanu, Joseph A Gurka, Annette Nordenbo, Ian D Cameron

J Neurol Neurosurg Psychiatry 2007;78:539–541. doi: 10.1136/jnnp.2006.096388

The pharmacological management of dysautonomia, otherwise known as autonomic storms, following acute neurological insults, is problematic and remains poorly researched. This paper presents six subjects with dysautonomia following extremely severe traumatic brain injury where gabapentin controlled paroxysmal autonomic changes and posturing in the early post-acute phase following limited success with conventional medication regimens. In two subjects, other medications were reduced or ceased without a recurrence of symptoms. It is proposed that medications that can block or minimise abnormal afferent stimuli may represent a better option for dysautonomia management than drugs which increase inhibition of efferent pathways. Potential mechanisms for these effects are discussed.

Dysautonomia, otherwise known as “autonomic storm”, is a distinct clinical syndrome affecting a subgroup of survivors of severe traumatic brain injury (TBI).¹ The syndrome consists of paroxysmal autonomic nervous system (ANS) changes (for example, increased heart rate, respiratory rate, temperature, blood pressure and sweating) accompanied by various forms of muscle overactivity (for example, decerebrate or decorticate posturing, dystonias, rigidity and spasticity). Numerous authors have noted a link between the onset of paroxysms and various noxious, although in some cases quite trivial, stimuli, including endotracheal tube suctioning and passive movements such as turning, moving a limb or bathing.^{1–7}

Dysautonomia should be managed aggressively as there are good reasons to believe that lack of diagnosis and undermanagement contributes to unnecessary morbidity. In particular, core temperatures above 38–39°C produce neuronal death in various animal models of brain injury.^{8–9} These temperatures are present in 68% of people following severe TBI¹⁰ whereas mean maximal temperatures in dysautonomic subjects remain above this level for longer than 2 weeks.¹ The higher metabolic demands of posturing patients,¹¹ and prolonged abnormalities of gastrointestinal tract function,¹² result in a highly catabolic state producing an estimated 25% loss of body weight.¹ The resulting malnourishment places the individual at risk of developing critical illness neuropathy. Spastic tetraparesis in patients at rest and dystonic posturing during paroxysms are commonplace and, coupled with weight loss, increase the risks of pain, pressure areas and contractures. Lack of voluntary movement and the potential for “locked-in” syndromes to occur^{1–13} can result in undermanaged pain or a misdiagnosis of persistent vegetative state.

Pharmacological management is difficult and there are limited data available to guide decision making. Anecdotally, a number of medications have been reported to be beneficial but efficacy is often unpredictable or incomplete. The best available evidence for treatment efficacy, in order of available

evidence, is intravenous morphine, midazolam, drugs with sympathetic activity (alpha agonists and some beta blockers), bromocriptine and intrathecal baclofen.⁶ The efficacy of gabapentin in the management of dysautonomia has not been reported to date.

CASE REPORTS

Subjects were males in their late teens or early twenties who survived extremely severe TBI following high speed motor vehicle crashes. The injury suffered by subject No 3 was complicated by prehospital cerebral hypoxia. Subjects were transferred to inpatient rehabilitation with dysautonomic features in evidence (diagnosed according to previously published criteria¹). All subjects were minimally responsive at the time of admission to rehabilitation and had spastic tetraparesis.

The findings presented in this report followed the successful reduction of pain and spasticity in two subjects with late stage dysautonomic changes following severe TBI (subject Nos 1 and 2 in table 1). In these subjects, dysautonomic paroxysms had largely settled and gabapentin was commenced to treat presumed neuropathic pain syndromes. This reduced paroxysmal spasticity and pain in subject No 1 and improved spasticity and posturing in subject No 2 with gabapentin doses of 300 mg twice daily and 600 mg twice daily, respectively.

Subject No 3

Subject No 3 displayed dysautonomic paroxysms with abnormal posturing and agitation during episodes. Bromocriptine was initiated (5 mg three times daily, increasing to 10 mg three times daily) with minimal effect. He was commenced on regular oral morphine, titrated to minimise the degree of sedation and to reduce, but not stop, dysautonomic episodes. An intrathecal baclofen (ITB) pump was implanted 2 months after admission, reaching a stable dose of 370 µg daily. This markedly decreased tone and dysautonomic features while at rest and oral morphine was ceased. He continued to experience dysautonomic episodes when stimulated, particularly with muscle stretches and ranging of joints. A presumed neuropathic pain syndrome was treated with gabapentin 300 mg three times daily, 4 months after admission. This immediately decreased his dysautonomic paroxysms and apparent pain, with improved sleep and reduced agitation. Regular morphine was weaned off and then ceased without recurrence of symptoms and the ITB dose was weaned to 225 µg/day without an increase in spasticity.

Subject No 4

Subject No 4 developed severe dysautonomia in the ICU and was treated with beta blockers (50 mg metoprolol four times daily) and intravenous morphine. Multiple severe

Abbreviations: ANS, autonomic nervous system; ITB, intrathecal baclofen; TBI, traumatic brain injury

Table 1 Injury related variables and dysautonomic features at admission to rehabilitation

Subject No	Time to rehab admission (days)	Initial GCS	CT findings	Dysautonomic features					
				HR	RR	BP	Temp	Sweat	Post
1	89	4	R frontal lobe laceration, R SDH with midline shift, L temporal contusions, cerebral oedema, #BOS	-	-	-	+	+	+
2	66	3	Multiple petechial haemorrhages c/w DAI, R SDH with midline shift, pontine contusion, #L orbital floor	-	-	-	+	+	+
3	38	5	L SDH with midline shift, widespread petechial haemorrhages c/w DAI	+	+	?	+	?	+
4	42	4	L parietal contusions, R sided brainstem contusions, #BOS	+	+	?	+	+	+
5	29	3	L frontotemporal contusion with midline shift, L midbrain contusion, DAI, traumatic SDH	+	+	+	+	+	+
6	20	3	R frontoparietal SDH with midline shift, DAI, cerebral oedema	+	+	+	-	+	+

#, fracture; BOS, base of skull; c/w DAI, consistent with diffuse axonal injury; GCS, Glasgow Coma Score; L, left; R, right; SDH, subdural haematoma.

+/-, presence or absence of tachycardia (HR), tachypnoea (RR), hypertension (BP), unexplained fever (Temp), increased sweating (Sweat) or posturing (Post).

dysautonomic episodes continued on transfer to a neurosurgical high dependency unit and bromocriptine (dosages as for subject No 3) and intermittent doses of subcutaneous morphine were commenced with minimal effect. All microbiological screens were negative. Based on the previous subjects, gabapentin 300 mg twice daily was commenced on day 41 after the injury.

On admission to the rehabilitation ward the following day, the dysautonomic symptoms had settled and the subject was less agitated, had an improved sleep pattern and did not require morphine. Joint ranging and casting were performed without distress. The coincidental timing of the change in ward and cessation of his symptoms called the earlier diagnosis into question and gabapentin was ceased on day 49. All dysautonomic features recurred within 2 days, along with agitation and apparent pain. Gabapentin was recommenced on day 56 with dysautonomic paroxysms abating within 48 hours. Metoprolol and bromocriptine were sequentially ceased without return of ANS dysregulation.

Subject No 5

Subject No 5 was reviewed in the ICU 2 days prior to rehabilitation. At that time he was unresponsive and had severe autonomic dysfunction, marked sweating and extensor posturing of his lower limbs. These features were treated with clonidine, morphine and sufentanil infusions without effect. Three hours after an initial dose of gabapentin 300 mg, the subject exhibited a decrease in tone and sweating. Gabapentin dosage was titrated up to 600 mg three times daily with an ongoing reduction in the number and duration of paroxysms. One month later, the subject had an ongoing central fever (temperature approximately 38.5°C with normal C reactive protein and leucocyte count). Dysautonomic features could still occur during stimulation.

Subject No 6

On admission to rehabilitation, subject No 6 exhibited dysautonomic paroxysms of elevated physiological variables, sweating and increased tone. Episodes were inducible (when positioned lying on either side) but could also occur without an obvious stimulus. He was initially treated with slow release morphine with minimal effect. Gabapentin was introduced after 1 month with a reduction in the frequency and severity of

episodes. Following the administration of gabapentin, paroxysms could be halted by changes in his positioning.

DISCUSSION

Six patients with dysautonomia following TBI were treated with gabapentin with a positive therapeutic response. The first two subjects were treated for neuropathic pain and spasticity without a clear change in their dysautonomic episodes. With this experience, gabapentin was introduced earlier during recovery in four further dysautonomic subjects with either resolution or diminution of paroxysmal ANS changes and posturing. The pattern of drug administration for subject No 4 was consistent with an open label alternating treatment (A-B-A-B) single case trial.

The subjects had been variously trialled on all classes of medication (other than midazolam), proposed to be efficacious for dysautonomia. Neither bromocriptine nor metoprolol appeared to reduce the number or intensity of paroxysms in these subjects. ITB reduced the severity but not the frequency of paroxysms as well as partially relieving muscle overactivity. Sodium valproate (a GABA receptor mediated anticonvulsant) had no effect on dysautonomia in subject No 1. Narcotic analgesia produced a limited response, thought to be due to the use of small doses to minimise the sedating effects in these patients.

The successful use of gabapentin for this condition has not been reported previously. Gabapentin is a GABA analogue which appears to have its effect on neuropathic pain via the alpha2delta subunit of voltage dependent Ca^{++} channels in the postsynaptic dorsal horns of the spinal cord.¹⁴⁻¹⁶ This effect is independent of GABA B receptors.¹⁴ It has a potent inhibitory effect in several types of neuropathic pain (mechanical and thermal hyperalgesia and allodynia)^{15, 17} and has also shown positive results in the treatment of tonic spasms associated with multiple sclerosis.¹⁷ Gabapentin also has cerebral effects and has been reported to be neuroprotective in animal models of brain injury.¹⁸

In TBI, most reports of gabapentin usage have related to seizure and spasticity management. Experience in the management of central/neuropathic pain syndromes in TBI is difficult to locate in the literature. While approximately 50% of moderate/severe TBI patients present with chronic pain problems,^{19, 20} the prevalence of neuropathic pain is less clear. However, the effective treatment of pain in severe TBI survivors has been reported to reduce irritability and agitation and

improve cognitive function,²⁰ as well as improving general outcomes following trauma.²¹ This poses a problem as it is not usually possible to determine the extent of pain experienced by a dysautonomic patient, neuropathic or otherwise, because of their limited ability to interact with their environment.

In previous research, ITB has been reported to control unresponsive "autonomic storm" phenomena during the initial recovery phase although the pathophysiological basis for this effect was unknown.^{22–23} Baclofen is a GABA B receptor agonist and little of the drug reaches the brain when administered intrathecally, resulting in a primary effect at inhibitory interneurons in the spinal cord.^{24–25} At this level, ITB has both antispasticity^{26–27} and antinociceptive effects.^{28–29} While both gabapentin and ITB act in the dorsal horn of the spinal cord, in the present case series ITB was less effective than gabapentin where the two interventions were used concomitantly. ITB reduced spasticity and the overall severity of ANS disturbance without significantly decreasing the frequency of paroxysms or dystonic posturing. Gabapentin appeared to reduce or prevent paroxysms in affected subjects, allowing an overall reduction in medications, including ITB, without recurrence of symptoms.

While gabapentin may simply be treating neuropathic pain in the subjects in this case series, the diagnosis of neuropathic pain is not sufficient to explain these subjects' stereotypical dysautonomic response patterns. Based on the effect of gabapentin in neuropathic pain subtypes and the pharmacology of ITB (discussed above), it is possible that both drugs act to normalise modulation of afferent stimuli in dysautonomic subjects by increasing inhibitory drivers within the spinal cord, preventing the onset of the efferent arm of the syndrome. If confirmed, this represents a more holistic approach than using drugs that only reduce efferent activity (eg, decreasing ANS features with beta blockers).

The main weakness of this series is that only subject No 4 was rechallenged with gabapentin to confirm the drug effect, but all subjects showed a consistent pattern of response on commencement of the drug. The pattern of these responses suggests a similarity between dysautonomia and autonomic dysreflexia, a theoretical model that can readily be tested in future research. At the very least, this case series suggests that neuropathic pain may act as a driver for dysautonomia and should be considered in any treatment paradigm.

Authors' affiliations

Ian J Baguley, Roxana E Heriseanu, Joseph A Gurka, Brain Injury Rehabilitation Service, Westmead Hospital, Westmead NSW, Australia
Annette Nordenbo, Brain Injury Unit, Hvidovre University Hospital, Hvidovre, Denmark
Ian D Cameron, Rehabilitation Studies Unit, University of Sydney, Sydney, Australia

Competing interests: None.

Correspondence to: Dr Ian J Baguley, Brain Injury Rehabilitation Service, Westmead Hospital, PO Box 533, Wentworthville NSW 2145, Australia; ianb@biru.wsahs.nsw.gov.au

Received 23 April 2006
 Revised 26 November 2006
 Accepted 30 November 2006

REFERENCES

- 1 Baguley IJ, Nicholls JL, Felmingham KL, *et al*. Dysautonomia after traumatic brain injury: a forgotten syndrome? *J Neural Neurosurg Psychiatry* 1999;**67**:39–43.
- 2 Sandel ME, Abrams PL, Horn LJ. Hypertension after brain injury: case report. *Arch Phys Med Rehabil* 1986;**67**:469–72.
- 3 Boeve BF, Wijdicks EF, Benarroch EE, *et al*. Paroxysmal sympathetic storms ("diencephalic seizures") after severe diffuse axonal head injury. *Mayo Clin Proc* 1998;**73**:148–52.
- 4 Russo RN, O'Flaherty S. Bromocriptine for the management of autonomic dysfunction after severe traumatic brain injury. *J Paediatr Child Health* 2000;**36**:283–5.
- 5 Cuny E, Richer E, Castel JP. Dysautonomia syndrome in the acute recovery phase after traumatic brain injury: relief with intrathecal baclofen therapy. *Brain Inj* 2001;**15**:917–25.
- 6 Baguley IJ, Cameron ID, Green AM, *et al*. Pharmacological management of dysautonomia following traumatic brain injury. *Brain Inj* 2004;**18**:409–17.
- 7 Lemke DM. Riding out the storm: sympathetic storming after traumatic brain injury. *J Neurosci Nurs* 2004;**36**:4–9.
- 8 Minamisawa H, Smith M-L, Siesjo BK. The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. *Ann Neurol* 1990;**28**:26–33.
- 9 Wass CT, Lanier WL, Hofer RE, *et al*. Temperature changes of > or = 1 degree C alter functional neurologic outcome and histopathology in a canine model of complete cerebral ischemia. *Anesthesiology* 1995;**83**:325–35.
- 10 Albrecht RF, Wass CT, Lanier WL. Occurrence of potentially detrimental temperature alterations in hospitalized patients at risk for brain injury. Intrathecal baclofen alleviates autonomic dysfunction in severe brain injury. *Mayo Clin Proc* 1998;**73**:629–35.
- 11 Clifton GL, Robertson CS, Choi SC. Assessments of nutritional requirements of head-injured patients. *J Neurosurg* 1986;**64**:895–901.
- 12 Ott L, Young B, Phillips R, *et al*. Altered gastric emptying in the head-injured patient: relationship to feeding intolerance. *J Neurosurg* 1991;**74**:738–42.
- 13 Scott JS, Ockey RR, Holmes GE, *et al*. Autonomic dysfunction associated with locked-in syndrome in a child. *Am J Phys Med Rehabil* 1997;**76**:200–3.
- 14 Sutton KG, Martin DJ, Pinnock RD, *et al*. Gabapentin inhibits high-threshold calcium channel currents in cultured rat dorsal root ganglion neurones. *Br J Pharmacol* 2002;**135**:257–65.
- 15 Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. *Anaesthesia* 2002;**57**:451–62.
- 16 Cheng JK, Chiou LC. Mechanisms of the antinociceptive action of gabapentin. *J Pharmacol Sci* 2006;**100**:471–86.
- 17 Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs* 2000;**60**:1029–52.
- 18 Dooley DJ, Mieske CA, Borosky SA. Inhibition of K(+)-evoked glutamate release from rat neocortical and hippocampal slices by gabapentin. *Neurosci Lett* 2000;**280**:107–10.
- 19 Lahz S, Bryant RA. Incidence of chronic pain following traumatic brain injury. *Arch Phys Med Rehabil* 1996;**77**:889–91.
- 20 Nicholson K. Pain, cognition and traumatic brain injury. *NeuroRehabilitation* 2000;**14**:95–103.
- 21 Cohen SP, Christo PJ, Moroz L. Pain management in trauma patients. *Am J Phys Med Rehabil* 2004;**83**:142–61.
- 22 Cuny E, Richer E, Castel JP. Dysautonomia syndrome in the acute recovery phase after traumatic brain injury: relief with intrathecal Baclofen therapy. *Brain Inj* 2001;**15**:917–25.
- 23 Becker R, Benes L, Sure U, *et al*. Intrathecal baclofen alleviates autonomic dysfunction in severe brain injury. *J Clin Neurosci* 2000;**7**:316–19.
- 24 Kroin JS, Bianchi GD, Penn RD. Intrathecal baclofen down-regulates GABAB receptors in the rat substantia gelatinosa. *J Neurosurg* 1993;**79**:544–9.
- 25 Allerton CA, Boden PR, Hill RG. Actions of the GABAB agonist, (–)-baclofen, on neurones in deep dorsal horn of the rat spinal cord in vitro. *Br J Pharmacol* 1989;**96**:29–38.
- 26 Ivanhoe CB, Tilton AH, Francisco GE. Intrathecal baclofen therapy for spastic hypertonia. *Phys Med Rehabil Clin N Am* 0 AD/11 2001;**12**:923–38.
- 27 Guillaume D, Van Havenbergh A, Vloeberghs M, *et al*. A clinical study of intrathecal baclofen using a programmable pump for intractable spasticity. *Arch Phys Med Rehabil* 2005;**86**:2165–71.
- 28 Smith PA. Neuropathic pain: drug targets for current and future interventions. *Drug News Perspect* 2004;**17**:5–17.
- 29 Baguley IJ, Bailey KM, Sleva-Younan S. Prolonged anti-spasticity effects of bolus intrathecal baclofen. *Brain Inj* 2005;**19**:545–8.