UQU Med. J Vol. 4, No.2, pp. 27-33 (2014)
01-06 © The University Press

UQU Med. J

Case report and literature review

Spasticity as a complication of antiepileptic drugs: case report and literature review

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الشناج نتيجة مضاعفات الأدوية المضادة للصرع: تقرير حاله

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الملخص

يعرف الشناج بأنه زيادة في ردود الفعل لتمدد العضلات -المعتمد على السرعة - مع زيادة مصاحبة لهزات الوتر (ردود فعل طوري أو مرحلي). يعتبر الشناج من أكثر الأعراض شيوعاً ويشكل تحدياً كبيراً لفريق التأهيل الطبي. الشناج الناجم عن تناول العقاقير المضادة للصرع هو أمر نادر الحدوث.

تقرير حاله: نتقدم بتسجيل حالتين لمريضين تعرضا لشناج عابر مصاحب لتناول كميات كبيرة من أدوية مضادة للصرع ونحاول أن نتفهم الأسباب.

االحلاصة: الشناج نتيجة تناول جرعة زائدة من الأدوية المضادة للصرع (لاموتريجين وحامض فالبرويك) هو أمر نادر الحدوث. في الواقع، أن حدوث من هذه الأعراض كمضـــاعفة لتناول عقار حامض الفالبرويك لم يتم تســـجيلها من قبل. المريض الذى حدث لة الشناج نتيجة تناول عقار لاموتريجين تواكب معة نوبات تشنج متكررة. ان الآلية التي تسببت في حدوث الشـناج غير معروفة ولكن نعتقد أن هناك اختلال في التوازن بين المدخلات المثبطة والمثيرة مما تسـبب في حدوث هذه الحالة.

ABSTRACT

Background:
Spasticity has been narrowly-defined as a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks (phasic reflexes). It is a common clinical finding and a major challenge to the rehabilitation team. Spasticity caused by antiepileptic drugs is a rare occurrence.
Case report: We report two patients with transient, marked spasticity in association with the antiepileptic drugs; Valproic acid (VPA) and lamotrigine (LTG) overdose. The patient with LTG overdose has also developed status epilepticus.
Conclusion: Spasticity as a complication of antiepileptic drugs overdose (VPA and LTG) or toxicity is a rare occurrence. The mechanism, by which spasticity occurred, is unknown but an imbalance between the inhibitory and excitatory inputs might be the cause.

Keywords: *Spasticity, AEDs, Valproic acid, Lamotrigine*

INTRODUCTION

Spasticity has been narrowly-defined as a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks (phasic reflexes). Spasticity is a common clinical finding and a major challenge to the rehabilitation team. It is usually caused by chronic neurological conditions, notably head and spinal cord injury, stroke, cerebral palsy, traumatic brain and multiple sclerosis. Spasticity caused by antiepileptic drugs (AEDs) is a rare occurrence. We report two patients from neuroscience center at University Hospital, London Ontario Canada, with Valproic acid (VPA) and lamotrigine (LTG) overdose, respectively .

Case 1

A 53-year-old woman, with a background history of bipolar disorder and hypertension, was found by her husband unresponsive with bottles of VPA and Ramipril beside her bed. She was brought to a peripheral hospital where she was found to be hemodynamically unstable, with low blood pressure and shallow breathing. She was intubated, artificially ventilated and transferred to our center for further management and care. She also received activated charcoal, through a nasogastric tube (NGT) and had bowel irrigation .

Vital signs at presentation at our centre included a normal temperature, a heart rate of 55 beats per minute and a persistently low blood pressure at around 70/30 mmHg. Inotropic support was started using a combination of vasopressin, norepinephrine, epinephrine and dopamine.

Cardiovascular, chest and abdominal examinations were unremarkable. The Glasgow Coma Scale (GCS) was 3/15, pupils were equal at 5 mm and minimally reactive to light, and oculoccephalic, gag, and corneal reflexes were absent. Tone was spastic in all four extremities, the lower more than upper. Deep tendon reflexes were symmetrically brisk with sustained clonus elicited. The Babinski sign was positive bilaterally.
Initial blood work showed normal complete blood count (CBC), coagulation profile, electrolytes, glucose, amylase, urea and liver functions tests (LFT). Serum creatinine was

elevated at 163 µmol/L (normal range 62-124) and then increased one day later to 270 µmol/L. Serum lactate was high at 9 mmol/L (normally 0.5-2.2 mmol/L). Transient elevation of creatine kinase (CK), up to 933 U/L (normal range 25-195 U/L) was noted without a significant rise in troponin.

Serum VPA level was 6000 µmol/L (therapeutic range 350-700). Toxicology screen was negative for benzodiazepine, phencyclidine, cocaine, amphetamine, opiates, barbiturates, tricyclic antidepressants, acetaminophen, and salicylates. Electrocardiogram (ECG) showed a prolonged QT interval but no features of ischemia.

Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were normal. Electroencephalography (EEG) obtained on the third day of admission showed significant slowing, maximal in the posterior head region (suppression) with slight reactivity to verbal stimuli. No epileptiform discharges were noted.

The patient was admitted to intensive care unit (ICU) and received Continuous Veno-Venous Hemodialysis (CVVHD) sessions for the first three days. She was maintained on carnitine, up to 3600 mg/day, throughout her hospitalization.

Two days after admission, the patient started to have minimal limb movement. Her pupils became briskly reactive to light, and she regained her corneal and oculocephalic reflexes. Tone remained spastic in all four extremities. Three days later, she started withdrawing to painful stimuli and was moving all limbs spontaneously. She became hemodynamically stable and was weaned off all inotropes. Her renal function tests normalized and she had adequate urine output. On the tenth day, she was obeying commands extubated and subsequently transferred to the ward. Two weeks following overdose, she was sent back to her referring hospital. She had a normal neurological examination with complete resolution of spasticity, hyper-reflexia, and up-going toes.

Case 2

A 46-year-old man who had a history of bipolar disorder and a single generalized tonic-clonic (GTC) seizure, post alcohol withdrawal, 2 years ago. He developed repeated attacks of prolonged GTC seizure few hours following suicidal ingestion of LTG, estimated at 6000 mg. He was managed in emergency department (ER), university hospital, London Ontario Canada with intravenous lorazepam, phenytoin, phenobarbital, midazolam, propofol, and then thiopental. He was intubated, artificially ventilated and transferred to ICU where activated charcoal was given through NGT.

Systemic examinations, including vital signs, were normal. Neurologically, the patient was comatose with GCS of 5/15. He had flexionto pain in the upper extremities, but not the lower. Cranial nerves, that could be tested, were normal. Brainstem reflexes were present. He was generally spastic with brisk deep tendon reflexes. Sustained Clonus was elicited in both ankles. Plantar responses were flexor bilaterally.
Initial investigations showed normal CBC, electrolytes, urea, creatinine, blood gasses and LFT. CT and MRI of brain were normal. Cerebrospinal fluid (CSF) was normal. LTG serum concentration was markedly elevated at 100 µmol/L (therapeutic range: 1-4 µmol/L). Toxicology screen was negative for phencyclidine, cocaine, amphetamine,

opiates, barbiturates, tricyclic, antidepressants, acetaminophen, and salicylates; however, benzodiazepine screening was positive.

Continuous EEG monitoring showed mild to moderate, non-specific slowing with no epileptiform discharges. He remained hemodynamically stable throughout hospitalization and started to recover rapidly. The spasticity and clonus disappeared. Repeated EEG three days later became completely normal, paralleling the complete recovery of the first patient.

DISCUSSION

More than 20 antiepileptic drugs are currently available for use. In the past, carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid have been the usual medications to treat seizures and epilepsy. Traditionally, these medications have been called" older" group. Since 1993, at least 10 new drugs have been released .

VPA is a short-chain branched fatty acid, which was introduced in early of 1960s. It is one of the most effective broad-spectrum AEDs for all types of seizures and epilepsies. It is considered the drug of first choice for the treatment of typical absences, myoclonic seizures, and GTC seizures, especially if these occur as part of the syndrome of idiopathic generalized epilepsy1. It is thought that it exerts its antiepileptic activity by at least two mechanisms, including elevation or augmentation of brain gamma aminobutaric acid (GABA) and frequency-dependent blockade of sodium channels2.

The mainstay of treatment of VPA overdose is supportive care. Nalaxone has been reported, in several case studies, to be useful in reversing CNS depression3,4. The mechanism by which Nalaxone exerts its effect here is unknown. Because of hemodynamic instability, CVVHD was done in the first case; as opposed to regular hemodialysis that was recommended by others; in patients with severe VPA toxicity (5).

LTG is a novel AED, a member of the phenyltriazine class, and is structurally unrelated to other antiepileptic drugs in current use. It is recommended for adjunctive use in partial seizures in children aged 2 years or older and in adult patients. It is also approved for adjunctive use in Lennox-Gastaut generalized seizures in adults and children6.

LTG is approved for monotherapy in adult patients converted from monotherapy with other enzyme-inducing antiepileptic drugs6. Although FDA approval is limited to these indications, LTG has been used experimentally in virtually all types of epilepsy including absence and reflex seizures, status epilepticus, and epilepsy refractory to other medications .

The exact mechanism of action of LTG is unknown, but it is thought to exert its antiepileptic activity by blocking voltage-dependent sodium current and by inhibiting the release of excitatory neurotransmitters, glutamate and aspartate. It also has little effect on serotonergic, dopaminergic, and adrenergic receptors7. LTG also acts as an

inhibitor of dihydrofolate reductase leading to decreased folate synthesis. This can potentially lead to significant drug interactions if other folate inhibiting drugs are co-administered. LTG has demonstrated melanin binding in rodent tissue. A minor 2-N-methyl metabolic product of LTG metabolism is known to cause prolongation of the PR interval, QRS complex widening and APV conduction block at high doses in rodents.

Spasticity has been narrowly defined as a motor disorder characterized by velocity dependent increase in tonic stretch reflexes (muscletone)inassociationwith exaggerated tendon jerks (phasic reflexes) and other features of the upper motor neuron syndrome (8). Spasticity is usually accompanied by permanent or intermittent weakness and clumsiness, flexor or extensor spasms, the 'clasp-knife' phenomenon, exaggerated reflexes, contractures and changes in posture.

The pathophysiology of spasticity is complex. It is likely that spasticity is not caused by a single mechanism, but rather by an intricate chain of alterations in different interdependent networks .

Normal muscle tone depends on the balance between inhibitory effects of interneurons including the presynaptic axo-axonic and Ia and Ib interneurons mediated by the dorsal reticulspinal tract and, facilitatory effects on extensor tone mediated by descending indirect activation pathway particularly the medial reticulospinal tract and to a lesser extent by the vestibulospinal tract9.
Figure 1 gives an overview of the spinal reflex circuits involved in the development of spasticity that have been investigated.over the past 50 years.

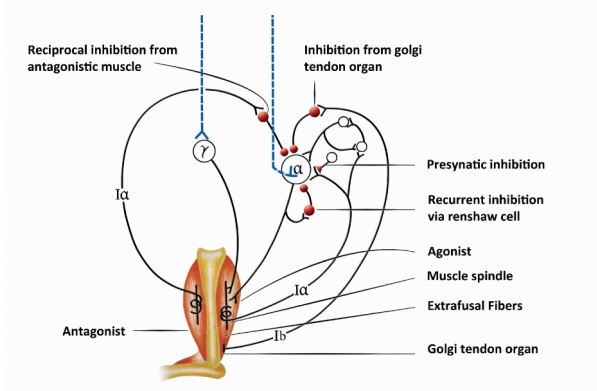

Figure 1: overview of the spinal reflex circuits involved in the development of spasticity.

The monosynaptic Ia excitation contributes to the major excitation underlying the dynamic and tonic components of the stretch reflex. However, many spinal reflex pathways may increase or decrease the effect of this monosynaptic excitation: excitation and inhibition from muscle spindle group II afferents; autogenetic inhibition from Golgi tendon organs (via Ib afferents); recurrent inhibition (via motor axon collaterals and Renshaw cells); presynaptic inhibition of Ia afferent terminals; and reciprocal inhibition from muscle spindle Ia afferents from the antagonist muscles.

It is unlikely that Renshaw cell (presynaptic) inhibition plays a role in our patients. The changes in reflex transmission in these pathways may depend both on an altered supraspinal drive, and on secondary changes at cellular level in the spinal cord below the lesion.

Reviewing the literature, only three cases of LTG-induced spasticity have been reported. Buckley et al. reported a 26-year-old man with temporal lobe epilepsy who had a deliberate self-poisoning with LTG. He had nystagmus, hypertonia and brisk reflexes. Symptoms and signs improved after stopping LTG. Briassoulis et al. reported a LTG

overdose in a 2-year-old child that resulted in upper motor neuron (UMN) signs, GTC seizures, and coma10.

Another case of LTG overdose in combination with VPA was reported in another adult patient11. The patient developed transient encephalopathy and diminished level of consciousness, with complete resolution of symptoms and signs after treatment.

The most likely proposed mechanism is deactivation of descending inhibitory pathways, especially the dorsal reticulospinal pathway, which is, in turn influenced by the cerebral cortex. Since our patients were profoundly intoxicated, the cortical facilitatory influence on the medullary reticular formation that projects to the dorsal reticularspinal pathway would be more affected than the ventral reticulospinal pathway that facilitates the spinal reflex arc .

We report two patients with VPA and LTG overdose that resulted in spasticity that recovered completely after the successful management in hospital. We propose that temporary loss of the inhibitory center in the brain stem had occurred which lead to the transient spasticity described above. The neurotransmitter(s) disturbance(s) that occurred may also be contributing factors. They are probably quite complex, as AEDs especially VPA may have multiple effects on the brain neurochemistry, including the opiate system, especially in the very high doses ingested by our patients. It may also cause reversible depression of all excitable tissues activity, the CNS being the most sensitive. It depresses the sensory cortex, decreases motor activity, alters cerebral function and produces drowsiness, sedation, and hypnosis.

CONCLUSION

Spasticity as a complication of AEDs overdose or toxicity is a rare occurrence. In fact, some AEDs, such as VPA and LTG are used to treat spasticity. We also report another patient with LTG overdose causing status epilepticus and spasticity. The mechanism by which spasticity occurred is unknown, but an imbalance between the inhibitory and excitatory inputs might be the cause.

ACKNOWLEGMENTS

We thank Dr. Nirmeen Zagzoog, Dr. Ahmed Attar and Dr. Abduljaleel Abdu for their support and cooperation.

DISCLOSURE OF BENEFIT:

We declare that there are no conflicting interests, and we are not supported or funded by any drug company.

REFERENCES

1. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. ILAE. Treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2006; 47(7):1094-120.
2. Uebachs M, Opitz T, Royeck M, Dickhof G, Horstmann MT, Isom LL, Beck H. Efficacy loss of the anticonvulsant carbamazepine in mice lacking sodium channel beta subunits via paradoxical effects on persistent sodium currents. J Neurosci. 2010;30:8489–8501.

3. Sanaei-Zadeh H. Use of naloxone in valproate overdose. Indian J Crit Care Med. 2012;16(4):246-7
4. Roberge RJ, Francis EH. Use of nalaxone in valporic acid overdose: case report and review. J Emerg Med. 2002; 22(1); 67-70.
5. Le Quang Thuan, Ngo Duc Ngoc, Pham Due. Effectiveness of Continuous Veno-Venous Hemofiltration and Intermittent Hemodialysis in the Treatment of Severe Acute Phenobarbital Poisoning. Asia Pacific Journal of Medical Toxicology 2013; 2(1):10-13.
6. Fallah R., Akhavan Karbasi S., Golestan M. Efficacy and Safety of Lamotrigine in Lennox - Gastaut Syndrome. Iran J Child Neurology. 2009; 3(3): 33-38.
7. Piotr Czapin´ski, Barbara Blaszczyk, Stanislaw J. Czuczwar, Mechanisms of Action of Antiepileptic Drugs. Curr Top Med Chem. 2005, 5 (3): 3-13.
8. Lance J. W. (1980). "Symposium," in Spasticity: Disordered Motor Control, eds Feldman R. G., Young R. R., Koella W. P., editors. (Chicago: Year Book Medical Pubs;), 485–495.
9. Bannatyne, BA. Liu, TT. Hammar I. Stecina K. Jankowska E. Maxwell, D. J. Excitatory and inhibitory intermediate zone interneurones in pathways from group I and II afferents; differences in axonal projections and inputs. J. Physiol. 2009; 587(2) 379-399.
10. Briassoulis G, Kalabalikis P, Tamiolaki M, Haizis T. Lamotrigine childhood overdose. Pediatr. Neurol. 1998; 19(3):239-42.
11. Davison AS, Milan AM, Roberts NB.The consequences of valproate overdose. Clin Chem. 2011; 57(9):1233-7