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Case Report

Autonomic Dysreflexia: Atypical Complication from Immediate Release Tapentadol

Claudia Diaz, BSc, PhD[1]*;Veli Solyali, BChiroSc, MChiro, PGCertResearchPrep, BForensicSc/BCriminology (Student)[2]

[1]*Charles Sturt University, Albury, NSW 2640, Australia*
[2]*Faculty of Science, Engineering and Built Environment, Deakin University, Geelong, Australia*

Corresponding author
Claudia Diaz, BSc, PhD
Senior Lecturer in Biomedical Sciences, Charles Sturt University, Albury, NSW, Australia; Tel. 0011 612 6051 9225; E-mail: cdiaz@csu.edu.au

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ABSTRACT

Neurological disorders are a ubiquitous part of our lives, and with innovative technological advancements there are increasing numbers of people being diagnosed with a variety of conditions. While these advances uncover the underlying pathological process, the requisite need to manage a patient's condition necessitates renewed vigour in the realm of key therapeutics. This case study looks at a patient with a rare neurological condition, transverse myelitis (TM), and a complication that many spinal cord injury patients suffer, autonomic dysreflexia (AD). However, what makes this case unique is when the patient was administered with immediate-release Tapentadol, a synthetic opioid, the patient suffered more frequent and prolonged attacks of AD. The exploration of the functional anatomy of TM as it applies to this case is highlighted, and how the role of Tapentadol was a causative agent in increasing the patient's AD.

Keywords
Spinal cord injury; Transverse myelitis; Pharmacokinetics; Opioids.

Abbreviations
TM: Transverse myelitis; CNS: Central nervous system; AD: Autonomic dysreflexia; VAS: Visual analogue scale; MET: Medical emergency team.

OVERVIEW

Transverse myelitis (TM) is an uncommon acquired neuro-immune spinal cord condition, characterised by inflammatory responses that can manifest with an acute or subacute progression of weakness, sensory deficiency and autonomic dysfunction.[1-3] TM has many and often varying aetiologies, chief among them a post-infectious complication, all the way to idiopathic. Nevertheless, irrespective of the underlying cause, the result for the patient is that the once normal flow of signals in the central nervous system (CNS) undergo a demyelination process, because of the inflammatory and autoimmune response.[2] As each case of TM will differ from case to case, each TM patient is unique, and a reminder of the basic principle that the anatomical structure governs physiological function.

While there is a wealth of literature available on the more common neurological disorders, TM is a rare neuro-immune condition, and it is beyond the scope of this case report to delve into all facets of the condition. However, the exploration of the complication of autonomic dysreflexia (AD) will be examined. First, through a clinical anatomy lens, we survey the underlying aetiology and pathophysiology borne by normal *versus* abnormal anatomy. Second, we explored the effects of analgesic pharmacological agents on the anatomical areas we examined earlier. Ultimately, applying functional anatomy and pharmacokinetics through our case study, we intend to better understand how TM and adverse reactions, such as AD, can impact treatment protocols, through documentation of this research.

CASE REPORT

In this case study, we discuss a 38-year-old male with TM presenting to the hospital emergency department, *via* paramedic assistance due to a sudden and insidious onset of AD. The patient

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had undergone recent laparoscopic surgery to remove a necrotic piece of bowel tissue, on the external aspect of the junction of the descending and sigmoid colon, 48-hours prior. The working diagnosis prior to imaging was diverticulitis, as the patient presented with a fever of 40 °C, abdominal tenderness, nausea and a visual analogue scale (VAS) score of 9 out of 10 for pain. Diagnosis, following imaging and at the time of surgical excision was epiploic appendagitis. The patient was discharged a few hours following the procedure, with prescribed rest and oxycodone for breakthrough pain relief. Upon returning home, the patient's demand for pain relief developed into pre-operative pain, and 10 mg of oxycodone was administered orally every six-hours. This pattern continued until the onset of the AD, and the call to the paramedics.

Autonomic dysreflexia is a loss of harmonised autonomic responses, which result in amplified sympathetic responses to stimuli below the level of spinal cord damage, as is the case with our TM patient, leading to turgid vasoconstriction and hypertension.[4] The patient's lesion due to the TM was located at the spinal cord level of T6, and due to the surgical intervention and ongoing irritation in his left iliac region, a region below T6, a cascade of neural signals was sent up the spinal cord and set the AD in motion. This is due to the lesions at T6 not allowing for the signals of the parasympathetic nervous system to counterbalance the influx of sympathetic overflow,[5] causing hypertension, flushing of the face, nasal congestion, thumping headache, piloerection, sweating above T6, cool and damp skin below T6. By the time the paramedics had arrived on the scene, the patient had started to convulse and had a seizure. He was treated *en route* to the emergency department with glyceryl trinitrate sublingual spray (0.4 mg/spray) and given a nasal dose of 0.1 mg of fentanyl, twice. The patient was stabilised in the emergency department and transferred into the hospital wards for observation, and to monitor his pain levels. Under the guidance of a consultant anaesthetist and pain specialist, the patient's medications were carefully monitored and oxycodone was ceased and replaced with Tapentadol: 50 mg sustained-release bd (twice a day), and 50 mg immediate-release qid (four times a day). While Clonidine was titrated up to 100 mg tid (three times a day), from bd and 180 mg of Diltiazem was prescribed by a consultant cardiologist as a prophylactic measure for the patient's hypertensive episodes, following a coronary angiogram to rule-out serious cardiac issues.

Within a day of commencing the Tapentadol course, the patient's episodes of AD began to increase in number and each progressive episode lasted longer. On one of the episodes the patient lost consciousness and a medical emergency team (MET) was called over the hospital emergency system. Upon regaining consciousness, the patient did not recall the episode or the events leading up to the MET call. Cardiac monitoring was subsequently used for a period of 96-hours. When a dose of the Tapentadol 50 mg immediate release was administered orally to the patient, within a 30 to 60-minute period, he would become hypertensive and start having an attack of AD. Oral glyceryl trinitrate (0.4 mg/spray) was administered when the monitors picked-up a spike in blood-pressure raising anything beyond a systolic level of 150 mmHg. During the peak of his AD episodes, monitors recorded hypertension at 240/130 mmHg and a cardiac beat per minute at 148. When the cardiologist and pain specialist reviewed the output from the monitor, they removed the Tapentadol immediate release from the treatment schedule and replaced it with Buprenorphine 0.4 mg of sublingual tablets tid. The patient's episodes of AD subsided over the following days, and he was discharged home, with a follow-up consultation with both specialists within the month.

DISCUSSION

Due to the pervasive nature of laparoscopic surgery to correct a piece of necrotic tissue in the left lower bowel region of the TM patient, while facing the consequence of sepsis, and having pain level increase pre- and post-surgery, the discharge procedure should be questioned in this complex case. Serious abdominal complications, including but not limited to gastrointestinal bleeding, gall stones, or appendicitis have previously raised concerns[4] related to AD and abdominal procedures for patients with spinal cord injuries at or above T6. The pathophysiology for AD to occur is due to the major splanchnic outflow, T6 to L2, which becomes disconnected from supraspinal control. Stimulation in the dorsal and spinothalamic tracts above the lesion level causes the intermediolateral column neurones to become activated by the collateral branches, causing norepinephrine spillover, resulting in hypertension, which can activate baroreceptors that induce vasodilation and bradycardia by the vagus nerve.

The activation of the body's sympathetic nervous system prepares an individual for a "fight-or-flight" response,[6] in preparation for heightened levels of activity to vital organs that require an increased chance of enduring a threat or confrontational situation. Such increases include the dilation of pupils to increase vision, constriction of blood vessels to areas the body deems not under threat, such as the skin or digestive tract, and diversion of more blood to skeletal muscles; dilation of bronchi in the lungs, thus increasing the capacity for oxygenation; increase in cardiac output increases, as the blood vessels around the heart dilate and the heart rate increases; and simultaneously, the release of epinephrine and norepinephrine that is stimulated by the adrenal medulla into the bloodstream. To initiate this physiological cascade of events, the CNS houses, in the spinal cord throughout the thoracic region and the upper two lumbar spinal segments, an arrangement of preganglionic neurones in an area of the cord known as the intermediolateral cell column (or grey matter), within the lateral horn.[7] The axons commencing in the intermediolateral cell column in the thoracic cord, the preganglionic cells, range a short distance to the sympathetic chain ganglia, running parallel and adjacent to the thoracic vertebrae: these are the primary source of sympathetic neurones of the autonomic nervous system which give rise to the fight-or-flight mechanisms to the body: smooth muscle, cardiac muscle and glands.[6] Additionally, there is a subdivision within the thoracic preganglionic fibres in the visceral nerves that course through to the adrenal medulla known as the splanchnic nerves are generally considered for having modified endocrine functioning, namely, the secretion of catecholamines into the bloodstream.

To counteract this overstimulation by the sympathetic nervous system, the parasympathetic nervous control is located predominantly throughout the brainstem region and travels through cranial nerves, primarily with the vagus nerve. As this is

above the level of T6, where the patient's lesion is found on the spinal cord due to the TM, neural signals descending the spinal column to attenuate the activity of the sympathetic overload, and AD, were unsuccessful in reaching their desired location. Therefore, pain signals being directed post-surgically from the patient's bowel triggered the AD by sending repeated pain signals to the spinal cord. This set out a chain reaction by the sympathetic nervous system, compounded by the addition of the opioid pain medication, and the lesion at T6. Thus, the inability for the signals from the brainstem to stabilise this reaction back to a homeostatic state caused the repeated sequence of attacks of AD.

The exploration as to the differences between the Tapentadol immediate release and sustained release will now be explored, as there is scant literature on patients with TM being treated with Tapentadol, and suffering from repeated attacks of AD.

As opioid use is well tolerated and established in an acute pain scenario,[8] semi-synthetic and synthetic opioid pharmacological agents have become established in the past decade, and one such example is Tapentadol. Tapentadol is the most recent of the synthetic opioids to become widely distributed.[9] Typically, opioids are a potent analgesic, as they exert their major pharmacologic effects on the CNS.[9] The effect of not losing consciousness is the underlying clinical benefit to utilising opioids as a therapy, while the analgesia may be accompanied by feelings of exultation, drowsiness or a transient cognitive decline.[8] What makes opioids unique is their ability to bind to specific receptor sites, of which there are three: μ (mu), κ (kappa), and δ (delta). For this case report, we will concentrate on the μ receptor, as Tapentadol's pharmacokinetics relies on this receptor binding site.[10] The pharmacologic profile of the μ receptor is that it generates CNS depression, respiratory depression, miosis, euphoria, a reduction in digestive motility, hypothermia, bradycardia, and physical dependence and tolerance.[9] Tapentadol is a centrally-acting analgesic, which has been synthetically prepared to combine two mechanisms of action: act as a μ-opioid receptor and noradrenaline uptake inhibitor.[10] The drug was approved for use in the United States in 2008,[9] in 2011 for the Australian market,[11] where the current case study is being reported. Tapentadol was available in two forms, a sustained release oral tablet and an immediate release oral tablet in a variety of concentrations.[10]

In a post-marketing study carried out by the drug manufacturer Grünenthal GmbH,[10] the overall safety and adverse drug reactions of Tapentadol were analysed for reported cases, globally. The most prevalent side-effect was nausea in their systematic review for all patients grouped together. Other side-effects included: dizziness, headache, drug ineffectiveness, hallucination, vomiting, somnolence, feeling abnormal, hyperhidrosis, fatigue, confusion, constipation, dyspnoea, and pain.[10] Of note, there were no reports of anything akin to AD, however, the authors did note that these were the reported events and there was the possibility that there may be unreported side-effects.

As this case report centres around the drug Tapentadol in its two forms, immediate-release and sustained-release, it is important to distinguish between them and ascertain why they had such a profoundly divergent outcome on the patient. Both drugs are designed to act by undergoing phase I metabolism by N-demethylation and alkyl hydroxylation,[9] and their agonistic behaviour to bind to a μ-opioid receptor, and inhibit the reuptake of norepinephrine, thus increasing the blood levels of norepinephrine. This is where the distinction occurs, the benefits to extending the release of the active ingredient, Tapentadol into the bloodstream and inhibiting the reuptake of norepinephrine, attenuates adverse effects, while sustaining bloodstream levels for a longer period, rather than in a short burst, which is the case with the immediate-release.[12,13] When a dose of immediate-release is ingested, rates of absorption are sped-up. Thus, the availability of the active ingredients are available within 30-minutes to 1-hour, and its peak levels are at 1.25 hours.[14] In contrast, sustained-release Tapentadol reaches its peak between 3 to 6-hours.[14]

This extreme overload on the patient's body and the ongoing attacks of AD can be attributed to the functions of the hormone norepinephrine, where an increase in heart rate and force of contractility occurred, and the diversion of blood to skeletal muscles, as the vasoconstriction to non-vital visceral organs and skin (in a fight- or-flight situation), and hypertension resulted from the vasoconstriction of systemic blood vessels. This phenomenon was described earlier as the fight-or-flight response of the body, or the sympathetic nervous system getting ready to go into battle or run away from danger. Unfortunately for the patient, his lesion was located at T6 and safeguard mechanisms to shut down or reverse this process were blocked from getting the message through the neural cabling system, the spinal cord.

CONCLUSION

Patients with complex or rare medical conditions provide the medical fraternity with a platform to allow the profession to not only acquire a growing body of knowledge, and establish frameworks for which healthcare providers are equipped with the training, and experience to be able to recognise medical emergencies sooner for the benefit of these patients. The above case study highlights the importance of a working knowledge of applied anatomy as a fundamental and underpinning the very crux of diagnostic rapidity, but also exactitude. TM is a serious neurological disorder, which can have effects on varying functions, dependent on the location of the patient's lesion. For many people with spinal cord injuries above the level of T6, unfortunately the perils of AD are all too familiar; however, if the injury is below this level this neurological complication is not feasible. The addition of pharmacologic agents to disrupt AD has been advantageous in its treatment, yet, it is also these drugs that can intensify the signs and symptoms of AD within moments of ingesting them. With the cessation of immediate-release Tapentadol in this specific case, the patient no longer suffered from attacks of AD.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

The authors have full consent of the patient to participate in this

case report, and retain their full informed consent form.

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