



Case report

Change of pitch due to carbamazepine and oxcarbazepine independently

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1. Introduction

Absolute pitch (AP) is the term used to denote the cognitive ability to spontaneously and effortlessly identify and vocally produce specific musical tones without a reference note.¹ Abnormalities of pitch perception are a recognized rare side effect of carbamazepine (CBZ). The mechanism of this side effect is not clear. The same symptom may also be associated with oxcarbazepine (OXC) although this is even rarer. We report a twenty-two year-old woman with partial and prolonged secondarily generalized seizures who complained of a one semitone lowering of pitch perception during CBZ therapy. After stopping CBZ and switching to OXC, she noticed that pitch perception was one semitone higher than normal.

2. Case report

A twenty-two year-old right handed English woman had been followed up in outpatients since the age of thirteen, with the diagnosis of symptomatic focal epilepsy with complex partial and prolonged secondarily generalized seizures. MRI brain showed bilateral periventricular nodular heterotopia thought to be the etiology of her epilepsy. She was also known to have autoimmune

hypothyroidism for thirteen years. She had no family history of epilepsy and her neurological examination was unremarkable. Lamotrigine, topiramate and levetiracetam were tried as monotherapies and were discontinued because of side effects and inadequate seizure control. CBZ which had not been used as a first-line therapy to avoid worsening of hypothyroidism, was used after the aforementioned drugs and had been both the most effective and the best tolerated agent. The patient was a keen pianist and cellist and had AP. She was hoping to embark upon a career as a professional musician. She was able to identify any given musical note without an external reference. She noted, during review, that she had experienced a global down-shift of pitch by one semitone. This initially occurred after dose changes only and remitted within a few weeks while continuing CBZ. CBZ was increased up to 600 mg bd but higher dose did not impact on seizure control and more side effects in particular increased tiredness developed. CBZ was stopped and after switching to OXC she again noticed altered pitch perception. The switch was performed directly from one drug to the other. She noticed that pitch seemed one semitone higher than normal. Again this occurred after dose increases only and lasted for about one week before remitting whilst continuing OXC. On OXC 450 mg mornings and 600 mg evenings, she suffered five partial seizures a month. Lacosamide (LCM) was added and gradually increased to 250 mg bd. She did not have any change in pitch perception whilst on LCM.

3. Discussion

CBZ is a first-line anti-epileptic drug in partial and generalized seizures which is also indicated in trigeminal neuralgia and various affective disorders. Its major side effects are dizziness, sleepiness and cerebellar symptoms.² Auditory disturbances are a rare side-effect. Twenty-six cases of pitch-shift following CBZ administration have been reported.³ Twenty-five of the reported cases were Japanese. The reported problem was mainly lowered pitch but two of the cases were said to have experienced higher pitch. AP is a term which denotes the cognitive auditory ability to spontaneously and effortlessly identify and vocally produce specific musical tones without a reference note.¹ In other words recognizing AP is the ability to immediately attach the sound name "do", "re", "mi" to the heard sound and sing the appropriate note on hearing the sound name.⁴ Data suggest a notably higher prevalence of AP in Asians compared to other ethnic groups in various music programs. Overall 32.1 percent of Asians had AP versus 7 percent

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of non-Asians in one combined survey of music programs⁵ and this is linked to the variations in the frequency and nature of musical training in early childhood in these populations.⁶ In addition to hereditary factors, training from childhood is necessary, but not sufficient, for the acquisition of the AP.⁴

Abnormalities of pitch perception are a recognized side effect of CBZ. Whilst rarely reported, it is possible that the effect itself is a common side effect with but it is only recognized in those patients, usually highly musically trained, who are able to articulate this subtle symptom. The mechanism of this effect is not clear. There are several indications that CBZ affects the auditory system. De la Cruz and Bance reported a case of attempted suicide in which the patient had taken 36 g CBZ and complained of reversible hearing loss and tinnitus.⁷ The brainstem auditory-evoked response of a patient who experienced auditory disturbance with CBZ was found to be normal⁷ suggesting that the hearing conduction pathway was not impaired. Various mechanisms have been posited to explain this phenomenon, including impairment at the recognition level⁸ a disorder of perception affecting the limbic system⁹ or affecting the outer hair cells of the organ of Corti.¹⁰ A detailed recent analysis of CBZ-induced pitch shift in a concert pianist suggested that the drug probably shifts frequency filtering likely at brainstem level, without affecting tone-scale representation in higher centres. Given the lack of impact on musical timbre an impact at the cochlear level was felt unlikely.¹¹

There are many reported cases of CBZ-induced reversible pitch change but, as far as we know, pitch change in patients with AP whilst on OXC has not been reported previously in the literature. The occurrence of this side effect is likely to be explained by the similar mode of action of both drugs. It is notable that our patient did not report any pitch shift with LCM.

The primary mechanism of action of CBZ and OXC is use-dependent blockade of voltage-dependent sodium channels. Given the tendency to develop pitch-related adverse effects with both CBZ and OXC it could be inferred that sodium channels may be involved in the physiology of AP. Lacosamide, which was tolerated without any change of pitch, is also a sodium channel blocker but with a slightly different mode of action.¹² LCM inactivates the slow sodium channels whereas CBZ and OXC inactivate the fast sodium channels. This difference may be responsible for the lack of pitch-related side effects associated with LCM in this patient.

In summary, we have described for the first time the adverse effect of a one semitone sharpening of pitch with OXC in a patient with AP, who had one semitone flattening of pitch with CBZ and no change of pitch perception with LCM. This may help raise awareness of this side effect and contribute further to the understanding of pathophysiology of AP.

Conflict of interest statement

T.J. von Oertzen received research and educational grants from UCB pharma. S. Gur-Ozmen and Niranjana Nirmalananthan have no conflict of interest to declare.

Patient consent

Obtained.

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