
Article:
van Oppen, J.D. orcid.org/0000-0002-2570-7112, Patel, N. and Tarique, A. (2020) Hyperkinetic reaction to dihydrocodeine. BMJ Case Reports, 13 (1). e233264. ISSN 1757-790X

https://doi.org/10.1136/bcr-2019-233264

This article has been accepted for publication in BMJ Case Reports, 2020, following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/10.1136/bcr-2019-233264.

BMJ Case Reports

TITLE OF CASE

Hyperkinetic reaction to dihydrocodeine

SUMMARY

A young man was using dihydrocodeine analgesia for ear pain having had suppurative otitis media. He attended the Emergency Department with restlessness and twitching movements in his arms and legs. He had pyrexia with otherwise normal vital signs. He had no signs of cerebellar pathology. Investigations were normal. The working diagnosis was of hyperkinetic reaction to dihydrocodeine. Symptoms resolved within 48 hours of withdrawing the drug. Serotonin toxicity is a rare side effect of dihydrocodeine. There is a theoretical basis for increased side effects when taken with cannabidiol-based substances (CBD).

BACKGROUND

Dihydrocodeine is a common prescription in emergency and primary care settings for acute and chronic pain.[1, 2] Side effects are well-recognised, commonly including nausea, constipation, dizziness, sedation, and respiratory depression, and less-commonly dependence, hyperalgesia, and hormonal dysfunction.[3] Opiate-induced myoclonus has been rarely reported.[4, 5]

Cannabidiol (CBD) based substances are increasingly used medicinally. Indications with and without evidence for efficacy include pain, nausea, seizures, and spasticity. The significance of CBD in drug interactions is not well understood,[6] although potential pharmacokinetic interactions have recently been described.[7]

CASE PRESENTATION

A gentleman in his thirties attended the Emergency Department with restlessness and twitching movements of his arms and legs. He was usually fit and well. Four days previously he had started amoxicillin for suppurative otitis media. He had been using 4g paracetamol and 240mg dihydrocodeine daily for analgesia, and other than topical cannabidiol (CBD) oil for eczema he used no other medications. He was pyrexic with otherwise normal vital signs. Examination showed a tympanic membrane perforation and no other obvious infective focus. He was alert and had normal tone with akathisia, hyperreflexia, and inducible clonus. There were no signs of cerebellar pathology.

INVESTIGATIONS *If relevant*

A CT head examination was normal: there was no intracranial extension of ear infection. Inflammatory markers were only mildly elevated. Urea and electrolytes were normal, and creatine kinase was normal.

DIFFERENTIAL DIAGNOSIS *If relevant*

The Emergency Department triage practitioner was alerted to possible sepsis due to presentation with fever and shaking movements which were initially mistaken to be rigors. The gentleman received intravenous ceftriaxone and was moved to our resuscitation room with initial consideration of encephalitis or intracranial abscess formation.

The clerking doctor was reassured by him feeling and appearing generally well, his normal CT examination and his normal blood tests. A toxic serotoninergic response to dihydrocodeine was considered as the likely cause of his somatic and autonomic symptoms.

~~**TREATMENT** *If relevant*~~

~~***TIP:*** *Include pharmacological and non-pharmacological, e.g. surgery, physiotherapy, supportive care.*~~

OUTCOME AND FOLLOW-UP

The person was reviewed by an Otorhinolaryngologist at presentation. Their impression was of resolved middle ear infection and antimicrobials were stopped after the first dose. This suggests that the onset and recovery of the person's movement symptoms were unrelated to the original infective process or its antimicrobial treatment. The gentleman was reviewed by a Neurologist, whose impression was of hyperkinesis as a reaction to dihydrocodeine. The drug was stopped, and the person's movement symptoms resolved during 48 hours' inpatient observation.

DISCUSSION *Include a very brief review of similar published cases*

Dihydrocodeine has previously been reported to precipitate serotonin syndrome in a patient concurrently receiving venlafaxine and rizatriptan.[8] Myoclonus has also been reported as a neuroexcitatory side effect of opioid medications.[9, 10] This gentleman had somatic (akathisia) and autonomic (pyrexia), but not cognitive (agitation) signs. His symptoms were likely to represent a side effect of dihydrocodeine. The Hunter criteria decision rules[11] were applied retrospectively: this may have been a case of serotonin toxicity.

Dihydrocodeine undergoes metabolism to morphine by the cytochrome P450-2D6 (CYP2D6) enzyme, and is metabolised further by CYP3A4. This person could be a rare ultra-rapid CYP2D6 metaboliser, yielding higher concentrations of morphine leading to the subsequent side effects. An alternative, hypothetical, explanation for dihydrocodeine side-effects is the short-term CYP3A4 inhibition caused by transdermal cannabidiol.[12] A highly lipophilic drug,[13] cannabidiol may cause drug interactions if absorbed to adequate plasma concentrations.

LEARNING POINTS/TAKE HOME MESSAGES *3-5 bullet points*

- Side effects to opioid medications such as dihydrocodeine commonly include nausea, constipation, and dizziness. Rare side effects should be considered when patients attend with unusual symptoms and signs.
- Serotonin syndrome is characterised by autonomic, cognitive, and somatic symptoms and signs in combination. The Hunter criteria can be used as a diagnostic decision aid.
- Rarely, opioids can cause neuroexcitation and movement disorders as side effects.

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~~FIGURE/VIDEO CAPTIONS~~

~~***TIP:** We do not have a limit on illustrations, but choose only what illustrates your case most effectively and ensure that the patient cannot not be recognised by cropping the image as close as possible.*~~

~~*We encourage colour images and videos.*~~

PATIENT'S PERSPECTIVE

My symptoms started out as mild pain in my left ear and graduated to significant pain along with dizziness & nausea. I attended A&E and was prescribed dihydrocodeine and antibiotics. The dihydrocodeine I was taking slightly dulled the pain (and gave me a temporary sense of calm), but within a day of using it I began vomiting regularly throughout the day. The dizziness and nausea increased, the vomiting became more frequent, my right ear began leaking reddish fluid, and pain began in the other (left) ear. I then booked an appointment with my GP, who prescribed an increase in the dosage of dihydrocodeine, and prescribed Naproxen. During the next few days, all the symptoms mentioned above worsened, and my temperature increased sharply.

I returned to A&E and when my temperature was taken at the desk I was seen immediately by a nurse. Until I was asked about it, I was completely unaware that I'd been shaking/twitching. My wife informed the staff that this had been going on for a few hours. This was alarming to me and I then became conscious of it. I found that if I concentrated on calming myself, I could reduce the frequency of the twitching - but it persisted, nonetheless. (The feeling that I was not in control of it caused me to panic slightly.) I had a CT scan and saw a neurologist, who suggested the twitching may be a side effect of dihydrocodeine. I spent the next couple of days in the hospital and, during my time under care, the symptoms reduced and I was discharged.

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Date: 20 December 2019