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Indomethacin-intolerant hemicrania continua: treatment with botulinum toxin

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Abstract

Hemicrania continua (HC) is responsive to indomethacin, which is useful both for acute treatment and for chronic suppressive therapy. However, this medication is poorly tolerated in many patients. The treatment of indomethacin-intolerant HC is poorly defined. We present a patient with HC who developed acute kidney injury on indomethacin and proved refractory to multiple other treatment modalities. She had an excellent response to botulinum toxin, with a duration of benefit similar to that reported previously in HC and in chronic migraine. Botulinum toxin may be a therapeutic option in patient with HC who do not tolerate indomethacin. The possible mechanisms of action of botulinum toxin in HC are discussed.

Keywords: Hemicrania continua; indomethacin; botulinum toxin

INTRODUCTION

Hemicrania continua (HC) is a relatively rare type of side-locked headache, classified as a subtype of trigeminal-autonomic cephalalgia by the International Classification of Headache Disorders, third edition (ICHD-3, 2013)[1] and comprising 1.3-2.3% of referrals to specialist headache clinics.[2] While the clinical features of HC are characteristic, with continuous unilateral dull or pressure-type background pain - usually localized to the ophthalmic distribution - associated with episodic exacerbations involving other areas of the head as well as cranial autonomic features and agitation during exacerbations[1-3], diagnosis is often delayed as the condition is uncommon and may be confused for other primary headaches, particularly migraine. Seventy percent of patients may fulfil diagnostic criteria for migraine with aura during exacerbations.[2,3] An important diagnostic feature of HC is its responsiveness to the non-steroidal anti-inflammatory drug (NSAID) indomethacin in doses ranging from 25-600mg/day, and this medication remains the first choice for the treatment of HC.[3-5]

However, indomethacin is poorly tolerated in a proportion of patients with HC due to gastrointestinal and other side effects. Up to 30% of patients (46 of 159) with HC were unable to tolerate this medication in one meta-analysis and had to discontinue treatment.[4,6] The treatment of indomethacin-intolerant HC is poorly defined. One case series and a few anecdotal reports have documented a response to botulinum toxin therapy in this condition.[7-9] We report a patient who developed acute kidney injury with indomethacin and had an excellent response to botulinum toxin, adding to the slender body of evidence supporting this therapeutic intervention in HC.

CASE REPORT

A 47-year-old nurse presented with a new-onset severe unilateral left peri-orbital headache described as a continuous deep boring or stabbing pain radiating to the temple, ear, or jaw. Associated watering of the left eye and nasal stuffiness were noted with exacerbations of the headache. She also reported occasional sharp right occipital pain as well as dull bitemporal pounding headaches but denied any vomiting, aura, or sensitivity to light or noise. Her mother and sister have migraines.

Minimal left miosis and lid droop were noted on examination, with a normal MRI of the brain. Headache was completely relieved within 30 minutes of an oral 50mg-dose of indomethacin and a diagnosis of HC was made in accordance with ICHD-3 criteria.[1] She remained on 75mg/day of indomethacin for the next three years, but then developed acute kidney injury and had

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to cease the indomethacin. Headache reappeared in a few days, with severe and unremitting pain. She then trialled numerous medications, including gabapentin, topiramate, acetazolamide, melatonin, verapamil, and amitriptyline with either no benefit or intolerable side effects. A brief trial of low-dose celecoxib (100mg daily) produced >90% relief of headache, but further deterioration in renal function after 5 months meant immediate cessation of this medication, with return of renal parameters to baseline.

The patient was reluctant to trial of invasive therapies like sphenopalatine ganglion block or an occipital nerve stimulator, and instead informed us that her 3-monthly cosmetic botulinum toxin injections produced slight but appreciable improvements in the headache. She was then treated with onabotulinumtoxin A using a dose of 155 units according to the standard Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol. At three months 50% improvement and, after a second dose, at six months >90% relief from pain and cranial autonomic symptoms was reported with infrequent use of paracetamol as analgesia. Of note, she experienced marked worsening of pain 10 weeks after the injections – taken to imply wearing-off of the toxin effect, and this improved after repeat injection. Given the persistence of the sharp occipital pain, bilateral occipital nerve blocks using methylprednisolone sodium succinate and 2% lignocaine to the lesser and greater occipital nerves were added to her fourth treatment cycle. She has subsequently received four further 3-monthly doses of botulinum toxin using the same protocol with an excellent response to each dose lasting 10-12 weeks.

DISCUSSION

The exquisite sensitivity of certain trigeminal-autonomic cephalalgia (HC and chronic paroxysmal hemicrania) to indomethacin enables the use of this medication as a diagnostic test. Indomethacin is useful both as acute therapy and as chronic suppressive therapy, but headache predictably recurs within days of ceasing indomethacin.[10] The prevalence of indomethacin-related side effects in patients with HC varies between 20% and 75%.[3,11] While gastrointestinal irritation is very common, acute kidney injury and paradoxical headache worsening, which may be either migrainous or a thunderclap headache attributed to reversible cerebral vasoconstriction are also encountered.[12-15]

Drugs found to be effective in case reports and open-label studies include Cox-2 inhibitors, topiramate, melatonin, gabapentin, ibuprofen, piroxicam, naproxen, aspirin, amitriptyline, verapamil, and steroids.[11] Other options include supraorbital or greater occipital nerve blocks and neuromodulation.[7] Indomethacin had a significantly higher odds of pain-free patients compared to all other types of treatment, although botulinum toxin and supraorbital nerve block had a similar proportion of responders in a recent meta-analysis. Other NSAIDs or selective Cox-2 inhibitors have a lower response rate with reported doses of celecoxib between 200 and 600mg/day.[2,4]

Garza and Cutrer used botulinum toxin in an indomethacin-intolerant patient with HC as a last resort before proceeding to invasive neuromodulation. 100U were administered bilaterally into the procerus, corrugators, frontalis, temporalis, splenius capitis and trapezii following a chronic migraine protocol. While there was moderate pain relief lasting three months, the cranial autonomic symptoms continued unabated. Interestingly, these had not been relieved by indomethacin, and the authors attributed this dichotomy to possible independence of parasympathetic activation from ophthalmic nociceptive afferents.[8] Khalil and Ahmed administered botulinum toxin as per the PREEMPT protocol to a patient with HC, who reported complete cessation of symptoms in 72 hours, with a wearing-off of the benefit after 10 weeks. Repeat toxin administration produced further benefit lasting 10-12 weeks.[9] Miller *et al*. published the only case series to date, with five of nine patients reporting >50% reduction of moderate or severe headache days to either mild headache days or pain free after a mean of 167U (range, 110-185U) of toxin, also following the PREEMPT protocol. The median reduction in total headache days was 90% and in moderate-to-severe headache days 80%.[7]

Botulinum toxin can be considered if other medication trials are unsuccessful, but a good biological rationale for its effect in HC is missing.[15] Multiple mechanisms may be operative, inhibiting central and peripheral sensitisation. Axonal transport of the toxin may directly inhibit central sensitisation in the brain, while reduction of neurotransmitter release from motor and sensory nociceptive neurons produces peripheral blockade of neurogenic inflammation via inhibition of release of vasoactive peptides via the trigeminovascular reflex[16-18], decreasing the activation of second-order neurons within

the trigemino-cervical complex and dorso-lateral pons in the brainstem.[18] A benefit on autonomic symptoms was noted in our patient as well as that of Khalil and Ahmed, which could also imply an effect on the posterior hypothalamus, which has been implicated in the genesis of dysautonomia in HC.[9,19,20] The clinical similarities between HC and migraine alluded to above as well as previously reported similarities on functional imaging may indicate a pathogenetic overlap and provide a basis for the efficacy of botulinum toxin in both these headache disorders, distinct from the other trigeminal-autonomic cephalalgias in which botulinum toxin may not be as beneficial.[7,19] The duration of the treatment effect was consistent across all previous reports as well as our patient, similar to that seen in chronic migraine, indicating that the observed benefit was not merely a placebo response.

In summary, our patient adds to the body of evidence supporting the efficacy of botulinum toxin for the treatment of HC in indomethacin-intolerant patients, alleviating headache severity, autonomic symptoms, and the consequent disability.

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