J Headache Pain (2005) 6:417–419
DOI 10.1007/s10194-005-0234-6

BRIEF REPORT

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Warfarin as a therapeutic option in the control of chronic cluster headache: a report of three cases

Received: 17 April 2005
Accepted in revised form: 8 June 2005
Published online: 1 August 2005

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Abstract Chronic cluster headache remains refractory to medical therapy in at least 30% of those who suffer from this condition. The lack of alternative medical therapies that are as effective as, or more effective than, lithium carbonate makes new therapies necessary for this highly disabling condition. Based on a previous report, we gave oral anticoagulants to three patients with chronic cluster headache. Two of them remained cluster headache-free while taking warfarin. In the third patient, the use of warfarin for three weeks initially increased the frequency and intensity of cluster headache attacks but subsequently induced a prolonged remission. In spite of the paucity of data available, oral anticoagulation appears to be a promising therapy for chronic cluster headache.

Key words Cluster headache • Chronic cluster headache • Cluster headache therapy • Oral anticoagulants • Warfarin

Introduction

Cluster headache is perhaps the best defined trigeminal autonomic cephalalgia. Its less frequent form, chronic cluster headache, frequently eludes available medical therapies [1]. Three cases of chronic cluster headaches that were responsive to oral anticoagulation are described. The paucity of effective therapies to treat this condition [1, 2], and the puzzling effectiveness of warfarin in the cases described here, justify reporting of this uncontrolled evidence.

Case reports

Patient 1

A 46-year-old white male presented with cluster headache since the age of 32 years, and with chronic cluster headache since the age of 35 years. He was submitted to currently available prophylactic therapies for cluster headache such as prednisone, deflazacort, verapamil, lithium carbonate, methysergide, divalproate, pizotifen, lamotrigine and topiramate, and to several other unconventional therapeutic drugs. He only responded to steroids, which produced a partial and transitory response. He took prednisone for a prolonged period, which may have contributed to the chronification of his cluster headache. A retrogasserian balloon compression led to a transitory remission. In September 2003, after an earlier communication of the case subsequently described by Souza et al. [3], warfarin 2.5 mg/day up to 10 mg/day was prescribed. Cluster headache attacks decreased during the titration period and were followed by a sustained remission in the succeeding two months, allowing him to discontinue prednisone. The attacks recurred when warfarin was withdrawn, but their frequency and intensity decreased again from 6 daily full-blown episodes to a headache-free condition after two mild episodes following

the re-introduction of warfarin at 2.5 mg/day (RNI=1.26). The patient is on warfarin and remains headache free after 20 months of follow-up. A transcranial Doppler with agitated saline solution carried out during warfarin therapy showed no evidence of a right-to-left shunt.

Patient 2

A 56-year-old man presented because of cluster headaches that had started at the age of 45 years and had been chronic since the age of 53 years. He had been unsuccessfully submitted to therapy with prednisone, lithium carbonate, verapamil, sodium valproate and methysergide. In September 2004, warfarin 2.5 mg/day was started and titrated up to 5 mg. The patient's RNI reached 2.81 after 14 days. The intensity of his cluster headache attacks decreased, but the attacks still occurred up to five times a day. When the warfarin dose was increased to 10 mg/day, the intensity of his attacks increased, but he would then remain up to two days without attacks. As his RNI had increased to 7.4, the warfarin dose was decreased to 5 mg/day (RNI: 3.4). At this time, the patient became pain-free and five days later warfarin was discontinued, allowing methysergide to be discontinued two weeks later. He remained pain-free without medication at the eighth month of follow-up. A transcranial Doppler with agitated saline solution after warfarin was stopped revealed evidence of an important right-to-left shunt.

Patient 3

A 45-year-old man presented with a 17-year history of cluster headache. In 2004, he became unresponsive to the usual medication (prednisone, ergotamine tartrate, verapamil, methysergide and lithium carbonate) and his cluster headache became chronic. In December 2004 warfarin was titrated from 2.5 mg/day up to 5 mg/day, with complete remission of the cluster headache episodes on the third day of therapy, allowing verapamil, methysergide and lithium to be withdrawn. His RNI is being kept between 2.0 and 3.0, and there were no recurrences at his last follow-up visit seven months after the beginning of therapy. A transcranial Doppler with agitated saline solution during warfarin therapy revealed evidence of a right-to-left shunt.

Discussion

Therapy for chronic cluster headache remains a debatable issue for neurologists and headache specialists. In fact, there is a lack of systematic trials in this field [1, 2]. Conversion to the episodic type has been reported to occur in approximately one third of patients with chronic cluster headache [4–6], and spontaneous remissions to occur in only 5% [4]. The large number of different surgical procedures used in efforts to control the symptoms of chronic cluster headache illustrates the refractoriness of this condition [1, 7]. A recent trial with acenocoumarol has confirmed previous anecdotal reports of the efficacy of anticoagulants in migraine prophylaxis [8], but, conversely, warfarin was reported to precipitate a cluster-like headache in a single patient [9]. In 2003, Souza et al. [3] reported that warfarin used to control deep venous thrombosis in a chronic cluster headache patient resulted in his cluster headache attacks abating [3]. A placebo effect, although possible, seemed unlikely in patients with the chronic variety of the disease [10].

Current concepts in cluster headache suggest that three areas appear to be involved in the pathogenesis and expression of cluster headache: the trigeminal nociceptive pathways, the autonomic system and the hypothalamus.

The most well-known pharmacological effect of warfarin, which is a derivative of 4-hydroxycoumarin, is its inhibition of blood clotting as a result of interference with the hepatic synthesis of the vitamin K-dependent clotting factors. The K vitamins are fat-soluble substances that belong to the naphthokinones group. Their main biological functions are those related to bone metabolism and to their role as a cofactor of γ-glutamyl-carboxylase, which catalyses the post-translational conversion of glutamic acid to γ-carboxyglutamic acid in vitamin K-dependent proteins [11]. These vitamins exist in two naturally occurring forms, K1 (phyllokinone) and K2 (menaquinone). Although vitamin K1 is the predominant form of vitamin K in the liver, heart and pancreas, vitamin K2 in its MK-4 form (menaquinone, with four isoprenoid rings) is the predominant form of vitamin K in the brain [11]. The role of vitamin K in the CNS remains to be clarified, but several effects on neuronal and glial metabolism have already been identified [11].

Warfarin anti-cluster headache properties could be explained by interference with both peripheral and central mechanisms. Warfarin was reported to have a marked anti-inflammatory effect in the formaldehyde- and carrageenan-induced rat paw oedema model. This effect could be observed not only when warfarin was administered prior to the induction of inflammation, but also when it was given to animals with inflammatory reactions that had developed previously [12], a pattern of response that suggests a peripheral effect. Interference with menaquinone's ability to induce inducible nitric oxide synthase (iNOS) [13] could also be accounted for by a peripheral effect, as iNOS plays a role in the neurogenic inflammation model.

Conversely, the effects of quinones in the nervous system may occur through biochemical pathways other than their action as a cofactor of the γ-glutamylcarboxylase. Warfarin, by limiting the postribosomal carboxylation of vitamin K precursors, and thus halting the synthesis of vitamin K, may interfere with the influence of the quinones in PKA- and MAPK-mediated cellular processes [14], including the release of CGRP or other substances involved in the inflammatory cascade by trigeminal neurons.

Furthermore, both PKA and MAPK participate in cell processes of different hypothalamic neuronal populations [15], which may render cluster headache-related hypothalamic neurons vulnerable to a warfarin-induced reduction in the availability of menaquinone. A central effect is suggested by the extreme and consistent changes in the clinical behaviour of the cluster headaches in the cases described here.

A third hypothesis for the efficacy of warfarin may be related to its anticoagulant properties. As with migraine, patent foramen ovale (PFO) has been reported to be more prevalent in cluster headache patients than in controls [16]. In cluster headache patients, arterial desaturation is considered to be a trigger for cluster headache attacks in patients with PFO and obstructive sleep apnoea syndrome. A right-to-left shunt was detected by contrast transcranial Doppler (cTCD) in two of our three patients. Warfarin could perhaps interfere with embolic phenomena rather than with arterial desaturation [16], but this hypothesis seems unlikely because in patient 2, who showed the most important right-to-left shunt, remission persisted after warfarin was discontinued. In spite of an insufficient understanding of the mechanisms involved, the apparent efficacy of warfarin as a new treatment for cluster headache sufferers points to new lines of study for this highly disabling condition.

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