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Full Length Research Paper

A clinical trial of the effect of St. John's wort on migraine headaches in patients receiving sodium valproate

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St John's wort (*Hypericum perfortum*) a medicinal plant used for depression has been shown to increase the levels of brain serotonin, which may also influence migraine headache. This study was designed to evaluate the effect of *H. perforatum* on the frequency and intensity of migraine headaches in patients. In a clinical trial, 100 patients aged 15 to 45 years, with migraine headaches were randomly assigned to two study groups. The trial was conducted in four phases of 45 days. In the pretreatment phase, patients were drug free. In the first treatment phase, both patient groups received sodium valproate (200 mg/tablet), twice daily. In the second phase, patients in study group 1 continued to use sodium valproate and patients in study group 2 received tablets of *H. perforatum* thrice daily in addition to sodium valproate. In the third phase of study, patients were medicated identically to the first phase of the trial. Patients were free to take indometacin 25 mg capsules as a rescue medication for migraine throughout. Co-administration of *H. perforatum* coated tablets with sodium valproate in the second trial phase reduced (P=0.04) the intensity of migraine attacks and evoked a more marked decline in their frequency. Therefore, *H. perforatum* might be beneficial in migraineurs.

Key words: St. John's wort, migraine headache, sodium valproate.

INTRODUCTION

Migraine is a disabling health problem among adults and children. More than 6% of men and 15 to 17% of women experience migraine headaches (Stewart et al., 1994) and the estimated annual cost of lost productivity in the United States as a consequence of migraine is more than 20 billion dollars (Stewart et al., 2003). More than 5% of patients present to the emergency department with acute severe migraine (Vinson, 2002). It has also been reported that 49% of individuals treated for migraine headache have a recurrent headache within 24 h, which is distressing not only for patients but problematic for overcrowded emergency departments (Bond et al., 2007).

Many agents are used to treat acute severe migraine and clinical guidelines recommend non-steroidal anti-inflammatory drugs (NSAIDs), sumatriptan, dihydroergotamine, ergotamine, chlorpromazine and prochlorperazine, amongst others (Raskin, 1993; Dodick 2006; Bond et al., 2007; Amanzio et al., 2009). These agents are moderately effective in relieving acute migraine headaches (in 60 to 70% of cases) (Raskin, 1993). Acute headache medication usage should be limited in order to avoid medication overuse headache and the management of chronic migraine should focus on prophylactic therapy in order to avoid this phenomenon (Garza et al., 2009).

Preventive medications for chronic migraine treatment are less well-studied than for episodic migraines (Dodick et al., 2006). In this context, first line prophylactic medications for chronic migraine include: Beta-blockers, amitriptyline, topiramate and valproic acid or its derivatives. Approximately 50% of patients treated with

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one of these medications will have at least a 50% reduction in the frequency of headaches after three months of treatment, given adequate doses of medication (Victor et al., 2010).

Second-line pharmacological agents for migraine prevention include botulinum toxin injections, calcium channel blockers, feverfew, fluoxetine, gabapentin, levetiracetam, magnesium, memantine, pregabalin, riboflavin, tizanidine and others. These drugs have been studied only on a limited basis and their effectiveness in migraine prophylaxis is uncertain. However, for patients with refractory chronic migraine who have failed treatment with first-line agents, second-line agents are usually used. It should be noted that side effects of these medications are common and may limit their usage (Amanzio et al., 2009).

The employment of alternative therapies is on the increase (Ni et al., 2002), and the use of herbal medicines has been the fastest growing market segment in the United States (Watkins, 2002). St. John's wort (*Hypericum perforatum*), is one of the most ubiquitous medicinal plants available and has been used for hundreds of years for a variety of diseases (Blumenthal, 1999; Watkins, 2002; Subhan et al., 2009).

In recent times, it has received attention in the treatment of depression along with other herbal remedies (Cieza et al., 2003; Subhan et al., 2010) and numerous clinical trials have demonstrated its effectiveness in this respect (Stevinson and Ernst, 1999; Kim et al., 1999; Linde et al., 2005).

A marked increase in serotonin and 5-HIAA levels, following *H. perforatum* dosing has been reported in rat brain cortex (Calapai et al., 1999). In addition, systemic administration of the polyprenylated acylphloroglucinol derivative hyperforin, an active component of Hypericum, has also induced a lasting (>5 h) and marked (100 to 200%) increase in extracellular concentrations of serotonin in the locus coeruleus of the rat (Kaehler et al, 1999). Thus, changes in serotonin levels within different brain regions may well be a pivotal *H. perforatum* mechanism involved in the reduction of intensity and frequency of migraine attacks. In the Chaharmahal-va-Bakhtiary province of Iran, extracts of *H. perforatum* are used to treat migraine headaches. Such herbal extracts inhibit serotonin re-uptake (Muller et al., 1998; Singer et al., 1999; Vormfelde and Poser, 2000), and this neurotransmitter is involved in the pathogenesis of migraine headache (D'Andrea et al., 2004). It is the aim of this study to evaluate the activity of an *H. perforatum* extract on the frequency and intensity of migraine headaches.

MATERIALS AND METHODS

Subjects

In a clinical trial 100 patients with migraine headache referred to the neurology clinic of Shahrekord University of Medical Sciences, were selected based on International Headache Society criteria (Headache Classification Subcommittee, 1988). The protocol was approved by the Ethics Committee of the Shahrekord University of Medical Sciences, prior to the commencement. All patients gave their informed consent to participation in the study, which was conducted in accord with the provisions of World medical association declaration of Helsinki (2008).

Patients with at least three migraine attacks per month were included in the trial and following an examination, those with any iron deficiency, epilepsy, a cardiac disorder, pregnancy or drug hypersensitivity were excluded. .

Trial protocol

Patients were randomly (based on the entrance to the protocol) assigned to two study groups of 1 and 2 (50 per group). The trial was conducted in four phases each of 45 days duration as previously described by Mirzaei et al. (2009). Patients were asked to rate the intensity of their headaches as either pain free or on an additional verbal/numerical 9-point headache scale analogous to the mild, moderate or severe 3-point scale as described by the international headache society clinical trials subcommittee (2000). In the pretreatment phase (before visiting the doctor), patients were interviewed by a neurologist, regarding the frequency and intensity of their headaches during the preceding 45 day period. In the next (first) phase, patients in both groups, received two tablets of sodium valproate (200 mg/tablet, Tehran-daru, Iran), per day for 45 days. In the second phase, patients in the study group 1 continued to use sodium valproate plus placebo tablets and patients in the study group 2, received *H. perforatum* tablets (Perforan®, 160 mg/tablet, Goldaru, Iran), three tablets per day in addition to sodium valproate. The third phase of drug treatment commenced following a 5 day wash out in which patients were medicated identically to the first phase of the trial (two tablets of sodium valproate per day for 45 days). Patients were allowed to take indomethacin capsules (25 mg each) throughout the three study phases as a rescue medication during migraine attacks. During all three phases of the trial, the frequency and intensity of attacks were recorded.

Statistical analysis

Data were statistically analyzed using SPSS software. Comparisons between the two study groups were carried out by student t-test. The trends in the frequency or intensity reduction of migraine attacks were statistically analyzed using repeated measures ANOVA. $P<0.05$ was considered as significant.

RESULTS

Demographic aspects

Thirty nine patients in study group 2 and thirty seven in study group 1 completed the study. Their ages ranged from 15 to 45 years at the time of entry to the clinic. The mean age of the patients was 26.3±10.2 years, there being no significant age difference ($P>0.05$) between groups (25.6±9.1 years for the study group 2 and 26.8±12.5 years for the study group 1). Six patients (15.4%) in the study group 2 and 5 patients (13.5%) in the study group 1 had classic migraine and the remaining patients suffered with common migraine.

Table 1. The quantity of indometacin (25 mg capsules) taken as a rescue medication during each of the three treatment phases of the trial.

Treatment phases	Groups		
	Group 2 (*H. perforatum* treatment)	Group 1	P value
First	7.6±4	6.5±2.4	0.15
Second	5.2±3.3	4.6±2.2	0.39
Third	5.1±2.9	5.1±2.5	0.99

Table 2. Effect of *H. perforatum* on frequency of migraine attacks.

Treatment attacks			Group 2 (*H. perforatum*) treatment	Group 1	P- value
Frequency	Phases	Pretreatment	6.8±2.6	5.4±1.8	0.008
		First	4.7±1.9	3.8±1.4	0.02
		Second	2.9±1.9	3.0±1.4	0.95
		Third	3.9±1.4	3.2±1.3	0.014

Values are mean±standard deviation.

Clinical study evaluation

There was no difference (P>0.05) in the duration of attacks between study group 2 (17±9.1 h) [range=4 to 36] and study group 1 (19.2±10.3 h) [range=4 to 48] during the pretreatment period. Moreover, no statistical differences were observed in the quantities of 25 mg indometacin capsules taken as a rescue medication between the two groups in any of the three phases of the trial (Table 1).

In addition, there was a significant difference in the mean frequency of migraine headache between study groups 1 (6.8±2.1) and 2 (5.4±1.8) not only during the pretreatment period (P=0.008) but also in the first phase (P=0.02) of the study. However, there was a significantly sharper decline in frequency in the *H. perforatum* treatment group (study group 2) compared to study group 1 in the second phase (Table 2).

There was no difference in the intensity of migraine attacks during pretreatment or the first study phase between the two study groups. However, following *H. perforatum* usage in the second phase of the study, the intensity of attacks was reduced significantly compared to study group 1 (P=0.04) (Table 3). Furthermore, comparison of the two groups with respect to attack intensity or frequency revealed no difference between phases one and three of the study.

DISCUSSION

The main aim of this study was to investigate the activity of *H. perforatum* coated tablets on migraine headaches experienced by patients maintained on sodium valproate. Sodium vaproate administration has previously been shown to reduce the frequency and intensity of migraine attacks and it is considered a useful and well-tolerated prophylactic medication (Frediani et al., 2001; Dodick, 2006).

Employing *H. perforatum* as an adjunct to sodium valproate, in the second phase of this study, significantly reduced the intensity of migraine attacks and produced a more abrupt decline in their frequency compared to study group 1. There is however no available literature regarding either *H. perforatum* activity on migraine headache per se or apropos any tenable mechanism(s) that might mediate its reduction of migraine symptoms in the clinic. During migraine headache, cortical spreading depression, neurogenic inflammation and cortical vascular contractile dysfunction are features of its pathophysiology (Goadsby et al., 2002; Bolay et al., 2002). Activation of brain tissue induces the release of peptides from the perivascular trigeminal region resulting in inflammation and dilation of extraparenchymal vessels and additionally, neuropeptides and cytokines are also implicated in neuroinflammatory and vasomotor changes associated with migraine (Bolay et al., 2002). During migraine attacks, a distinct release pattern of inflammatory markers occurs in the systemic circulation and this includes increased levels of C-reactive protein (CRP) (Welch et al., 2006; Vanmolkot and de Hoon, 2007), interleukins, tumour necrosis factor-alpha (TNF-α), and adhesion molecules (Munno et al., 2001; Empl et al., 2003). Furthermore, oxidative stress aggravates the concomitant inflammatory process (Munno et al., 2001; Russell and Olesen, 1995). *H. perforatum* possesses both anti-inflammatory and antioxidant properties (Dost et al., 2009), thus it has been shown to reduce colonic inflammatory damage, blood catalase level, tissue glutathione reductase, and increases blood glutathione

Table 3. Effect of *H. perforatum* on the intensity of migraine attacks.

Treatment attacks			Group 2 (*H. perforatum*) treatment	Group 1	P-value
Intensity	Phases	Pretreatment	8.5±1.4	8.6±1.3	0.79
		First	4.9±1.8	4.7±1.2	0.64
		Second	3.3±1.2	3.8±1.1	0.04
		Third	4.1±1.5	4.0±1.1	0.73

Values are mean±standard deviation.

level (Dost et al., 2009). It may be hypothesized therefore, that the anti-migraine activity of *H. perforatum*, is at least in part, attributable to its anti-inflammatory and antioxidant properties.

H. perforatum contains a variety of active constituents including naphthodianthrons (principally hypericin and pseudohypericin), phloroglucinol derivatives (mainly hyperforin, adhyperforin and furohyperforin), flavonoids (such as kaempferol and luteolin), volatile oils, plant acids, aminoacids, vitamin C, tannins, and carotenoids, most of which have antioxidant activities which may contribute to the antimigraine activity of this herbal remedy (Evans, 2008).

Other pharmacological properties of *H. perforatum* involve inhibition of monoamine oxidase, binding to brain benzodiazepine receptors, and re-uptake inhibition of neurotransmitters such as serotonin, dopamine, norepinephrine and acetylcholine (Butterweck and Schmidt, 2007).

During the peak of a migraine attack, thrombocyte serotonin concentration tends to decline sharply (Izzati-Zade, 2008) and the level of 5-hydroxyindolacetic acid (5-HIAA), the metabolite of 5-HT, is raised (Welch, 2002) whereas in between attacks, serotonin levels are elevated (Goadsby et al., 2002; Bolay et al., 2006). These data suggest that the serotonergic system is perturbed in such a manner that there is impairment of granular serotonin stored in thrombocytes during a migraine attack and subsequently it is released into the plasma. It should be noted at this juncture that the level of serotonin in thrombocytes reflects a similar serotonergic pattern in the brain (Rasmussen, 2001).

In support of this hypothesis, it has been shown that during migraine attacks, serotonergic and noradrenergic brainstem nuclei are activated (Vanmolkot and de Hoon, 2007). Additionally, the effectiveness of selective agonists such as sumatriptan at serotonin receptor subtypes (5-$HT_{1B/D}$) in migraine further implicates the serotonergic system (Munno et al., 2001).

In our study, co-administration of *H. perforatum* coated tablets with sodium valproate in the second trial phase reduced the intensity of migraine attacks and evoked a more marked decline in their frequency. This finding is consistent with the migraine prophylactic action of another antidepressant, amitryptyline, reported in an earlier study (Rafieian-Kopaei et al., 2005).

Amitryptyline inhibits the reuptake of serotonin in serotonergic neurons and increases serotonin level in the brain. A similar effect has been reported in the locus coeruleus (Kaehler et al, 1999) and brain cortex (Calapai et al., 1999) of the rats, following *H. perforatum* administration. Thus, changes in serotonin levels within different brain regions may well be a pivotal *H. perforatum* mechanism involved in the reduction of intensity and frequency of migraine attacks.

In conclusion, *H. perforatum* appears to be effective in migraine attacks and antioxidant; anti-inflammatory as well as serotonergic activity may well be highly pertinent component mechanisms in this anti-migraine activity.

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