Feverfew and Migraine Headaches

In 1973, at the suggestion of a friend, and apparently based on the advice of a traditional Welsh healer, a Welsh woman Mrs Anne Jenkins tried taking three fresh leaves of feverfew (Tanacetum parthenium) each day in an attempt to rid herself of severe and recurrent migraines. After ten months, Mrs Jenkins’ headaches had vanished and did not return as long as she kept taking feverfew. Her enthusiasm rapidly led to widespread use of feverfew in the UK. Dr. Stewart Johnson, a London migraine specialist, became interested and initiated a survey that was then followed up by a clinical trial. The survey revealed some interesting findings:

- About 72% of those surveyed (253 suffering from true migraine) found that feverfew was helpful for the prevention of their headaches; 78% of the 23 people suffering from tension headaches also found that feverfew reduced headache frequency and severity. Of 242 patients who recorded the frequency, 33% no longer had attacks, and 76% had fewer migraines each month compared to before taking feverfew.
- Associated nausea and vomiting decreased or disappeared. A proportion of patients experienced the migraine aura without the attack.
- When attacks did occur, they responded better to conventional painkillers (e.g., aspirin). Feverfew users experienced no adverse interactions with their orthodox medication.
- Many patients also suffering from arthritis found their symptoms somewhat relieved by feverfew.
- The onset of the effect was slow and gradual, often taking several months, and the average dose used was very low – about two-and-a-half fresh leaves (1.5 inches long by 1.25 inches wide) per day. The average duration of treatment was 2.3 and 2.6 years for men and women, respectively. When individuals stopped taking feverfew, their migraines tended to return soon after.
- The survey also revealed some side effects in a small percentage of users. Adverse effects included mouth ulcers or inflammation. In contrast, a percentage of users experienced improved digestion, a sense of well-being, and improved sleep.

This work was followed up by a double-blind, placebo-controlled, pilot clinical trial involving 17 patients who had been self-medicating with raw feverfew every day for three months. Eight of these patients received two capsules per day containing freeze-dried feverfew leaf powder (25 mg each), and nine received placebo for 24 weeks. Prior to the trial, the reduction in the frequency of migraines during self-treatment with feverfew was significant for both groups. Compared to the migraine frequency while self-medicating, there was no change in the frequency or severity of symptoms in the feverfew group during the trial. The placebo group, however, experienced a significant increase (p < 0.05) in the frequency and severity of headaches when the results of the previous three months were considered. The placebo group also experienced a higher incidence and severity of nausea and vomiting than the feverfew group (p<0.05). The authors claimed a prophylactic benefit for feverfew in preventing migraine attacks. Curiously, fewer adverse events were reported by those taking feverfew (four patients reported none), compared to placebo (all patients taking placebo reported at least one event). Apparently, because of ethical reasons (feverfew was considered to have unknown safety by the scientists), the trial had this unusual design. The patients were already using feverfew, so the trial therefore observed the results of patients unknowingly stopping their herbal treatment. Such an abrupt discontinuance led to the recurrence of severe migraines in some patients. Perhaps more importantly, the study showed that long-term feverfew users were normal in terms of a large number of biochemical and hematological parameters.

A few years later, 59 patients with classical or common migraine completed a randomized, double-blind, placebo-controlled crossover study. Only 17 of these patients had previously tried feverfew. After a one-month, single-blind, placebo run-in, patients were randomly allocated to receive
either one capsule of freeze-dried, powdered feverfew (averaging 82 mg and containing 2.2 mmol parthenolide, approximately two medium-sized leaves) or placebo for four months and then crossed over to the other treatment for a further four months. Feverfew was associated with a 24% reduction in the mean number of attacks and a significant reduction in the degree of vomiting (p < 0.02) in each two-month assessment period. There was also a trend towards a reduction in severity of attacks, although the duration of individual attacks was unaltered. Significant improvement in the feverfew group was also observed for visual analogue scores (p < 0.0001). Treatment with feverfew did not produce any adverse effects. Although there was no wash-out period between feverfew and placebo treatments, patients receiving placebo after feverfew did not experience a decreased deterioration compared to placebo levels from the first phase of the trial. No ex vivo reduction in serotonin secretion from platelets after ingestion of feverfew at four months could be demonstrated.

A team of Dutch scientists who had been very active in the field of feverfew research tested the efficacy of a standardized extract for the prevention of migraine headaches. In a randomized, placebo-controlled, double-blind, crossover design, 50 patients who had never taken feverfew before and experienced at least one migraine attack per month were selected at random and divided into two groups. Both groups received powdered feverfew capsules (total of 100 mg per day of dried leaves containing 0.2 mg parthenolide) in the preliminary phase, which lasted two months. In the second and third phases, which continued for an additional two months, a double-blind, placebo-controlled, crossover study was conducted. The difference in pain intensity of migraines before and after treatment with feverfew (measured in phase I) was highly significant (p < 0.001). In phase II, patients receiving feverfew continued to experience a decrease in pain intensity, while pain intensity increased in those on placebo. The difference between the two groups was significant (p < 0.01). Moreover, a profound reduction was observed in the typical migraine symptoms such as vomiting, nausea, and sensitivity to noise and light (p < 0.001). Transferring the feverfew-treated group to placebo in phase III resulted in an increase in pain intensity and other symptoms. In contrast, shifting the placebo group to feverfew therapy resulted in an improvement in pain and other symptoms. However, no information was provided concerning the frequency of migraine attacks.

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A German research team next studied the efficacy of a supercritical CO2 extract of feverfew in two randomized, double-blind, placebo-controlled trials. In the first trial, the efficacy and tolerability of three different doses per day of the extract (6.24 mg, 18.75 mg, and 56.25 mg, corresponding to about 170 mg of original dried herb. The feverfew preparation used in this study did not exert any significant preventative effect on the frequency of migraine attacks, although patients seemed to have a tendency to use fewer analgesic drugs while they were using feverfew.

This result was not in accordance with the results from the above studies, and the authors suggested that this might be because the previous studies were conducted in patients who had already found feverfew to be beneficial (which is not actually the case — see above). Another reason provided by the authors could be the dried plant preparation used or the fact that an extract was prescribed, rather than the crude leaf. (The original popularity of feverfew was based on consumption of the fresh leaves, although the two earlier clinical trials used freeze-dried leaves.) Initial users of raw feverfew found that it took six months of use or longer to establish a reduction in migraine frequency, so perhaps the duration of the trial was insufficient. It is also possible that only a subset of migraine sufferers are feverfew responders, and a benefit in this subset might be missed in a randomized clinical trial.

In a subsequent double-blind, placebo-controlled trial, 57 chronic migraine sufferers (43% suffered more than ten attacks per month) were selected at random and divided into two groups. Both groups received powdered feverfew capsules (total of 100 mg per day of dried leaves containing 0.2 mg parthenolide) in the preliminary phase, which lasted two months. In the second and third phases, which continued for an additional two months, a double-blind, placebo-controlled, crossover study was conducted. The difference in pain intensity of migraines before and after treatment with feverfew (measured in phase I) was highly significant (p < 0.001). In phase II, patients receiving feverfew continued to experience a decrease in pain intensity, while pain intensity increased in those on placebo. The difference between the two groups was significant (p < 0.01). Moreover, a profound reduction was observed in the typical migraine symptoms such as vomiting, nausea, and sensitivity to noise and light (p < 0.001). Transferring the feverfew-treated group to placebo in phase III resulted in an increase in pain intensity and other symptoms. In contrast, shifting the placebo group to feverfew therapy resulted in an improvement in pain and other symptoms. However, no information was provided concerning the frequency of migraine attacks.

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parameters, a statistically significant difference was not found. The frequency of migraine attacks for a predefined confirmatory subgroup of patients (n=49) with at least four migraine attacks during the baseline period decreased in a dose-dependent manner (p=0.001). The highest absolute change of migraine attacks was observed under treatment with 6.25 mg t.i.d. (mean ± SD= -1.8 ±1.5 per 28 days) compared with placebo (0.3 ±1.9; p=0.02). Overall 52 of 147 (35%) patients reported at least one adverse event. The incidence of these in the active treatment groups was similar to that in the placebo group, and no dose-related effect was observed for any safety parameter.

This was followed up by the second trial that assessed the efficacy of only the 18.75 mg/day dose against placebo. Patients (n=170) suffering from migraine according to the IHS criteria were treated for 16 weeks after a four-week baseline period. The primary endpoint was the average number of migraine attacks per 28 days during treatment months 2 and 3 compared with baseline. Safety parameters included adverse events, laboratory parameters, vital signs, and physical examination. The migraine frequency decreased from 4.76 by 1.9 attacks per month in the feverfew group and by 1.3 attacks in the placebo group (p=0.0456). Logistic regression of responder rates showed an odds ratio of 3.4 in favor of feverfew (p=0.0049). Adverse events possibly related to study medication were 9/107 (8.4%) with feverfew vs. 11/108 (10.2%) with placebo (p=0.654). The authors concluded that the feverfew extract was effective and showed a favorable benefit-risk ratio.

The authors claimed that 6.25 mg of extract containing 0.5 mg parthenolide corresponded to 1.05 g of feverfew leaf (presumably dried), so the doses used in both the above studies appear to be high. However, since feverfew can contain up to 1.6% lactones as parthenolide, the dried herb equivalence of the CO2 extract doses might be rather overstated in relation to good quality leaf.

A recent study has suggested that a higher dose of feverfew than used in the earliest studies (600 mg/day), together with a relatively small dose of willow bark (Salix alba, 600 mg/day), might bring on a quicker result in migraine prophylaxis. The herbal combination was standardized for parthenolide (0.2%) and salicin (1.5%). A prospective, open-label study was performed in 12 patients diagnosed with migraine without aura. Twelve weeks’ treatment with the herbal combination was administered to determine the effects of therapy on migraine attack frequency, intensity, and duration, and quality of life, together with tolerability for patients. With the herbal treatment, attack frequency was reduced by 57.2% at six weeks (p < 0.029) and by 61.7% at 12 weeks (p < 0.025) in nine of ten patients, with 70% patients having a reduction of at least 50%. Attack intensity was reduced by 38.7% at six weeks (p < 0.005) and by 62.6% at 12 weeks (p < 0.004) in all of ten patients, with 707o of patients having a reduction of at least 507o. Attack duration decreased by 67.2% at six weeks (p < 0.001) and by 76.2% at 12 weeks (p < 0.001) in all ten patients. Two patients were excluded for reasons unrelated to treatment.
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effect is due to the parthenolide and other sesquiterpene lactones in feverfew, and neutralization of sulfhydryl groups either inside or outside the cell is involved. Another theory is that feverfew has anti-inflammatory activity. In one study parthenolide inhibited cyclo-oxygenase (which converts arachidonic acid to prostaglandins) in vitro. Parthenolide also inhibited the expression of mitogen-activated protein kinases. The alpha-methylene-gamma-lactone group conferred the inhibitory activity. However, aqueous extracts of whole plant and leaf inhibited prostaglandin biosynthesis but did not inhibit cyclo-oxygenase. Parthenolide did not inhibit cyclo-oxygenase activity in vitro with enzyme derived from sheep seminal vesicles. Other evidence suggests that sesquiterpene lactones, including parthenolide, inhibit the release of arachidonic acid from membrane phospholipid stores rather than its conversion into thromboxane B2 via the cyclo-oxygenase pathway.

Chloroform extract of feverfew evoked changes in the metabolism of arachidonic acid that were similar to those observed in glutathione-depleted platelets. It also inhibited uptake and liberation of arachidonic acid into or from platelet membrane phospholipids, which may be the result of altered cytoskeletal-membrane interaction.

Sulfhydryls (SH) groups are essential for phospholipase A activity (and the liberation of arachidonic acid), which may have been affected by feverfew. Chloroform extracts of feverfew produced dose-dependent inhibition of the generation of thromboxane B2 and leukotriene B4 by stimulated leucocytes. The activity was due to other lactones as well as sesquiterpene lactones. However, it is uncertain whether any of these anti-inflammatory effects are relevant in humans at the doses of feverfew typically used.

Clinical Practicalities

Probably because of the initial use and promotion of a low dose of the fresh leaves by Mrs. Jenkins, there is a tendency to recommend quite low doses of feverfew for migraine prophylaxis. However, the use of such doses often means that it can take six to nine months before effective migraine prophylaxis occurs. With this length of time, the patient can give up before any benefit occurs. Hence, the use of higher doses of feverfew in migraine prevention is recommended to establish a faster clinical effect. Also, it should be combined with other relevant supplements to maximize the magnitude and speed of the onset of migraine prophylaxis. Typically, doses of at least 3 to 5 mL per day of the 1:5 tincture in 60% ethanol (to extract the lactones) or its equal in tablets or capsules (600 to 1000 mg/day of dried herb equivalent) are recommended. The author has found this dosage strategy to be successful in many patients. Once sufficient prophylaxis is induced, the dose can be backed off to a suitable level to maintain the reduced frequency of headaches.

Notes
