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Feverfew and Migraine Headaches

by Kerry Bone

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 10 months Mrs Jenkins' headaches had vanished and did not return so 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:[1]

- 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 (eg 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 3 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 3 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 reported at least one event).[2,3] 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 1-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 4 months and then crossed over to the other treatment for a further 4 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 2-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.[4] No *ex vivo* reduction in serotonin secretion from platelets after ingestion of feverfew at 4 months could be demonstrated.[5]

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 followed for 4 months of active treatment and 4 months of placebo. Active treatment consisted of 143 mg per day of a granulated ethanolic extract of feverfew containing 0.5 mg of parthenolide and 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.[6]

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 6 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 10 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 2 months. In the second and third phases, which continued for an additional 2 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 it 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.[7] In this trial, rather than acting to reduce the frequency of migraines, it appeared that feverfew reduced their severity. A longer treatment time or higher doses may have also seen an impact on migraine frequency.

A German research team next studied the efficacy of a supercritical CO_2 extract of feverfew in two randomized double-blind placebo controlled trials. In the first trial the efficacy and tolerability of 3 different doses per day of the extract (6.24 mg, 18.75 mg and 56.25 mg corresponding to 0.5 mg, 1.5 mg and 4.5 mg of parthenolide) were compared to a placebo.[8] The patients (n=147) suffered from migraine with and without aura according to International Headache Society (IHS) criteria and were treated with one of the study medications for 12 weeks after a 4-week baseline period. The primary efficacy parameter was the number of migraine attacks during each 28 days of the treatment period compared with baseline. Secondary endpoints were total and average duration and intensity of migraine attacks, mean duration of a single attack, number of days with accompanying migraine symptoms, number of days with inability to work due to migraine as well as type and amount of additionally taken medications for the treatment of migraine attacks. With respect to the primary and secondary efficacy 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.[9] Patients (n=170) suffering from migraine according to the IHS criteria were treated for 16 weeks after a 4-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 versus 11/108 (10.2%) with placebo (p=0.654). The authors concluded that the feverfew extract was effective and shows a favourable 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),[8] 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 CO_2 extract doses might be rather overstated in relation to good quality leaf.[10]

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%).[11] 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 6 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 6 weeks (p<0.005) and by 62.6% at 12 weeks (p<0.004) in all of ten patients, with 70% of patients having a reduction of at least 50%. Attack duration decreased by 67.2% at 6 weeks (p<0.001) and by 76.2% at 12 weeks (p<0.001) in all of ten patients. Two patients were excluded for reasons unrelated to treatment. Self-assessed general health, physical performance, memory and anxiety also improved by the end of the study. The herbal treatment was well tolerated and no adverse events occurred.

Although this was an open-label trial and hence lacking a placebo group, the results are quite striking. They suggest that combining feverfew in higher doses with willow bark might result in significant clinical improvement in migraine frequency within 6 weeks. The obvious next step is to conduct a placebo-controlled trial for this combination.

Mechanism of Action and Quality Marker Compounds

The pathophysiology of migraine is not fully understood, hence the mechanism of action of feverfew in migraine prophylaxis remains to be adequately defined.

The alpha-methylene-gamma-lactone group of parthenolide and the lactones may provide much of the biological activity of feverfew. As the nucleophile in biological systems is very often a thiol (sulfhydryl) group, the activity is probably due to the alpha-methylene-gamma-lactone group acting as an alkylating agent of such thiol residues[12] and thus disrupting cell function. (Thiol groups, such as cysteine residues in proteins or enzymes, are important constituents of the plasma membrane and cytoskeleton.[13] The assembly of microtubules in the latter is known to be involved in phagocytosis and degranulation of neutrophils.[14])

It had been proposed that a significant increase in serotonin release from platelets triggers the complex chain of events leading to a migraine attack.[15] and that migraines are caused by abnormal platelet activity and abnormal serotonin metabolism.[16] However this theory no longer has widespread currency. In accordance with this earlier theory, the fact that feverfew interacts with the protein kinase C pathway causing an inhibition of granule secretion from platelets suggested an antimigraine effect and polymorphs (antiarthritic effect).[17] It has been demonstrated that this effect is due to the parthenolide and other sesquiterpene lactones in feverfew[18] and neutralization of sulfhydryl groups either inside or outside the cell is involved.[19]

Another theory is that feverfew has anti-inflammatory activity. In one study parthenolide inhibited cyclo-oxygenase (which converts arachidonic acid to prostaglandins) *in vitro*.[20] Parthenolide also inhibited the expression of inducible cyclo-oxygenase and proinflammatory cytokines in macrophages, which correlated with the inhibition of mitogen-activated protein kinases. The alpha-methylene-gamma-lactone group conferred the inhibitory activity.[21] However, aqueous extracts of whole plant and leaf inhibited prostaglandin biosynthesis, but did not inhibit cyclo-oxygenase.[22] Parthenolide did not inhibit cyclo-oxygenase activity *in vitro* with enzyme derived from sheep seminal vesicles.[23] Other evidence suggests that sesquiterpene lactones, including parthenolide, inhibit the release of arachidonic acid from membrane phospholipid stores rather than its conversion into thromboxane B_2 via the cyclo-oxygenase pathway.[23]

Chloroform extract of feverfew evoked changes in the metabolism of arachidonic acid that were similar to those observed in glutathione-depleted platelets.[24] It also inhibited uptake and liberation of arachidonic acid into or

from platelet membrane phospholipids,[25] which may be the result of altered cytoskeletal-membrane interaction.[14] SH groups (sulfhydryls) are essential for phospholipase A_2 activity (and the liberation of arachidonic acid),[26] which may have been affected by feverfew.[25] Chloroform extracts of feverfew produced dose-dependent inhibition of the generation of thromboxane B_2 and leukotriene B_4 by stimulated leucocytes. The activity was due to other lactones as well as sesquiterpene lactones.[27] 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 6 to 9 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.

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