Editorials

Feverfew - an ancient remedy for modern times?

Cinchona bark had been used in Peru to treat 'marsh agues and intermittent fevers' before its introduction into Europe in 1633. After its properties also became evident to Europeans, the bark was in great demand and consequently it was expensive. This led the Reverend Edward Stone to seek a cheap and effective substitute and in 1763 he discovered the curative powers of the bark of the willow tree. Many years later the active component of cinchona bark was found to be quinine, and willow bark yielded salicylic acid, from which a derivative acetylsalicylic acid (aspirin), was subsequently synthesized.

Another plant that for centuries has been recommended for its medicinal properties is feverfew (*Tanacetum parthenium*). This is an aromatic, hardy annual with chrysanthemum-like leaves and daisy-like flowers that grows prolifically in gardens and other open spaces. Like cinchona and willow bark it has been used for 'intermittent fevers'. It has also been used for a variety of other conditions. Berry[1] perused the old herbals and pointed out that the ancient uses of feverfew may be categorized broadly into three main groups: treatment for fever, headache and migraine; for difficulties in labour, threatened miscarriage, and regulation of menstruation; for relief of stomach ache, toothache and insect bites. Unlike cinchona and willow bark, feverfew has not yet yielded a clinically useful drug such as quinine or aspirin. Nevertheless, in recent years there has been a considerable amount of scientific interest in the plant. This interest has paralleled a massive surge of lay-interest in feverfew and in its medicinal properties and it is currently widely used as a prophylaxis against headache and migraine, for relief in arthritis, and for treatment of psoriasis.

What are the indications of clinical effectiveness other than those that derive from the old herbal literature? Firstly, there are many anecdotal reports of efficacy[2-5]. Secondly, Johnson[2] evaluated the results of a questionnaire completed by migraineurs who had tried feverfew, and concluded that feverfew was providing significant benefit in this group of people. Thirdly, as a follow-up to this work, Johnson *et al.*[6] carried out a double-blind study in which 17 people who were already taking feverfew regularly for prophylaxis against migraine were randomly assigned to receive either feverfew or placebo. Those switched to placebo experienced a significant increase in the frequency and severity of headache, nausea and vomiting, while those who continued to take feverfew did not. A group of investigators in Nottingham have just completed a large, double-blind, randomized, placebo-controlled, crossover study of feverfew in migraine, and studies on arthritis and psoriasis are also in progress.

Feverfew has long been referred to as 'a medieval aspirin' and in 1772 J Hill (*The family herbal*) claimed that 'in the worst headache this herb exceeds whatever else is known'[7]. This claim was made only 9 years after the Reverend Edward Stone's[8] presentation to the Royal Society on the beneficial effects of the bark of the willow tree, so it is tempting to speculate that 'whatever else is known' included willow bark. If so, might feverfew contain a drug that is superior to aspirin for the treatment of headache and other conditions? What attempts have been made to identify such a drug and to establish the mode of action of feverfew and its constituents?

Interest in the biochemical properties of feverfew was stimulated when Collier *et al.*[9] reported that an extract of feverfew inhibited prostaglandin synthesis in seminal vesicles. Aspirin also inhibits prostaglandin synthesis but a different mode of action was thought to be involved for feverfew. Since then, other evidence that feverfew inhibits synthesis of prostaglandins (and also thromboxanes and leukotrienes) in various cells and tissues has been obtained and the effect may be via inhibition of phospholipase A_2[10-13]. Makheja and Bailey[10] reported that an extract of feverfew inhibited platelet aggregation and Heptinstall *et al.*[11] confirmed this although they doubted that this was a direct consequence of inhibition of the synthesis of prostaglandins and thromboxanes. They found that feverfew also reduced the secretory capacity of platelets and also of leucocytes. They speculated that inhibition of release of serotonin from platelets might be relevant to any beneficial effect of feverfew in migraine, since serotonin is implicated in this condition, and that the effect of feverfew on white cells could account for its claimed benefit in rheumatoid arthritis. More recently, it has been shown that feverfew extracts inhibit various white cell activities in addition to secretion[14], and also inhibit the release of histamine from mast cells[15]. O'Neill *et al.*[16] also observed cytotoxic effects after prolonged incubation of mononuclear cells with feverfew *in vitro* and has speculated on the relevance of this to rheumatoid arthritis.

Feverfew contains a series of compounds known as sesquiterpene lactones and one such compound is parthenolide. Groenewegen *et al.*[17] have fractionated the constituents of extracts of feverfew that are responsible for the anti-secretory effects and have identified them as parthenolide and parthenolide-like materials. Such compounds contain a chemical unit (an α-methylene butyrolactone unit) that reacts with compounds that contain sulphydryl groups and evidence has been provided that the anti-secretory effects of feverfew might involve such a mode of action[18,19]. Studies on extracts of feverfew *in vitro* are a convenient, but poor, substitute for studies on the mechanism of action of the herb in man and, so far, direct evidence that any of these observations that have been made *in vitro* are relevant to man has not been obtained.

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Assuming that feverfew really is of value in migraine and other conditions, what is its availability and how should it be taken? Feverfew is commonly taken orally either as fresh leaves or in tablets or capsules. Feverfew has a bitter taste and users try to disguise this by taking it with food. The commonly accepted dosage for the fresh material is two or three small leaves a day. In their study of feverfew in migraine Johnson *et al.*[6] gave 2×25 mg dried feverfew leaf in capsules, once a day for 6 months. However, the optimum dose or duration of treatment has not been established. Commercial feverfew products can be described as herbal or homeopathic and are purchased in health shops and pharmacies. The stated amounts of feverfew per tablet or capsule for different products varies from 25 to 250 mg[20]. However, Groenewegen and Heptinstall[21] examined a selection of feverfew products and on the basis of an assay in which they measured the effects of extracts of the products on secretory activity and compared the results with those obtained for fresh leaf, concluded that herbal preparations always contained smaller amounts of feverfew than might be anticipated. This may be because the products contain whole plant rather than leaf so that the activity of the leaves may be diluted out by stalk material. Activity may also depend on the stage of growth of the plant and there may also be problems with instability. Groenewegen and Heptinstall[21] also examined homeopathic preparations of feverfew and since these preparations are usually labelled '6×' (i.e. a one in a million dilution) they found that the amounts of feverfew in these homeopathic brands were lower than the limit of detection of their assay.

If feverfew is already widely used (and such use may increase when the current clinical trials are completed), is it safe, what are the side effects and are there any contra-indications? Herbal remedies are not yet subject to the statutory safety tests required for conventional pharmaceuticals and evidence for the safety of the herb relies on anecdotal experience. Genetoxic effects have been looked for but none have been found[22]. There have been no reports of any serious adverse effects of taking feverfew. Side effects include mouth ulceration and abdominal pain[2,6]. The occasional case of contact dermatitis has been reported by those who handle feverfew (see ref. 20). Until more is known about feverfew it is considered that it would be unwise to give it to children or to take it during pregnancy or lactation.

Most physicians would regard the present situation with feverfew as unsatisfactory. More information is needed on its clinical efficacy, mode of action, safety, side effects and contra-indications. There is also a need for better standardization of commercial products. Although most physicians would reckon that the time for recommending feverfew as a medicine is not yet here, lay interest in feverfew is high, as reflected by the recent publication of two paperback books[4,5] on the properties of the herb. Patients will be asking their doctors about feverfew and many will be trying it unsupervised. It is important that physicians ask about the use of alternative medicines such as feverfew, keep an ear open for possible adverse effects, drug interactions and so on, and report to the CSM using the yellow card system. In addition, they should be in a position to give their patients the few facts on feverfew that are currently available, as outlined above.

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