

SAFETY OF HERBAL V ORTHODOX DRUGS one of the key issues under consideration by the IMB.

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Safety of herbal vs. orthodox drugs is one of the key issues under consideration by the Irish Medicines Board (IMB). The IMB have established an expert Scientific Committee on Herbal Medicine Products to evaluate and report on the safety of herbs. A number of herbs including Hypericum perforatum (St John's Wort), Ginkgo Biloba, Tribulus terrestris (Bai Ji Li), etc, as reported in the Irish Medical Times (Vol. 34. No18 April 2000), have been designated prescription only by the IMB and are now only available on prescription by a medical doctor. In a classic Catch-22 scenario, these valuable herbs do not have Irish product licenses and very few doctors have formal training in herbal medicine in Ireland so this ruling effectively amounts to a ban.

Over the past few years there has been an increase in the number of reports regarding the toxicity of herbal remedies though practitioners of herbal medicine would argue that the issue of safety of Chinese herbs should not be considered in isolation from the principles and practice of Traditional Chinese Medicine (TCM). TCM has developed through extensive observation and clinical testing over the last 3000 years as a system of medical theory and practice, which is different from, but no less valid than, Western Medicine. It has its own consistent theoretical concepts, philosophy of health and disease, theory of disease aetiology, system of disease classification and coherent diagnostic and treatment framework. Over the last 3000 years TCM has developed a unique holistic understanding of health and disease, a view that has many correlations with modern physics, psychology, sociology and ecology.

Maciocia (1999) points out that many of the reports of alleged toxicity of Chinese herbs concerns situations where they were prescribed without regard to the above principles of Chinese medicine, where herbs were incorrectly identified, self-administered, contaminated with western drugs or with heavy metals (e.g. Shu Gan Wan contaminated with mercury), prescribed by an unqualified herbalist, or used as single herbs for spurious reasons.

Difference Between Drugs and Herbs

Drugs and herbs are different in their pharmacokinetics. Plants contain compounds such as alkaloids, glycosides, saponins, oils, tannin, saccharides, flavonoids, etc., whose absorption, distribution, metabolism and excretion may be studied in the same way as those of drugs, however, there are important differences between the use of drugs and that of whole plants. When the whole plant is used, it contains a balanced mixture of many different compounds. These have an effect on the body that is very different from that of a synthetic drug, or indeed that of an isolated active constituent of a plant. For example, antimuscarinic drugs act by blocking the parasympathetic response and thereby reduce intestinal motility and spasm. The problem with this approach is that, after absorption, a drug is distributed throughout the body, thus affecting other parts in addition to the intended one. Thus an antimuscarine drug prescribed for the bowel will also reduce gastric secretion, raise intra-ocular pressure, increase heart rate and stimulate the CNS. These side effects include such symptoms as constipation, palpitations, arrhythmias, reduced bronchial secretions, urinary urgency and retention, dilation of the pupils, with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin.

There is no synthetic drug that is free from side effects. The same applies to isolated ingredients of an herb. Ephedrine, for example has pronounced sympathomimetic effects, but the source of it, the plant *Ephedra sinica* (Ma Huang), has considerably less sympathomimetic effects when given as a whole because the balance of alkaloids contained in it, is such that through checks and balances it results in fewer, less severe side effects. Nevertheless, if *Ephedra sinica* is used unwisely it may cause sympathomimetic effects in patients with prostatic enlargement to the extent that urination ceases or may precipitate a glaucoma attack or stroke in hypertensive patients. These effects were well known to traditional herbalists and so Ma Huang has always been combined with other herbs (e.g. *Radix Paeoniae Lactiflorae* - Bai Shao) in order to further minimize its side effects.

The whole is greater than the sum of its parts

There are many examples of such homeostatic effects of the compounds present in the whole plant: *radix Ginseng*, for example can stimulate but also depress the CNS and *Radix Angelicae sinensis* can contract but also relax the uterus (Macioccia 1999). It is well known that isolated constituents of an herb may not give the same clinical response as a crude preparation of that herb. Frequently, the total therapeutic activity is greater than, or different from, the therapeutic activity of the individual

constituents. Synergism or antagonism resulting from the complex nature of the extract is probably the cause of such observations. Evans (1996) claims “it is thus possible that a fraction from a plant extract, although showing significant biological activity, possesses no single constituent with this activity. Conversely, a fraction showing no activity may still contain an active constituent”.

Plants act on the body in a complex, balanced homeostatic physiological way rather than acting in the manner of modern pharmacological drugs. From this perspective whole plants are closer to foods than to drugs. The synergy among herbs in a prescription is such that compounds are formed that are not in the individual herbs. M.Nose et al (1997) for example, in a study on the formula Xiao Chai Hu Tang found that its ethanol-precipitated fraction contains a polysaccharide that enhances phagocytosis by macrophages. In addition, when herbs are used in combination, because of the synergistic interactions of the various herbs, their overall action is greater than or different from what might be expected from the sum total of the prescription’s individual active ingredients. Ancient Chinese prescriptions are blended in a way that reduces the side-effects of their individual constituents. This is the art of formulating a balanced prescription.

The “Emperor”, his “Ministers”, “Assistants” and “Messengers”

Practitioners of Chinese herbal medicine use a fourfold structure that has evolved over many centuries of clinical experience, to formulate balanced prescriptions. The emperor herbs that perform the main function of the prescription, the minister herbs that assist the main herbs, the assistant herbs that usually moderate the influence of the previous two categories of herbs or counteract their side-effects; the messenger herbs that direct the prescription to the designed organ or part of the body. Phillipson (1999) found 12 different classes of chemical compounds in a formula of 10 herbs used in the treatment of eczema. To his surprise, he found that none of these worked when given alone and that all 10 were needed for a clinical effect. He noted that the traditional structuring of a formula with an “emperor”, a “minister”, and assistant and a messenger herb modifies the activity and toxicity of the whole.

The safety of herbal medicines is being questioned more and more by various authors and by potential regulatory authorities like the FDA in the USA and the IMB in Ireland. Their views are usually based on reports of alleged side-effects, adverse reactions, allergic reactions and idiosyncratic reactions to herbs. It is true to say that Chinese herbs can cause such side-effects and reactions but they do so very rarely

indeed. Most of the reports fail to put the incidence of adverse reactions into context and to explain the individual circumstances under which the adverse reactions occurred. There have been few attempts to quantify the incidence of adverse reactions to Chinese herbs. Chan et al undertook a prospective study of hospital admissions over an eight-month period in Hong Kong. Adverse reactions to Chinese herbs accounted for only 0.2% of admissions. If we take into account that most of these admissions were due to poisoning by untreated aconite (which we do not use) the incidence of adverse reactions to Chinese herbs is very small. The aconite problem is of course an example of poor Quality Assurance rather than a problem of Chinese herbal medicine as it is traditionally practiced. If a drug were produced incorrectly, the therapeutic strategy of a correctly formulated product would not be in question.

Many of the adverse reactions reported were caused by poor practice, self-medication, incorrect identification of herbs etc. The report on the practice of Chinese medicine in Australia, "Towards a Safer Choice", (Bensoussan et al 1996) claims that there is an inverse proportional relation between length of training of practitioners and the incidence of adverse reactions. Similarly, when adverse reactions are due to incorrect identification of a plant, this cannot be presented as an example of toxicity of herbs. Therefore, when good quality controls are applied and Chinese herbs are prescribed by experienced practitioners according to the principles and practice of TCM, adverse reactions are extremely rare.

Bias Reporting

Adverse reactions to herbs attract a disproportionate amount of attention in the media when compared to the scale of adverse reactions to orthodox drugs. There is severe bias that minimizes the side effects of drugs, but causes immediate hysteria if a few relatively minor side effects are associated with herbal treatment. The WHO Monitoring Centre in Uppsala in Sweden issued a summary of reports on adverse reactions to herbs worldwide over a 20year period. Two interesting observations emerge from an analysis of the summary. First of all, the total number of adverse reactions reported is 8984, a relatively low figure considering that it covers the whole world and extends over a period of 20 years. Secondly, combinations of herbs seem to cause fewer adverse reactions than single herbs. The summary also breaks down reports into four categories: single herbs; combinations of herbs; herbal and non-herbal combinations as sole suspect drug; and more than one suspect drug at least one of which is non-herbal. The reported adverse reactions in the second category, all-herbal combinations, are only 368 this is only 4% of the total reports of adverse reactions.

Bias Research

The use of clinical trials does not guarantee bias-free research. Sackette (1985) points out 56 known potential sources of bias in clinical research. Bias can creep into experiments at every stage of research, from reviewing the literature, through design, sampling, and analysis to interpretation and presentation of findings. Bias can even affect what papers eventually get published. A study, of 398 experts who review papers for publication, found that they were prejudiced against complementary medicine. This was a randomised, controlled double-blind study using two versions of a fictional report on obesity, which were identical except for the nature of the intervention (an orthodox drug as against a homeopathic remedy). One of the two versions and an assessment form were sent to each of the 398 experts. They were asked to rate the reports significance and publication potential. The findings revealed that the expert peer reviewers were three times as likely to favour an orthodox version over the unconventional version of the report.

The 4th most common cause of Death

A research study to estimate the incidence of serious and fatal adverse drug (ADR's) reactions in hospitalised patients published in the Journal of the American Medical Association in 1998 states that properly researched, regulated, prescribed and properly used drugs are the fourth most common cause of death in the USA. This is over 100,000 deaths per year. That's equivalent to a Boeing 747 crashing every day. The study also reported that over 2 million serious adverse drug reactions (defined as requiring hospitalisation or causing permanent disability) occur each year in the USA. 46 people die every day from Aspirin alone in the USA. Avoidable medical misadventure is the sixth most common cause of death according to the Centre for Disease Control (CDC). A study by the Harvard Medical practice published in 1991 in the New England Journal of Medicine estimated that 1 million people are injured by errors during hospital treatment each year and 120,000 die as a result of these injuries. This number compares with 43,649 motor vehicle deaths, 14,986 deaths from falls and 3959 drowning deaths. A report by Professor Breckenridge of Liverpool University claims that up to 20,000 deaths a year in Britain may be linked to ADR's, that ADR's may be implicated in 5% of all hospital admissions and that they may occur in as many as one in five hospital in-patients. Among patients taking five or more drugs, there is a 50% chance of an adverse reaction. The Australian Medical Journal claims that 9,000 people die from avoidable medical misadventure and that 50,000 people are maimed by medical misadventure every year in Australia. Similar statistics are reported in New Zealand and the UK.

How Independent Are The Regulatory Bodies?

Many voices call for more double-blind, randomised clinical trials on herbs in the name of “evidenced-based” medicine, however, drugs are far from safe and are often marketed after inadequate trails. Indeed the pharmaceutical industry has actively campaigned to lower drug approval standards, resulting in the Prescription Drug User Fee Act of 1992 in the USA and the 1997 Food Administration Act. These acts allow the FDA to collect fees from manufacturers to review new drug applications, transforming the pharmaceutical industry from a regulated industry into an FDA client. Laurie et al, writing in the Journal of American Medical Association, claim that the 10th fluroquinolone antibiotic – trovafloxacin – was approved by the FDA in 1997 despite a pre-marketing clinical trial for prostatitis in which 10% of patients had liver function tests results greater than three times the upper limit of normal. Since February 1998, 140 documented cases of serious hepatic events have been reported, including 9 patients who died or required liver transplants. Similarly, troglitazone, the 11th drug for diabetes in the USA, was approved even though 1.9% of patients in the pre-marketing trials had Liver function tests results greater than three times the upper limit of normal, and 0.4% and 0.2% had 10-fold and 20-fold elevations respectively. Troglitazone has now been associated with a minimum of 43 cases of liver failure, including 28 deaths. The IMB collected £5 million punts in licensing fees from drug companies in 1999.

Conclusion

Greater than 26,000 times more people die from preventable medical misadventure and properly regulated and controlled drugs than from herbal medicine. According to a statistical comparison of frequent causes of death in the USA, death is less likely from taking a Chinese herbal medicine prescription or dietary supplements, than from bee stings, sports injuries, lightning, animal bites, horse riding, drowning, radon gas etc. In conclusion, when good quality controls are applied, and Chinese herbs are prescribed by trained experienced practitioners according to the principles and practice of TCM, adverse reactions are extremely rare.

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