

A Critique of Case Studies Discussing He Shou Wu. An Analysis of Data Sources Used Within Hospitals and the Use of the Yellow Card Scheme

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Introduction

Prevalence of herbal medicine use in the UK

Numerous surveys have attempted to define the prevalence of alternative medicine use. In the UK, self-care life-time prevalence rates were much higher than practitioner only – in the region of 40–50 per cent compared with 10–30 per cent (Thomas *et al.* 1991, 2001; Ernst and White 2000). Thomas *et al.* (2001) report that over 12 months (data relative to 1998), herbal remedies accounted for 19.8 per cent of over-the-counter (OTC) transactions. Another UK survey conducted in 1999 found an overall one-year prevalence of 20 per cent and suggested that herbal medicine was more popular than any other form of alternative medicine (Ernst and White 2000) (cited in W.H.O. 2000). With the forthcoming regulation of herbal medicine in the UK and its continued integration into healthcare practices, public use is set to increase. The number of suspected adverse reactions to herbal remedies is likely to increase as a result.

Availability

He Shou Wu (*Radix Polygoni Multiflori*) is available from groceries in Chinatowns in Australia (Park *et al.* 2001). It can be sought without prescription from various websites located within Europe and the USA. In the UK it can only be prescribed after a consultation with a qualified herbalist.

TCM Mechanisms

Shou Wu Pian is the pill form of He Shou Wu (root tuber). He Shou Wu first appeared in the text *Materia Medica of Ri Hua Zi*. It is used in Chinese medicine to tonify the Liver and Kidney in order to treat the symptoms of weak lower back, dizziness, premature

greying hair, etc (Bensky and Gamble 1993). The raw herb is a laxative, but is rarely used because excessive dosage or prolonged use can cause diarrhoea and the loss of Yin.

Justification for a Review of Literature and Protocols

Currently, if a patient is admitted to hospital with a suspected adverse liver reaction caused by a Chinese herbal remedy, information available to the treating doctors can come from numerous sources, i.e. books, associations, experts, etc (MHRA personal communication). This information can be varied and subjective.

When a Chinese herbal remedy is associated with an adverse liver reaction, the Yellow Card Scheme is initiated. The Yellow Card Scheme is the spontaneous reporting scheme used by the Medicines and Healthcare products Regulatory Agency (MHRA) for collating adverse drug reactions (ADRs) to identify signals of drug safety issues with medicines and herbal products. Healthcare professionals including non herbalists and patients can report their suspicions of ADRs to the MHRA via the Yellow Card Scheme.

The Yellow Card Scheme's primary role is to detect signals - potential associations between a drug/herb or herbal reaction, which have not been previously identified. All signals are evaluated further, using other data sources, to see whether or not they represent a true association (adverse effect) with the medicine. Other data sources regularly used in the monitoring of drug safety in the UK include formal safety studies, published medical literature, information from pharmaceutical companies and other Regulatory Authorities throughout the world together with information on the level of usage (MHRA personal communication).

The MHRA has put in place the Herbal Medicines Advisory Committee (HMCA). HMCA has the same ranking as the Committee of the Safety of Medicines. If any question concerning herbal safety are raised, HMCA will determine whether herbs are safe or not, based on current evidence (D'Alberto and Kim 2006). The findings of HMCA are critical in determining whether specific herbs can or cannot be used in the UK. Its findings are passed onto government Ministers for a final decision.

Published medical literature such as those cited by the MHRA in its justification to impose a Yellow Card upon the herb He Shou Wu, are being published unchecked and unchallenged. Many such papers lack the quality needed to be cited as critical evidence, with a great percentage containing errors; such as issues of herbal quality, contaminants, predisposing issues of liver illness, preparation of the herb, pharmaceutical information, data sources, non GMP products, etc. These reports may claim individual herbs as dangerous, which may affect the decisions made by HMCA and the MHRA as to their continued use in the UK.

Aim of this study

To critique the four cases studies cited by the MHRA in their justification to impose a Yellow Card upon the herb He Shou Wu. In addition, to highlight how information cited in case studies could be better sourced and the Yellow Card Scheme better utilised.

Method

Articles included are those listed by the MHRA as evidence of the potentially adverse effects of the herb He Shou Wu (http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023590&ssTargetNodeId=663).

Results

Four articles were listed by the MHRA in their justification to impose a Yellow Card upon the herb He Shou Wu: Battinelli, Daniele, Mazzanti, Mastroianni, Lichtner, Coletta, Costantini 2004; But, Tomlinson, Lee 1996; Panis, Wong, Hooymans, De Smet, Rosias 2005 and Park, Mann, Ngu 2001. He Shou Wu is the main ingredient of Shou Wu Pian. All four studies discussed patients that had taken the patent Shou Wu Pian.

Discussion

All four studies have failures and shortcomings which affect their conclusions. The failures are further discussed below.

Herbal quality

One of the major dilemmas in determining the potential hepatotoxins of herbal preparations is morphologic identification of all ingredients. Individual ingredients may not be pure substances and not all components may be listed or, indeed, known. Chinese herbal products are not subjected to the controls and rigorous testing for safety and efficacy that drugs have undergone. However, new systems such as the GMP initiative and approved supplier schemes provide some reassurance of herbal quality. None of the four reports discussed if Shou Wu Pian was a GMP product, or whether it was sourced from an approved supplier, such as those endorsed by the Register of Chinese Herbal Medicine (RCHM). The name of the herbal manufacturer was not given, which would allow examiners to identify if the manufacturer was licensed by the Chinese government to export the herbal remedy. No batch number was specified which would allow researchers to identify if impurities had entered into a particular batch. In addition, no mention was made in any of the four reports as to the area in China where the He Shou Wu was cultivated and processed into Shou Wu Pian. There are currently six different areas in China where He Shou Wu is grown; Henan, Hubei, Guangxi, Guizhou and Sichuan (Bensky and Gamble 1993). By specifying this information, it would allow the reader to identify if any impurities could have been introduced by the cultivation and processing of the herb in a particular area, for example pesticides or heavy metal soil contamination (Saad, Azaizeh, Abu-Hijleh and Said 2006; Peraza, Ayala-Fierro, Barber, Casarez and Rael 1998).

There have been some reports of herbal products being adulterated with pharmaceuticals or contaminated with heavy metals (Ernst 2002). Three out of the four reports tested the patent Shou Wu Pian for any substitution of the active herb (Panis *et al.* 2005; But *et al.* 1996 and Battinelli *et al.* 2004). Of those three, none noted any additional pharmaceutical agents. The Park *et al.* (2001) study did not rule out adverse liver reactions caused by pharmaceuticals in the patent. Only one study Battinelli *et al.* 2004 tested for heavy metal content. It may be the case in three of the reports that heavy metal content was the cause of the adverse liver functions, although it was ruled out in the Battinelli *et al.* 2004 study.

Preparation

He Shou Wu is harvested in either spring or autumn (Bensky and Gamble 1993). The processed herb is the common form and is prepared by cooking He Shou Wu with Chinese yellow wine and the juice of the black soybean (But *et al.* 1996, Panis *et al.* 2005). Poor quality yellow wine or black soybean may have contaminated the final product; Shou Wu Pian and be the cause of the adverse liver reactions. The protocol used to prepare He Shou Wu has several components, all of which could introduce impurities, especially since not all He Shou Wu is prepared within a modern pharmaceutical factory and can be processed by local farmers using poor quality apparatus. This highlights the importance of the GMP initiative. It is therefore reasonable to suggest that the four cases of adverse liver function highlighted in the reports may be attributed to failures in preparing the raw form of He Shou Wu.

Pharmacology

In all four studies the subjects reported using the pill form of Shou Wu Pian. Because Chinese herbal patents are not made from concentrates the dosage is spread throughout the day. A typical dosage would be eight pills three times a day. All four studies noted the subject took the recommended or a lower dosage of Shou Wu Pian.

As Shou Wu Pian is given orally, it undergoes first pass metabolism. As a rule, about 75% of a drug given orally is absorbed in 1-3 hours, but numerous factors can alter this. Marked individual variations occur in the extent of first-pass metabolism of a given drug, which may produce a degree of unpredictability such as age, genetic factors, idiosyncratic reactions, disease and drug interactions (Rang, Dale and Ritter 1998). In conventional medicine, an active dose is calculated once it undergoes first pass metabolism. In Chinese medicine, there is a lack of research that accurately correlates the exact dosage needed for therapeutic effects versus toxic reactions (therapeutic index). Instead, dosage is based on historical literature involving practitioner experience.

In terms of herbal toxicity, the administered dosage is critical in determining whether the herb is toxic at a given dose. It is common when producing herbal patents for the dosage of individual herbs to alter from one patent to another even though they carry the same name. This is based upon information supplied to the pharmaceutical company by herbalists working for them. However, the differences in dosage levels are minor and unlikely to be the cause of adverse liver functions. In respects to Chinese medicine theory, altering the dosage of individual herbs is important in 'balancing' the formula's effects.

Western medical research

Polygonum species are generally regarded as safe (De Smet 1993). He Shou Wu contains two anthraquinones; emodin and physcion. In all four studies, none were able to conclusively demonstrate a link between the patient's irregular liver function and the use of He Shou Wu. However, it was noted in all four studies that cessation of the herbal supplement Shou Wu Pian coincided with the return of normal liver function.

Recent interest in the potential use of He Shou Wu in prevention and treatment of neurodegenerative diseases, especially Alzheimer's and Parkinson's' disease, has stimulated further research into its active components and therapeutic actions (Um, Choi, Aan, Kim and Ha 2006; Li, Matsumoto, Murakami, Tezuka, Wu and Kadota 2005; Dharmananda personal communication). The herb contains several derivatives of tetrahydroxystilbene that are antioxidant and anti-inflammatory compounds investigated for their effects on neurons (Zhang, Xing, Ye, Ai, Wei and Li 2006). He Shou Wu also contains the laxative compound emodin and a number of derivatives of emodin. This accounts for a potential adverse effect of the herb; causing loose stools when consumed in quantity. Emodin also serves as a liver-protective agent (Chiu, Mak, Poon and Ko 2002).

History of toxicity

But *et al.* (1996) performed a search using CHIMERA, a database of herbal poisoning reports in Hong Kong and found several adverse reactions attributed to He Shou Wu including rash, fever, abdominal pain, dyspnoea, visual problems and palpitations. However, amongst these adverse reactions, no mention was made in respects to liver function. In a separate report by Ernst (2003), no adverse reactions were associated with He Shou Wu amongst children. No adverse effects upon the liver have been reported in classically recorded Chinese materia medica texts.

Data Sources

In all four studies, the authors used each other's case reports as a source of information. Only one study (But *et al.* 1996) accessed additional information through the CHIMERA database. It was not made clear what other information sources the treating doctors in the four studies used during their investigations. The doctors did not contact the pharmaceutical companies and analysed their data, nor enquired with any specialist herbal advisory service or medical association or analysed classical Chinese medical literature for any reports of adverse liver reactions associated with Shou Wu Pian.

Doctors get their information from a number of sources including books, web sites, specialist societies and experts (Royal College of Physicians personal communication). The Royal College of Physicians lists five possible sources of information for doctors:

1. <http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/ComplementaryAndAlternativeMedicine/fs/en>
2. <http://www.library.nhs.uk/cam>
3. <http://www.bl.uk/collections/health/amed.html>
4. <http://www.nhsdirectory.org/default.aspx?page=CHM&t=y>
5. <http://www.intute.ac.uk> (Royal College of Physicians personal communication)

Of those five information sources, none had any information on Chinese dried herbs or patents. This lack of a coherent source of information on herbal remedies is confusing and problematic and may inadvertently label herbal medicines as dangerous. Some hospitals such as Guy's and St Thomas' have created specialist Chinese medicine advisory services. This however, is an isolated case and access is limited.

Reviewer's conclusions

Safety

There is a great need for doctors to publish case studies highlighting concerns with a herbal remedy. However, the number of errors present in their research undermines the reports findings. This is made evident by HMAC's own findings on He Shou Wu, which urges further investigation into "preparation and processing" of He Shou Wu into Shou Wu Pian (HMAC 2006). This suggests that errors in the protocol used to process the raw form of He Shou Wu into Shou Wu Pian could have introduced impurities into the final product. This may be a likely cause of the adverse liver reactions. More investigations are needed to evaluate if this is the case.

Implication for medical establishments

All four studies illustrate the lack of a coherent source of information on herbal remedies for doctors as well as protocols that should be in place to investigate possible adverse reactions to herbal remedies. There is a clear lack of understanding of herbal medicine in western hospitals. This allows for miss-diagnosis of adverse reactions in cases where herbs were and were not responsible. The present situation wastes time and money and more importantly, could affect patient's health.

It is feasible that information could be compiled into a book with an accompanying CD ROM and even be web

based with a telephone advisory service. It should outline important information on individual herbs and formulas, similar to that compiled by the British National Formulary (BNF). By providing accurate information to doctors, patients could be treated quicker and more effectively. In addition, the number of Yellow Cards issued against herbal remedies could be reduced.

The book, CD ROM and website could be named the Chinese Herb Index (CHI). It should include individual herbs and formulas with the following information:

- Mandarin and Cantonese names with English/Latin and pharmaceutical equivalent.
- TCM actions and indications.
- Modern pharmaceutical indications.
- Recommended dosage.
- TCM contraindications.
- Modern pharmaceutical contraindications.
- Classically cited side effects.
- Modern pharmacological side effects.
- Areas cultivated and processed.
- Method of preparation and processing.
- Definition and explanation of GMP (optional).
- List of RCHM approved suppliers (optional).

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