

Safety of herbal medicines in children

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A commentary on the paper by Ramsay *et al*

Herbal medicines are used extensively by children in the West. They are an important part of complementary and alternative medicines (CAM). A study of over 500 children in the southwest of England reported that almost one in four children had received CAM therapy.¹ Two studies in North America reported that over 10% of children had used at least one form of CAM therapy.^{2,3}

EFFICACY

It is important that health professionals adopt a non-judgemental approach with regard to parents who use CAM for their children. Many herbal medicines may be effective as we know that many plant derived chemicals are the basis of conventional drug therapies. Parents will often use a herbal medicine for their children on the basis that it is more "natural" and safer. One third of parents will use CAM because they feel that they are safer than conventional medicines.³

TOXICITY

There have been numerous studies in relation to the incidence of adverse drug reactions to children in hospitals.⁴ The toxicity of certain herbal medications is well recognised on the basis of case reports.⁵⁻⁹ The incidence of toxicity in relation to herbal drug therapy, however, is unknown. A recent systematic review of the toxicity of CAM concluded that there were insufficient data to determine the incidence of toxicity of herbal medicines.¹⁰ Table 1 gives examples and the mechanisms of toxicity.

The toxicity of herbal medicines may be due to intrinsically toxic constituents

of the herbal ingredients. Examples of this include viscotoxins, which are constituents of mistletoe and are both cytotoxic and cardiotoxic.¹¹ Other examples include cyanogenetic glycosides which are present in the kernels of a number of fruits. Gastric hydrolysis of these compounds results in the release of hydrogen cyanide.^{11,12} Other important mechanisms associated with the toxicity of herbal medicines include allergic reactions and contamination by heavy metals.

DRUG INTERACTIONS

It is important to appreciate that herbal medicines may interact with prescribed medicines. Concurrent use of herbal or homeopathic remedies alongside prescribed or over the counter medicines is frequent.³ Drug interactions are a significant problem in association with the use of St John's wort.^{11,13} St John's wort may induce drug metabolising enzymes within the liver as well as possibly affecting P-glycoprotein, which is a transport protein present throughout the body.^{11,13}

FORMULATION

The paper by Ramsay and colleagues highlights the important issues in relation to the formulation of herbal medicinal products.¹⁴ The Medicines Control Agency has expressed concerns regarding the variable quality of unregulated herbal products.¹¹ The paper by Ramsay *et al*, however is highly suggestive that potent corticosteroids have been deliberately introduced to herbal creams in order to increase their efficacy.

Unfortunately inappropriate formulation development is not restricted to complementary therapies. In 1937, 76

Americans, many children, died following the preparation of a sulphonamide solution in 72% diethylene glycol.¹⁵ These deaths resulted in legislative changes in the USA to ensure that the quality of medicines was formally assessed.

In many developing countries medicines are available in street markets and the source of the medicines is unknown. Forty seven children died in Nigeria following the deliberate use of diethylene glycol as a solvent for paracetamol instead of propylene glycol.¹⁶ There have been similar tragedies affecting children in Bangladesh and Haiti.^{17,18}

It is important that the quality of herbal medicines is significantly improved. This can only be achieved by parents, health professionals, and regulatory authorities working in conjunction with the suppliers of herbal therapies to ensure that they are of sufficient standard. Prosecution of suppliers who deliberately adulterate herbal creams is urgently required. Parents who wish to use herbal medicines should try to obtain them from reliable sources—that is, one of the main herbal practitioner associations.¹⁴

Arch Dis Child 2003;**88**:1032–1033

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Table 1 Toxicity associated with herbal medicines

Herbal product	Mechanism of toxicity	Toxicity
Tibetan Herbal Vitamin	Contamination with lead	Seizures, developmental delay, anaemia
Jin Bu Juan	Incorrect plant used (genus <i>stephania</i> not <i>polygala</i>)	Respiratory depression, bradycardia, CNS depression
Neem tree oil	Incorrect route (given orally instead of topically)	Encephalopathy
Various traditional	Direct toxicity of herbal product (contain pyrrolizidine alkaloids)	Hepatic veno-occlusive disease
Wau wa cream	Adulteration of product	Corticosteroid toxicity
St John's wort	Induction of drug metabolism leading to drug interaction	Depends on drug (often loss of therapeutic effect)

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Leptospirosis

Detection of leptospirosis in India

J M Vinetz

A commentary on the paper by Karande *et al*

Leptospirosis is a zoonotic disease of global significance.¹ In recent years, clinicians and epidemiologists have given increasing attention to this disease, with particular focus on two features: its epidemic potential; and severe manifestations, particularly pulmonary haemorrhage.^{2,3} However, in leptospirosis endemic regions, one quarter of patients (or more) presenting with simple fever have serological results suggesting the diagnosis of acute leptospirosis. Severe leptospirosis seems to be the tip of the iceberg of leptospiral infection: most people infected by *Leptospira* seem to have either have simple, undifferentiated fever (fever without focus) or subclinical illness.⁴

Fever is a cardinal manifestation of illness and is a common clinical complaint. In industrialised countries, an undifferentiated febrile illness is often referred to a "viral syndrome" or a "flu-like illness", with the expectation that it will resolve itself. In the developing world, depending on locale, an undifferentiated fever may be called "dengue" or "malaria", or depending on the verve of the investigator, a "ricketsial" or "ehrlichial" illness, etc. Regardless of geographic context, however, most often the diagnosis of an undifferentiated fever is on the basis of clinical observation without precise documentation by laboratory, and treatment is symptomatic or specific antimicrobial therapy provided empirically. I would suggest that the term "flu-like illness" is a misnomer and should simply be abandoned as dangerous and the result of fuzzy thinking.

What really is meant by "flu-like illness"? To this author, an influenza-like illness is characterised by the onset of general symptoms such as fever, headache, myalgia, arthralgia, accompanied by upper or lower respiratory symptoms such as sore throat, nasal congestion, and cough. While influenza has a prodrome indistinguishable from many other acute infections, its archetypal manifestations are respiratory. Therefore, regardless of geographic location, to describe fever accompanied by general complaints,

without respiratory symptoms, as "flu-like" or "viral syndrome" is fraught with hazard and should prompt consideration of other diagnostic possibilities. The underlying meaning of "flu-like illness" is profoundly important, however, particularly today in the era of bioterrorism (for example, pulmonary anthrax which starts out as an undifferentiated fever, later progressing to pulmonary manifestations) and the severe acute respiratory syndrome (SARS). One can only judge with apprehension the next influenza season when many true "flu-like" syndromes present to hospital!

"An outbreak of febrile illness occurred in the context of seasonal flooding in Mumbai"

So it was the diagnostic importance of undifferentiated fever that motivated Karande *et al* to study leptospirosis in Mumbai, as reported in this issue of the *Archives*.⁵ The authors took advantage of an outbreak of febrile illness that occurred in the context of seasonal flooding in Mumbai. As is typical with outbreaks of undifferentiated fever,^{2,6} public health authorities thought that the outbreak was a "viral" or "dengue-like" illness. When diagnostic testing showed no evidence of dengue virus transmission, other diagnostic possibilities were considered; among them, for some reason not described by the authors, leptospirosis. During a six week period following the Mumbai flood of July 2000, public health authorities in Mumbai issued a directive to admit all patients reporting to its public hospitals with undifferentiated fever and study them for leptospirosis. The paediatrics department at the authors' institution admitted 53 children aged 1 month to 12 years of age with suspected leptospirosis. About one third had serological results suggesting acute leptospirosis. Of equal importance, there were a number of other final diagnoses in these patients, including malaria and

typhoid. The risk of leptospirosis rose with age; most cases were 6–12 years old. Four clinical features seemed to be helpful in distinguishing leptospirosis from other causes of fever: contact with flood water, conjunctival suffusion (conjunctival erythema without discharge), abdominal pain, and rash (maculopapular and erythematous, most prominent on the trunk). The zoonotic origin of infection was not investigated. There were no fatalities; all confirmed leptospirosis cases received intravenous penicillin and recovered without sequelae.

The paper of Karande *et al* is nominally about leptospirosis but raises a central issue in emerging infectious diseases regarding the importance of undifferentiated fever occurring in an epidemic setting. The authors make specific recommendations about the importance of working up patients who come into contact with flood waters, and that children ought to avoid playing in and walking through flood waters. More important for public health, there needs to be a general awareness and deeper understanding of the concept of undifferentiated febrile illness. Astute clinicians and well equipped clinical laboratories need to be vigilant in observing and explaining outbreaks of undifferentiated febrile illness. Only in this way can we avoid the intellectual abyss of dismissing such clinical presentations as only "viral" or "flu-like" illnesses, and delay the recognition of important epidemics of known and newly emerging infectious diseases.

Arch Dis Child 2003;**88**:1033

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