

RENAL DISEASE WITH THE USE OF HERBAL REMEDIES

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ABSTRACT

Alternative and indigenous systems of medicine are popular. Especially amongst the poorer sections of society in the developing world. Their use in the developed countries has also increased in recent times. Herbal remedies are prepared by quasi-trained herbalists Largely outside the ambit of regulatory control and not tested for safety. Toxicity can occur when a herb with unknown toxicity is consumed, incorrect identification leads to substitution of an innocuous herb with a toxic one, preparations are contaminated with toxic non-herbal compounds or when a herb potentiates the nephrotoxic effect of a conventional therapy. Various renal syndromes were reported after the use of medicinal plants including tubular necrosis, acute interstitial nephritis, fanconi's syndrome, hyperkalemia / hypokalemia, hypertension, papillary necrosis, chronic interstitial nephritis, nephrolithiasis and cancer of urinary tract. It seems critical that care givers be aware of potential risk of such often underreported therapy and carefully question their patients about their use.

Keywords: Fanconi's syndrome, hyperkalemia, hypokalemia, nephrolithiasis, interstitial nephritis.

INTRODUCTION

The use of herbal medicine has increased dramatically in past many years and may lead to renal injury. The source and composition of these medicines vary in different parts of the world.. In most countries herbal medicine and products not regulated as medicines. Herbal poisoning may be secondary to the presence of drugs or heavy metals, interaction with pharmacokinetic profile of concomitantly administered drug or associated with a misidentified herbal species.

Plants have provided remedies for human maladies for centuries. Currently, approximately 120 distinct chemical substances are derived from plants are in use as drugs¹. Production of modern pharmaceutical compounds requires adherence to good manufacturing practice (GMP) conditions . Rigorous safety and efficacy studies are essential before getting approval for human use. Herbal medicines, often dispensed in crude form by traditional healers, are the mainstay of health care for a large proportion of the population in

underdeveloped countries due to a combination of non-availability of modern medical care, ignorance and poverty ^{2,3}.Over three-quarters of the population in sub-Saharan Africa depends on traditional medicine for primary health care,⁴⁻⁶ more than 60% of the Chinese use herbal therapy⁷ and a significant part of the rural population in the Indian subcontinent relies on indigenous (Ayurvedic and Unani) medical systems that use herbs, ash and heavy metals.⁸ The use of herbal medicine has increased in developed countries.⁹ Alternative remedies are perceived to be innocuous and may provide placebo effects from the rituals associated with their ingestion.¹⁰ Use of herbal medicine increased in the USA by 25% between 1990 and 1997.¹¹ Approximately 10% of US adults were using herbal remedies in 1999. Approximately \$US 4.2 out of the \$US 17.8 billion spent on 'dietary supplements' in 2001 were for herbs and other botanical remedies.¹² Approximately \$US 5 billion worth of over-the-counter herbal medicines were sold in the

European countries in 2003.¹³ Herbal medicine accounted for approximately 26% of all alternative and complimentary medicine use in Australia.¹⁴ The global annual turnover in herbal medicines is estimated at \$US60 billion, representing approximately 20% of the overall drug market.¹⁵ The nephrotoxic potential of herbal remedies is being increasingly recognized.^{3,16,17} Causality is suspected on the basis of a temporal association between the intake of an agent and the injury his is easier to establish in the case of acute toxicity where the interval between intake and presentation is short and the history of use of the offending agent is easy to recall, but harder in chronic diseases that progress slowly. Remote exposure may be forgotten or even denied for fear of social stigmatization. Herbal toxicity can develop in any of the following situations: ^{3,18,19} (i) consumption of a herb with unknown toxicity; (ii) incorrect identification leading to substitution of an innocuous herb with a toxic one; (iii) deliberate or inadvertent contamination with nephrotoxic non-herbal drugs (e.g. non-steroidal anti-inflammatory agents), pesticides or chemicals (e.g. heavy metal contamination from soil or water); (iv) Potentiation of the toxic effect of a conventional drug due to interaction with a compound present in the Herb; and (v) consumption of meat from an animal that has grazed on toxic plants (e.g. hemlock).

The kidney is the route of excretion of most of the substances present in the herbs. The high blood flow rate and large endothelial surface area of the kidneys ensures delivery of large amounts of toxin to the renal parenchyma. High concentrations may be reached in the medulla because of active tubular transport, especially during a state of fluid deprivation. Renal involvement associated with the use of traditional medicinal products can take several forms ¹⁶⁻¹⁸, including acute kidney injury, tubular function defects, dyselectrolytaemias, systemic hypertension, chronic kidney disease (CKD), renal papillary necrosis, urolithiasis and urothelial cancer. Patients with pre-existing CKD can develop complications due to herbal medicine use; some examples are *Ginkgo biloba*-induced haemorrhagic complications, glycyrrhizic acid-induced hypertension and hypokalaemia, alfalfa or noni juice (*Morinda citrifolia*)-induced hyperkalaemia, star fruit (*Averrhoa carambola*)-induced encephalopathy and cranberry juice-induced nephrolithiasis The precise mechanism of injury is not known in most cases Because adverse

event reporting is voluntary, toxicity has been documented mostly in case reports.

Chronic kidney injury has been described in association with ingestion of several botanicals Some examples are described below. The leaves of the creosote bush (*Larrea tridentata*), a Native American shrub, are commonly used to make tea in the south-western states of North America. Its roots and leaves are also dispensed in capsule or tablet form as a drug called chaparral. The active substance, nordihydroguaiaretic acid, is an antioxidant and blocks cell division.²⁰ it was thought to have anticancer properties, but hepatotoxicity precluded further testing. This compound is also used experimentally to induce cystic renal disease in rats.

Renal cysts and renal cell carcinoma have been reported following long-term consumption of chaparral tea.²¹ Liquorice (*Glycyrrhiza glabra*) has diuretic properties and causes hypokalaemia. Severe hypokalaemia can lead to rhabdomyolysis and acute kidney injury. Chronic hypokalaemic nephropathy secondary to long-term consumption of liquorice has been reported.²²

Yohimbine, present in the plant yohimbe (*Pausinystalia yohimbe*), is known to cause systemic lupus erythematosus (SLE). A case report described SLE-like syndrome with proteinuria and renal failure following ingestion of this compound that responded to steroids.²³ Willow bark (*Salix daphnoides*) has been implicated in the causation of renal papillary necrosis on the basis of a review of the autopsy of Ludwig van Beethoven.²⁴ The bark contains salicin, which is metabolized in the body to the well-known prostaglandin inhibitor, salicylate²⁵ Obstructive uropathy has been reported following ingestion of fruits of djenkol (jering) trees (*Pithecolobium lobatum* and *P. jiringa*),²⁶ Ma-Huang (ephedra, *Ephedra sinica*),^{27,28} starfruit (*A. carambola*),²⁹ and cranberry (*Vaccinium macrocarpon*) concentrate.³⁰ The toxic compounds can precipitate in the tubular lumina acutely leading to acute kidney injury, especially if consumed in large quantities with little water. Repeated ingestion may cause nephrolithiasis and chronic interstitial nephritis.

Chronic interstitial nephritis has been described following chronic ingestion of several botanicals.³¹⁻³² eg , Bladder-wrack (*Fucus vesiculosus*), a large brown alga, is a common food in Japan. It is used as a flavouring agent and dispensed as a drug in Europe.

Rapidly progressive renal failure resulting in end-stage renal disease has been reported to

occur in women who have taken weight-reducing pills containing the Chinese herbs *Stephania tetrandra* and *Magnolia officinalis*. This so-called Chinese-herb nephropathy (CHNP) is characterized by a pattern of interstitial fibrosis similar to that of Balkan endemic nephropathy. Since the herb powders taken by these patients did not contain tetrandrine, which is present in *S. tetrandra*, but did contain aristolochic acids, it was suspected that a nephrotoxic herb, *Aristolochia fangchi*, had inadvertently been substituted for *S. tetrandra*. This herb contains aristolochic acids, a mixture of nitrophenanthrene derivatives known for their potent carcinogenic action in rats and their mutagenic properties in bacterial and mammalian models. Moreover, Schmeiser et al. were able to detect DNA adducts formed by metabolites of aristolochic acid (aristolactams) in samples of kidneys removed from five patients with Chinese-herb nephropathy⁸ are specific markers of exposure to aristolochic acids and are directly involved in tumor genesis. For these reasons, patients with Chinese-herb nephropathy, or aristolochia nephropathy, appear to be at risk for the development of cancer.³³

In another finding, 12 Chinese people from different areas of Taiwan underwent renal biopsy for unexplained renal biopsy from 1995-1998. Medical history gave no clue to the cause of impaired renal function except for the ingestion of traditional Chinese herbs. Although these Patients ingested herbal drugs from various sources for different purposes, their renal biopsy samples showed amazing similar histological findings with extensive hypercellular interstitial fibrosis and atrophy and loss of tubules in all cases. They also had similar clinical features such as normal/mildly elevated blood pressure, early and severe anemia, low grade proteinuria, glycosuria. Morphologically and clinically, nephropathy was similar to Chinese herb nephropathy (CHNP) reported in Belgium. There by exists a striking relation between nephropathy to consumption of Chinese herbs.³⁴

A case study of Acute renal failure associated with folk remedies was studied in 78 patients in Africa. The definable causes of acute renal failure were pre renal (26.9%), acute tubular necrosis (26.9%), hepatorenal syndrome (6.4%), urinary tract infection (7.7%). Mortality was higher in adults than in infants. Vomiting (51.3%), diarrhea (43.6%), acidosis (80.8%) and volume depletion (62.8%) were most frequent clinical findings. Thus acute renal failure occurring after the use of folk medicine in South Africa is associated with

significant morbidity and mortality and it appears to be the most proximate cause.³⁵

Herbal dietary supplement represent a potentially and possibly overlooked cause of drug interaction in transplant recipients. Two patients were reported that ST John's wort may induce cytochrome 450, 3A4 / p- glycoprotein expression. Both of these are involved in metabolism and absorption of cyclosporine and other immunosuppressant. After 2 transplant recipients started self medicating with ST John's wort, their cyclosporine concentration were sub therapeutic. While on ST John's wort one patient developed acute graft rejection due to low cyclosporine concentration. In both patients termination of ST John's wort returned their cyclosporine concentration to normal therapeutic level. Thus efficient drug monitoring is required for patients on herbal drugs.³⁶

CONCLUSION

The use of herbal medicine has increased dramatically in past years and may lead to renal injury. Herbal poisoning may be secondary to the presence of drugs or heavy metals, interaction with pharmacokinetic profile of concomitantly administered drug or associated with a misidentified herbal species. It seems critical that care givers be aware of potential risk of such often underreported therapy and carefully question their patients about their use of this popular branch of alternative medicines. Public awareness and regulation of use of herbal medicines are required to eradicate this entity from the community.

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