

Does the Use of Traditional Chinese Medicine Cause Heavy Metal Contamination

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In China, the population widely accepts herbs as effective treatment for disease. In fact, herbs are considered drugs and are regulated by the People's Republic of China Pharmacopoeia. Just as is the case in the United States, there are inconsistent quality controls for the manufacture of herbal medicines. One author suggested that almost one-third of traditional Chinese medicines (TCMs) imported from China into California contain ingredients that may be harmful due to the presence of undeclared pharmaceuticals and or heavy metals.¹ The most common heavy metals found in TCM are lead, arsenic and mercury. Heavy metals may be included in TCM for several reasons. They may be included because they have had known medicinal value in the past. In addition, the products may be tainted to hurt the public. Moreover, the contamination may have occurred during the manufacturing process. Finally, the herbs used to manufacture the TCMs might have been grown in soil that was contaminated with these heavy metals.²

As a general rule, heavy metal toxicity results in gastrointestinal irritation, renal toxicity and multi-organ toxicity.³ Gastrointestinal irritation is the most common complaint and may be manifested as nausea, vomiting, diarrhea and abdominal pain.³ Renal toxicity is the second most common adverse event and may be caused by acute and subacute exposure to heavy metals. On the other hand, interstitial nephritis is more likely cause by chronic exposure to heavy metals.³ Multi-organ toxicity may affect the skin and central nervous system as well.³

Lead poisoning is determined by the results of a blood test.⁴ The normal range for lead in whole blood is < 10mcg/dL.³ Intervention is usually required when levels reach between 10-14mcg/dL.³ Signs of lead toxicity include central nervous system effects, peripheral neuropathy, hematologic abnormalities, nephropathy and infertility.³ Effects on the central nervous system seem to occur at blood lead levels above 30 mcg/dL.⁴ In children chronic low levels of lead can result in developmental toxicity. High levels in children and adults can result in encephalopathy.⁴

Arsenic toxicity differs based on the compound, its form and whether it is organic or inorganic. For instance, arsenic gas is the most toxic form of arsenic overall, whereas the trivalent form of arsenic, As³⁺ is the most toxic of the solid forms.⁴ In fact, less than 1mg/kg can be detrimental to children and 2mg/kg can cause death.⁴ An abnormal arsenic level in the blood for adults is > 100-200 mcg/L.⁵ The lethal dose range is 120 to 200mg.⁴ While organic arsenic is nontoxic, inorganic arsenic can cause a variety of symptoms.⁴ In acute arsenic poisoning, these include gastrointestinal effects such as submucosal vesicle formation which can subsequently rupture, muscular and fatal rhabdomyolysis dysfunction, metabolic and hepatic effects including development of negative nitrogen balance, fatty degeneration and cirrhosis and effects to the skin such as alopecia, brittle fingernails and Mee's lines (horizontal white lines appearing on the fingernails).⁴ Chronic arsenic poisoning can manifest in several ways as well. Dermatological symptoms include Bowen's disease, cutaneous cancers and hyperpigmentation.⁴ Neurological symptoms include encephalopathy, polyneuropathy and tremor. Liver involvement can be seen as hepatomegaly, jaundice or cirrhosis.⁴ Nephritis may occur. Hematologic findings include anemia, leukopenia, and

thrombocytopenia.⁴ Arsenic analysis can be done using blood, urine, hair and fingernail samples. Because arsenic in the blood is only present for 2 to 4 hours after exposure, urine levels may be considered more useful. Hair analysis does not distinguish between externally deposited arsenic and that found within the hair shaft and may be less useful in determining arsenic poisoning.⁴

The normal mercury level in the blood and urine is <10mcg/L and < 20 mcg/L, respectively.³ Intervention is suggested when levels in the blood or urine is > 35 mcg/L or > 150 mcg/L respectively.³ A urine excretion level of 300mg/L probably indicates mercury poisoning.⁴ Inorganic mercury poisoning may produce a variety of symptoms including gastrointestinal symptoms such as nausea, vomiting, gingivitis, stomatitis, esophageal erosions and renal lesions.⁴ Blood levels are influenced by recent exposures whereas urinary mercury levels seem to relate more to the kidney content of mercury.⁴

This paper will evaluate the evidence supporting TCM as a cause of heavy metal poisoning.

Ernst and Coon,⁶ performed a systematic review that looked at the reports of heavy metal poisoning being caused by TCM. The purpose of the review was to summarize and evaluate the published evidence concerning this topic. The authors selected articles from MEDLINE, Embase, Biosis, Chemical Abstracts, Amed, Cochrane Library and CISCOS databases. Each database was searched from its beginnings through December 2000. In addition they attempted to get unpublished data from both manufacturers and experts in the field. Articles in every language were sought. For an article to be included in the review it must have contained original data on the heavy

metal content of the remedy involved. Two experts extracted and validated the data independently.⁶

Twenty-two publications fulfilled predefined criteria and were included in the review.⁶ The researchers obtained nine case reports and five case series comprising 106 individuals as well as epidemiologic investigations and analytical studies. The researchers summarized the case reports and case series by author, year and country, type of TCM and age and gender of the patient. Authors hailed from Singapore, United States, Hong Kong and Taiwan. The types of TCM ranged from Chinese herbal pills, Pay-loo-ah, Nutrien, Tse koo choy, Qin fen, Haige fen, Cordyceps powder, Sinlak, lu huang chieh tu pien, watermelon frost and the nonspecific category called merely TCM. While the ages of most patients ranged from two months to 74 years of age, the ages of 14 patients in one case series were not mentioned in the review.⁶

In addition, the researchers included information on symptoms, confirmation of diagnosis of heavy metal poisoning, duration of medicine intake, treatment of the toxicity and clinical outcome.⁶ Poisonings related to arsenic, lead, thallium, mercury and cadmium. Arsenic poisoning was found in 92 individuals. The diagnosis was confirmed by hair, urine and TCM analyses as well as by the presence of Bowen's disease and arsenical keratosis. Duration of TCM use varied from short-term (undefined by researchers), 2 to 3 years up to 20 to 30 years, or long-term use (also undefined by researchers). Length of use was not specified in one case. Clinical outcomes of the arsenic poisoning included development of malignancies in 10 patients and one case of death; one case of small cell carcinoma of the lung (with no further details); one case of hepatic encephalopathy resulting in death after 8 days; one transfer to oncology with no

further details available; squamous cell carcinoma in 14 patients; and one patient with renal failure, liver failure and cerebral edema which resulted in the patient's death.⁶

Lead poisoning was found in 8 individuals.⁶ The diagnosis was confirmed by blood and urine levels as well as analysis of the TCM. Duration of TCM use varied from 4 weeks to 6 months. In one instance duration of use was not reported. Clinical outcomes included full recovery in 3 patients and mild delayed development in one child. Outcomes were not reported in two cases.⁶

Thallium and lead poisoning was found in two individuals and was confirmed by spectrographic analysis of the TCM.⁶ Use of TCM lasted as short as 2 weeks or as long as 3 months. No treatment was performed in the two patients and both individuals recovered fully. Mercury poisoning was found in 4 patients. Diagnosis was confirmed by urine and blood levels. Duration of TCM use ranged from 5 days to 3 months. One case did not report duration of use. Treatment included chelation therapy alone in 2 cases or in combination with diuretics and antibiotics in one patient. In another case, TCM was discontinued. One patient had residual problems at the 11-month follow-up. Two patients died. One patient fully recovered within 2 weeks. Cadmium poisonings occurred in 1 patient and was confirmed by urine cadmium levels. Duration of TCM was 3 months. Treatment included bicarbonate and potassium supplements. The patient developed permanent nephrogenic diabetes insipidus.⁶

Two epidemiologic investigations were found in the searched databases.⁶ One study screened over 2800 Taiwanese for elevated blood lead levels. It found that using TCM increased the risk for high blood lead levels by close to three times over patients not using TCM (odds ratio of 1.60 to 5.97 using a 95% confidence interval). The other

study tested over 300 Taiwanese children for blood lead levels. Using TCM “ba-baw-san” was significantly associated ($P = 0.038$) with average blood lead concentrations of 4.96 mcg/dL, SD, 2.71.⁶

Six analytical studies were found by the authors.⁶ The first study found 1 mcg lead in 3 samples of “chifong toukwan” which is taken for symptoms of arthritis. Another analysis of 2 samples of pay-loo-ah showed 10 mg mercury and 30mg arsenic in 100 g of pay-loo-ah. The next study included in the review found that 6 of 11 samples of TCMs contained lead. Lead was found using atomic emission spectrometry and graphite furnace atomic absorption spectrometry. The fourth study found mercury and arsenic content elevated in 8 “herbal balls”. The mercury content ranged from 7.8 to 621.3 mg per ball. The arsenic content ranged from 0.1 to 36.6 mg per ball. The recommended adult dose is typically 2 balls per day. The fifth study tested over 2000 samples of Chinese proprietary medicines in Singapore and found 42 different medicines that contained metals in amounts that exceeded legal limits. Mercury was found in 28 products, lead in 8, arsenic in 6 and copper in 1. Several products included both mercury and lead or mercury and arsenic. The last study analyzed over 300 batches of TCMs delivered to a German hospital. It found that heavy metal concentrations exceeded legal limits in 3.5% of the batches.⁶

The study had some strengths. The authors did fulfill their objective relating to summarizing published evidence. Including articles written in all languages is especially important in this topic about TCMs where the use is important in Asia and the West. This helps to ensure a more balanced and complete representation of the topic. They also tried to get unpublished data from experts and manufacturers. Obtaining information in

the manner helps to ensure their data is complete and their conclusions more sound.

Furthermore, the researches used two physicians to analyze and categorize the information appearing in case studies and series. The use of two individuals is preferred as it helps ensure accurate representation of the results of the cases included in the review.

The systematic review has several weaknesses. Although one of their objectives was to comment on the quality of the literature available, the researchers did not comment on the quality of either the epidemiologic or the analytical studies included in the review. It is important to know whether the tools used in those studies were appropriate for what they were trying to measure. In addition, the researchers did not establish a definite cause and effect relationship between heavy metal poisoning from TCMs by basing their conclusions on case studies and case series.

Tay and Seah ⁷ wrote a journal article published in 1975 about a series of cases of arsenic poisoning that seemed to be related to the use of an herbal preparation called Sin Lak, an anti-asthmatic pill. The purpose of the case series was to discuss the clinical and toxicological issues surrounding the 74 confirmed cases of arsenic poisoning related to the use of herbal preparations. Between April 1972 and June 1973 there were 106 suspected cases of arsenic poisoning in Singapore General Hospital. Researcher found that 74 patients had arsenic poisoning based on predetermined requirements: 1) use of Chinese herbal products; 2) classic symptoms of acute or chronic arsenic poisoning; 3) increased tissue arsenic content in the hair, nails, urine or blood; and 4) evidence of high arsenic content in the herbal preparations. Patients were included, too, if they had the

symptoms and history of use of Chinese herbal products even if they had normal arsenic levels in their hair, nails, urine or blood.⁷

The authors studied the patients in detail.⁷ They performed a full medical history including age, gender, ethnicity, occupation, symptoms and past illnesses. They obtained a full drug history including drug name, manufacturing location, indications for treatment, duration of treatment, dose taken, side effects and toxicological analysis relating to arsenic content. They performed quantitative analysis on the samples of hair, nails, blood and urine in order to determine arsenic concentrations. They obtained hair samples from all 74 individuals and performed analyses to determine arsenic levels. Only 4 samples of nails were taken as the vast majority of the patients had short nails. They analyzed the blood of 8 patients and urine in 42 patients. In order to test the reliability of the analyses they set up a control group for comparison of hair and urine samples. They performed the hair analysis in 79 normal subjects and urine analysis in 20 normal subjects and found complete absence of arsenic in those samples. In addition, herbal preparations containing more than 5 mg of arsenic were analyzed and amount of arsenic quantified.⁷

The case series revealed that the 74 patients had a variety of clinical manifestations including dermatological or cutaneous symptoms, neurological symptoms, gastrointestinal symptoms, hematological implications, renal or other systemic involvements and internal malignancies.⁷ Cutaneous findings were the most common and occurred in 92% of the patients. They included melanosis, hyperkeratosis of the palms and soles, “raindrop” depigmentations, palmar and plantar hyperhidrosis, multiple arsenical keratoses on the trunk and limbs, mucous membrane lesions, diffuse alopecia

and Mee's lines in the nails. In addition, 12 patients exhibited hypersensitivity reactions to the arsenic-containing products. Six patients developed skin cancers on their limbs and trunk. Three patients developed basal cell carcinoma, two had Bowen's disease and one patient developed squamous-cell carcinoma.⁷

Fifty-one percent of the patients developed neurological sequelae.⁷ The most common neurological finding was toxic polyneuropathy that occurred in 40% of patients. Other neurological symptoms found included fine finger tremor, persistent headache, lethargy, weakness, insomnia and mild to severe psychosis. Twenty-three percent of patients developed gastrointestinal symptoms. Thirteen patients presented with gastritis or gastroenteritis and 4 presented with acute toxic hepatitis. Twenty-three percent of patients developed hematological symptoms. Sixteen patients had mild iron deficiency anemia due to toxic bone marrow suppression. Nineteen percent of those in the study developed renal and other systemic involvements. Ten patients displayed transient albuminuria without azotemia. One developed a sudden fatal ventricular tachycardia. Four patients with chronic poisoning developed internal malignancies. Three patients died including two patients who had squamous-cell carcinoma of the lungs and one patient who had squamous-cell carcinoma of the gallbladder. The fourth patient survived sarcoma of the liver.⁷

Forty-seven of the patients took Sin Lak pills mainly for relief of bronchospasm.⁷ Half of these patients took the pills less than 6 months. One-third of the patients took them for 1 to 5 years, at times intermittently only when they needed them to reduce bronchospasm. Patients who presented with acute symptoms of toxicity took the pills for a short period of time. Those presenting with chronic symptoms had a longer history of

taking the medication. The other 27 patients took a variety of herbal medicines, some of which were banned as being unsafe. Most patients in this group were chronically poisoned and took the herbal medicines for relief of bronchospasm. Some patients took them for “fits”, sore throat, bronchitis, fatigue or insomnia. The duration of intake varied anywhere from 5 months to 15 years.⁷

It was not possible to determine the doses taken because many of the products were used intermittently as needed for relief of bronchospasm.⁷ However the authors were able to calculate the recommended dosage per patient per day. For the recommended daily dose for the Sin Lak pill was 10.3 mg of arsenic sulfide.⁷

The hair samples of 45% of the patients, contained over 1 ppm of arsenic, ranging from 1 to 5 ppm.⁷ The amount of arsenic did not seem to correlate to the severity of the poisoning or the number of systemic involvements. However, the concentration was greater in the chronic sufferers who had the disease for more than a year. Fifty-two percent had positive urine results with the levels being higher in the acute cases over the chronic cases. Urine levels did not seem to correlate to the severity of the poisoning.⁷

Treatment consisted of parenteral dimercaprol for 35 of the patients, 17 acute and 18 chronic cases.⁷ At the end of the 15-month survey, 5 patients died. One patient died of ventricular arrhythmia, three from arsenic-induced carcinomas of the lungs and gallbladder and one from unrelated renal failure. Of the rest, 12% were moderately disabled.⁷

The study had some strengths. The authors met their objective of discussing the clinical and toxicological issues surrounding the 74 confirmed cases of arsenic poisoning. In addition, it had a control group for the hair and nail analyses. It showed that patients

without signs of arsenic poisoning had negative test results. This gave some strength to the findings relating to the arsenic poisoned patients.

The study had some weaknesses. The study cannot be used to make conclusions about the prevalence of arsenic poisoning because it was limited only to patients with classic symptoms of arsenic poisoning. While it appears that there is a connection between these patients and the TCM they used, the sample is small and cannot be generalized necessarily to all patients who take TCMs.

Wong et al.⁸ performed a retrospective case review that studied the incidence and sequelae of skin lesions caused by chronic exposure to arsenic. The purpose of the study was to discuss the nature, incidence and sequelae related to chronic arsenicism and to review related literature. The authors reviewed 648 case reports of patients with a histologic diagnosis of Bowen's disease (BD), squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) occurring within the period from January 1990 to December 1996. These are among the sequelae that can occur to patients who have arsenic poisoning. Seventeen patients were found to have had a history of exposure to arsenic in addition to the presence of these cutaneous lesions. They interviewed the patients in addition to performing skin and physical exams. They obtained data relating to chronic use of arsenic and the related cutaneous lesions from interviews as well as from patients' records. The average age of the Chinese participants at time of consultation was 64.5 years. Fifteen of the patients had asthma of which 14 used Chinese proprietary medicines. One asthmatic and 2 non-asthmatic patients drank well water.⁸

Bowen's disease lesions were found in all 17 patients.⁸ Seven patients had a total of 11 squamous cell carcinomas. One of the 1 patients also had basal cell carcinoma.

Forty-three percent of the patients with SCC had more than one lesion occurring mostly in the distal extremities (73%). More than half of the SCCs began as arsenical keratoses or BD (55%). Patients with SCCs were mostly men. Patients who ingested arsenic at an older age were at a higher risk of developing SCCs. The patients with SCC had more palmar arsenical keratoses than those patients without SCC. Fourteen of the 17 patients took CPMs for asthma during the 1950's and 1960's. One of the CPMs commonly used in Singapore, Sin Lak Asthma Pill, was banned in 1972 because of its excessive content of inorganic arsenic sulfide.⁸

The strength of this study is that it did fulfill several of its objectives by discussing the nature and sequelae relating to chronic arsenic poisoning. Another strength is that the researchers obtained data relating to chronic use of arsenic from interviews with the patients as well as from their records. Information from interviews can enable the researchers to get more complete information that is not in their patient charts.

There were several weaknesses in the study. The authors designated only one physician to categorize the medical outcomes into their appropriate categories. Adding another physician would have increased the accuracy of the categorization. Because the number of cases is small, just one misclassification would have a large impact on the outcomes reported. In addition, no control group was used which weakened the cause and effect link between the occurrence of arsenic poisonings and the use of TCM. Without a control group, we are not able to tell if arsenic poisonings in that population occurred in the same way and the same degree.

In conclusion, the studies did show that a small number of patients who had symptoms of heavy metal poisoning also used TCMs. In addition, if the agent was used a short length of time the symptoms that developed corresponded with acute symptoms of arsenic poisoning. The longer it was used, the more severe the symptoms. Some patients with heavy metal poisoning died. The number of patients reviewed is small and the evidence consists mostly of case reviews and case series. There were no control groups in the retrospective case series to see whether there was a difference in the incidence of heavy metal poisoning in patients not using TCMs. The evidence is not strong enough to prove that heavy metal poisoning occurs as a result of the use of TCM.

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