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Hematopoietic toxicity from lead-containing Ayurvedic medications

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Summary

Background—Millions worldwide use Ayurvedic (traditional Indian) medicines. These medications are increasingly associated with lead poisoning, often accompanied by anemia. We compared the relative hematopoietic toxicity of Ayurvedic lead poisoning with a common form of occupational lead poisoning.

Material/Methods—We retrospectively studied 66 adult lead intoxications: 43 published Ayurvedic cases identified in published reports by searching MEDLINE (1966 to November 2005); 4 Ayurvedic patients seen at a referral center; and 19 lead paint intoxications from the same center. We considered patients' age, gender and blood lead at presentation, and then compared the groups with respect to hematopoietic parameters.

Results—Ayurvedic lead poisoning was associated with higher blood lead ($p<0.001$), more basophilic stippling ($p<0.001$), lower hemoglobin ($p<0.001$) and higher protoporphyrin ($p<0.001$). Multiple regression adjusted for blood lead and gender found Ayurvedic lead poisoning associated with a 36.2 g/L (95% CI -48.8, -23.6 g/L) greater decrement in hemoglobin ($p<0.001$) as compared to paint-removal poisoning.

Conclusions—Ayurvedic poisoning produces greater hematopoietic toxicity than paint-removal poisoning. Ayurvedic ingestion should be considered in patients with anemia. Ayurveda users should be screened for lead exposure and strongly encouraged to discontinue metal-containing remedies.

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[B]Data Collection
[C]Statistical Analysis
[D]Data Interpretation
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[G]Funds Collection

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Keywords

Ayurveda; lead poisoning; anemia; basophilic stippling; lead exposure; alternative medicine

BACKGROUND

Ayurveda (traditional Indian medicine) is used widely throughout the Indian subcontinent and among South Asian ethnic communities worldwide. Ayurvedic remedies are also increasingly popular in Westernized countries and available from ethnic markets, practitioners, health food stores, and the Internet [1]. Ayurvedic pharmacopoeia utilizes heavy metals, such as lead, arsenic and mercury. Experts estimate that 35-40% of Ayurvedic remedies intentionally contain at least one metal [2]. Analytic studies have found metals in 30-65% of Ayurvedic products sold outside the United States [3,4], and 20% of those sold in Boston [5]. Most recently, Ayurvedics containing toxic metals have been documented in the Chicago, Houston and Canadian markets [6-8].

Accordingly, sporadic Ayurvedic-associated intoxications have been reported worldwide [1, 9]. The diagnosis is typically lead poisoning, which is frequently discovered through the evaluation of anemia. Our clinical experience with several Ayurvedic-intoxicated patients suggested greater effects on the blood system than we usually encountered among other adult lead intoxications. To explore this hypothesis, we compared hematopoietic manifestations among Ayurvedic poisonings and those caused by a typical occupational exposure, lead paint removal.

MATERIAL AND METHODS

Patients

We retrospectively studied adult patients (≥18 years old) with lead poisoning, defined as a blood lead ≥1.93 μmol/L (≥40 μg/dl). They included: 1) four Ayurvedic-associated lead poisoning cases seen at the Cambridge Health Alliance's occupational and environmental medicine clinic; 2) 43 additional Ayurvedic lead intoxications identified by a MEDLINE search (1966 to November 2005, using the terms "Ayurveda or Ayurvedic" *and* "Lead Poisoning," and "Ayurveda or Ayurvedic" *and* "Anemia") [citations in appendix]; and 3) a consecutive series of 19 lead paint removal intoxications also evaluated at the Cambridge Health Alliance. We had previously identified the latter group of painters for a quality improvement project, independent from the present study and its hypothesis. The Cambridge Health Alliance's Institutional Review Board approved the investigation.

Data extraction

We defined anemia as hemoglobin values below the generally accepted lower limits of normal [10-12]: ≥140 g/L for men and than ≥120 g/L for women; or a statement affirming the presence of anemia in the case report. Among cases from the literature, if hemoglobin was not reported, when possible, we estimated it in g/L by dividing the hematocrit by 0.295. Similarly, if free erythrocyte protoporphyrin was not reported, when possible, we estimated it in μg/dl by multiplying the zinc protoporphyrin in μg/dl by 0.91.

Statistical analyses

Patients' characteristics were described using percentages for categorical variables and means ± SD for quantitative variables. We compared groups using the Fisher's exact test for categorical variables and the non-parametric Wilcoxon Rank Sum test for continuous variables. Linear regression was used to examine the effect of lead source on hemoglobin, after adjusting

for blood lead levels and gender. All p-values reported are two-tailed, and a p-value of less than 0.05 was considered to be statistically significant. SAS version 8.02 (SAS, Cary, North Carolina) was used for all analyses.

RESULTS

Among the 47 Ayurvedic poisonings, the correct diagnosis of lead poisoning was often delayed. In retrospect, unnecessary and invasive procedures as part of evaluations for anemia and abdominal pain were common. Bone marrow biopsies and endoscopies were performed in at least 13% and 15% of the cases, respectively.

Potential co-exposure to other metals was documented in 36% of the Ayurvedic cases by identification of the ingredients, analysis of the Ayurvedic preparation and/or biologic monitoring. Based on this information, at least 23% were co-exposed to arsenic.

Compared to the lead paint cases, the Ayurvedic patients on average presented with significantly higher blood lead, and greater effects for all hematopoietic parameters (Table 1). Comparing only men and limiting the Ayurvedic cases to those with blood lead <3.86 μmol/L, these nine Ayurvedic patients had comparable blood lead with the lead paint cases (3.33 ±0.34 μmol/L vs. 2.99 ±1.06 μmol/L, p=0.258), but significantly lower hemoglobin (92±13 g/L vs. 141±21 g/L, p<0.001).

We further examined the effect of lead source on hemoglobin with multiple regression analysis. We found Ayurvedic poisoning associated with a 36.2 g/L (95% CI -48.8, -23.6 g/L) greater hemoglobin decrement as compared to lead paint intoxication after adjustment for the effects of blood lead and male gender (Table 2).

DISCUSSION

Our investigation supports that Ayurvedic lead poisoning results in greater hematopoietic toxicity than lead paint intoxication, including markedly lower hemoglobin values, a difference which remained highly significant even after blood lead and gender adjustment. Lead inhibits heme biosynthesis, promotes hemolysis and shortens erythrocyte survival. This may eventually result in anemia, which is most often normochromic and normocytic [13]. Nonetheless, clinically significant anemia in adults is usually uncommon when blood lead is <3.86 μmol/L (80 μg/dl) [13,14]. Conversely, we found that 75% of Ayurvedic-poisoned patients with blood lead 1.93-3.86 μmol/L had hemoglobin values less than 100 g/L. Thus, improved recognition and earlier diagnosis of Ayurvedic poisoning by clinicians may decrease complications.

There are several likely explanations for our findings. Patients taking Ayurvedics are usually not evaluated for lead exposure until serious manifestations and more chronic intoxication have occurred. Second, about 25% of the Ayurvedic cases were also exposed to arsenic and likely other toxins. Arsenic is a known bone marrow toxin. Gender differences present another plausible explanation due to lower average hemoglobin in women than men and possible earlier heme synthesis inhibition. We found, however, that the effects of Ayurvedic lead source on hemoglobin decrement persisted after adjustment for both gender and blood lead.

We do acknowledge several limitations to our study. First, our sample size was small. Nonetheless, we found clinically significant differences between the Ayurvedic and paint-poisoned patients suggesting large differences. Second, we could not formally evaluate the effects of arsenic or other toxic substances in medications because this information was not available for all patients. Finally, most of our Ayurvedic cases were retrospective case reports potentially subject to a reporting bias towards more severe manifestations.

Ayurvedic lead intoxication and its significant hematopoietic toxicity have important clinical and public health implications. Since the completion of our study (November 2005), at least 13 additional cases of Ayurvedic lead poisoning have been reported in the literature [15-20]. Moreover, published reports are likely only the "tip of the iceberg." An estimated 750,000 U.S. adults have consulted an Ayurvedic practitioner [21], and remarkably, an estimated 80% of India's 1 billion population uses Ayurveda [2]. Many of these persons may be lead-exposed. Clinicians rarely ask about traditional medicines; patients are usually unaware of metal exposure; and the manifestations of lead poisoning are non-specific. Additionally, subclinical lead exposures can also cause significant adverse health effects [22,23]. Future research, therefore, should include lead screening among Ayurveda users, especially among more vulnerable groups like children and pregnant women.

CONCLUSIONS

Based on the present and previous investigations, the United States Food and Drug Administration and corresponding agencies in other countries should require heavy metal testing for all imported dietary supplements. Public health authorities should encourage Ayurveda users to consult their physicians about potential heavy metal exposure. Patients' use of metal-containing medications and/or those with unknown contents should be strongly discouraged. Clinicians should keep Ayurvedic intake in their differential diagnoses of anemia, abdominal pain and heavy metal toxicity.

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APPENDIX: SOURCE PAPERS FOR AYURVEDIC CASE REPORTS

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Table 1

Lead poisoning by exposure source

	Ayurvedic Medication Associated (N=47)	Lead Paint Removal Associated (N=19)	p-value
Age	39±14 (n=46)	38±14	0.644
% male	51%	100%	<0.001
Blood lead in μmol/L (μg/dl)	4.43±1.71 (92±36) (n=46)	3.01±1.07 (62±22)	<0.001
Presenting anemia	94%	37%	<0.001
Basophilic stippling	78% (n=37)	16%	<0.001
Erythrocyte Protoporphyrin in (μmol/L (μg/dl)	5.41±3.03 (304±170) (n=19)	2.08±1.00 (117±56) (n=18)	<0.001
Hemoglobin in g/L	95±18 (n=39)	141±21	<0.001

Table 2

Linear regression of hemoglobin decrement (g/L) as a function of lead source (Ayurvedic or paint removal) after adjusting for blood lead level and gender

	Coefficient (95% CI)	p-value
Ayurvedic poisoning	-36.2 (-48.8, -23.6)	<0.001
Blood lead	-3.9 (-7.1, -0.7)	0.019
Male gender	10.3 (-1.4, 22.0)	0.083

CI - Confidence Interval.