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Adverse effects associated with the use of South African traditional folk remedies

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Abstract

Although the toxicity of traditional folk remedies is well known in Africa, it is a subject which is surrounded by secrecy and has not been comprehensively studied.

Objectives: The aims of this study are to describe the clinical features of patients admitted to hospital with a confirmed history of using folk remedies, and to gather data on their toxicity in a systematic fashion.

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Design: Prospective case series.
Setting: Paediatric and adult wards of academic hospitals in Johannesburg, South Africa.
Subjects: The study population included 103 patients ranging from one day to 75 years of age, all of whom had recent folk remedy use.
Main Outcome Measures: All available clinical data were analysed. Primary outcomes were the presence of renal and liver dysfunction, death or discharge from hospital.
Results: The most common clinical features on presentation were dehydration (51%), vomiting (46%), jaundice (40%), diarrhoea (39%), altered mental status (37%) and oligoanuria (30%). Renal dysfunction was present in 76% of patients and liver dysfunction in 48%. The overall mortality was 34%. The odds ratio of death was 5.1 (95% CI 1.41 to 18.5) in patients with renal dysfunction (p = 0.0077) and 5.35 (95% CI 1.99 to 14.4) in patients with liver dysfunction (p = 0.0006).
Conclusion: Renal and liver dysfunction are frequently associated with use of folk remedies, and mortality in these patients is high. In view of the large numbers of African individuals living in the United States and Europe, it is important for physicians elsewhere to be aware of the potential toxicity of African folk remedies, and to inquire about their use.

Introduction

At least 80% of people in the South African black community use folk remedies obtained from traditional healers.[1,2] The reasons for use of these remedies include community pressure, spiritual needs and lack of access to physicians. Because of the large numbers of people using them, most remedies are not likely to be harmful, but as with western medicine, folk remedies are associated with "iatrogenic" complications. Information about the potential toxicity of folk remedies is limited however, because of secrecy surrounding their use, so making the systematic study of the spectrum of clinical presentations and the nature of any toxic substances difficult. Studies from all over Africa are hampered by similar problems, but it is clear that the use of folk remedies is associated with significant morbidity and mortality across the continent.[2-11]

The components of most African folk remedies remain unknown. In our laboratory so far we have begun analysis of urine samples as well as of some remedies themselves, from patients confirming use of a folk remedy. Thus far we have detected the presence of pyrrolyzidine alkaloids in one patient,[8] atractyloside (*Callilepis laureola*) in two patients,[12] severe metal poisoning in one patient[13] and analysis of two different samples of folk remedies taken by two patients revealed aloein compounds.[14,15]

Most studies from Africa have focused on acute renal failure (ARF) occurring in association with the use of folk remedies.[5-7,11,16,17] The spectrum of ARF in Africa is very different from that in Western countries, with folk remedies accounting for up to 35% of cases and mortality rates ranging from 24% to 75%.[5,18-23] Few studies, however, have documented the incidence of other organ dysfunction or described detailed clinical findings in patients using folk remedies. The purpose of the present study is to describe clinical features of patients presenting to hospital after use of folk remedies and to identify factors associated with morbidity and mortality. As the use of folk remedies is increasing in Western countries and many people of African origin are now residing outside Africa, we also aim to raise awareness of the potential risks of African folk remedy use.

Materials and Methods

Approval for collection of data and urine samples for analysis of suspected folk remedies was obtained from the ethics committee of the University of the Witwatersrand. Informed consent was obtained from each patient or their guardian. Physicians from the Departments of Paediatrics and Internal Medicine in the major hospitals affiliated to the University of the Witwatersrand, and from other small government hospitals in the surrounding urban areas, were asked to complete a brief case report form when folk remedy use was suspected, including admission clinical and laboratory data, an early urine sample and, when available, a sample of the folk remedy itself. All clinical data available on each patient was evaluated. Tests for human immunodeficiency virus (HIV) were conducted only with patient consent. All laboratory tests were performed in the individual hospital laboratories using standard techniques. Clinical management and laboratory testing were carried out at the discretion of the patient's physicians.

Statistical Analysis.

We calculated odds ratios with 95% confidence intervals to report the effect of each predictor on mortality. Logistic regression was used where more than one predictor category was analyzed simultaneously (as was the case with HIV status and route of administration). P values from the score test were used to maximize power and overcome possible non-convergence problems. A forward selection process was used to determine significant multivariate predictors of mortality to a $p \leq 0.05$. Confounders were added into the multivariate model if their addition changed the odds ratio of the existing covariates by 20% or more. We looked for effect modification by testing the interaction between liver and kidney dysfunction. If significant, this would indicate that the effect (odds ratio) of one depended on the presence

or absence of the other. In secondary analysis, we analyzed the relationship of route of administration to presence of renal or liver dysfunction. Specifically, we tested the odds of liver dysfunction when enemas were used, and renal dysfunction when the route was oral. We evaluated the effect of missing data regarding liver dysfunction in two ways. Firstly, we compared the distribution of other covariates among those with missing data to those whose data were complete. Secondly, we evaluated the effect of missing data on outcome by analyzing the odds of death due to missing data.

Definitions.

Acute renal dysfunction was defined as any elevation in serum urea and/or creatinine above the age-appropriate upper limit of normal (urea >12 mmol/L (34 mg/dL); creatinine >40 mmol/L (0.45 mg/dL) in children under one year, >80 mmol/L (0.9 mg/dL) in children one to five years; >120 mmol/L (1.36 mg/dL) in patients over five years). Severe renal dysfunction was defined as a serum creatinine greater than twice the upper limit of normal, persistent oligoanuria, worsening renal dysfunction with time, or the need for acute dialysis. Any patient in whom there was a suggestion of chronic renal failure (e.g. small kidneys, prior abnormal renal function, unexplained anemia) was excluded. Liver dysfunction was defined as any elevation in aspartate transaminase (AST), alanine transaminase (ALT) or gamma glutamyl transferase (GGT) >200 U/L; total bilirubin >30 mmol/L. Serum albumin was excluded as an indicator of liver dysfunction because a significant number of patients were malnourished, had intercurrent infections, proteinuria or other causes of hypoalbuminaemia besides liver dysfunction. Metabolic acidosis was defined as a serum bicarbonate ≥18 meq/L and/or and increased anion gap >20.

Patients.

Clinical data were collected over an 18 month period from 127 patients with suspected or confirmed recent use of a folk remedy. Of the 127 patients, 10 were excluded because use of a folk remedy could not be convincingly confirmed, and 14 were excluded because of inadequate data collection. Remedy use was confirmed only when a patient gave a definite positive history of use. One hundred and three patients with confirmed use of a folk remedy in their history were included for analysis. Renal function tests were available on admission in all patients, liver function tests in 83. HIV tests were available in 64 patients.

Results

Clinical Features.

Patients ranged from one day to 75 years of age, with 49 patients (48%) being less than one year and 43 patients (42%) being over 15 years of age. Sixty four patients (62%) were male (Table I). The median time between the last use of the folk remedy and admission to hospital was documented in 28 patients and was four days (range zero to 30 days). Remedies were taken orally in 45 patients (44 %), as an enema in 13 patients (13 %), both orally and as an enema in a further 13 patients (13 %), inhaled in two patients (2 %) and administered by an undetermined route in 30 patients (29%). Renal dysfunction tended to be more frequent in patients taking remedies orally, and liver dysfunction tended to be more common in patients using enemas, but these did not reach statistical significance. Mortality in patients using remedies orally or rectally was not statistically different.

Table I: Characteristics of 103 patients with recent use of folk remedies.

Characteristic	Percent
Age	
Child < 1 year	48
Adult > 15 years	42
Male	62
HIV Status	
Positive	31
Negative	30
Unknown	39
Presence of comorbidities	34
Route of herbal remedy	
Oral	56
Enema	26
Unknown	30
Liver abnormality	48
Renal dysfunction	76
Severe renal dysfunction	50
Died	34

The most common clinical features on presentation in all patients are listed in Table II. Metabolic acidosis was present in 70 patients (68%), of whom 31 had an increased anion gap. In three patients, the anion gap acidosis was too severe to be accounted for by the level of renal or liver dysfunction or shock. The causes of these three anion gap acidoses are unknown.

Table II: Clinical features on presentation.

	All Patients	Prior Studies	References
Metabolic acidosis	70 (68%)	63-86%	7,11
Dehydration	52 (51%)	43%	7
Vomiting	47 (46%)	38-83%	7,11,7
Jaundice/liver failure	41 (40%)	26-57%	7,17,31
Diarrhoea	40 (39%)	25-50%	7,11,17
Seizures/encephalopathy	38 (37%)	15-83%	7,11,17
Oligoanuria	31 (30%)	26-100%	7,13,17
Shock	26 (25%)	4-88%	7,11
Kussmaul breathing	26 (25%)	19-33%	7,17
Respiratory distress/cough	26 (25%)	20%	7
Fever	20 (19%)	25-67%	11,17

Comorbid Conditions.

Nineteen children below two years of age were determined to be malnourished, being underweight for age and/or having kwashiorkor or marasmus. Thirty five patients (34%) were found to have at least one concomitant medical condition, unlikely to have been the result of recent toxin

ingestion (Table III). In the remaining 68 patients, however, no other cause of illness was found besides the history of having recently used a folk remedy. The overall rate of HIV positivity was 50% in the 64 patients who underwent testing and was similar in patients below one year of age and adult patients (Table I). This is consistent with the prevalence of HIV in patients admitted to our general medical wards at present.

Table III: Coexisting clinical disorders in patients reporting use of folk remedies.

Clinical Disorder	Number of Patients
Infections	
Blood cultures positive	7
Urinary tract infections	6
Meningitis	2
Gangrene	1
Septic burn	1
Tuberculosis	2
Viral syndrome	1
Falciparum malaria	1
Abdominal Pathology	
Obstructive jaundice	2
Acalculus cholecystitis	1
Uncontrolled Diabetes/hypertension	3
Renal Disease	
Post-infectious glomerulonephritis	3
Haemolytic uremic syndrome	1
Membranoproliferative glomerulonephritis	1
Systemic lupus erythematosus	1
Other	
Prematurity, pregnancy, intrauterine fetal death, Cerebral palsy, psychosis, parasuicide attempt	6

Outcomes.

The overall mortality rate was 34 % (Table I). Factors that were evaluated for their impact on patient outcomes are presented in Table IV. Gender, patient age, HIV status and comorbid conditions were not related to patient mortality. Time to death was documented in 31 of the 35 patients who died, with a median of three days (range one to 30 days). Length of hospital stay was available for 55 of the 68 patients who were discharged, with a median of eight days (range one to 60 days). Median time to death was 3.5 days (range one to 30) in patients with renal dysfunction and three days (range one to 30) in those with liver dysfunction. Median time to hospital discharge was eight days in patients with renal dysfunction (range one to 60) and 15 days (range seven to 52) in those with liver dysfunction.

Renal dysfunction was present in 76% of all patients and liver dysfunction in 48% of patients who had liver function tests (Table I). Severity of renal dysfunction was not related to any of the analyzed outcomes, therefore all patients with renal dysfunction were considered together to increase statistical power. In univariate analysis (Table IV), both renal and liver dysfunction were associated with significantly increased odds ratios of death. There was no significant effect modification between renal and liver dysfunction (Table IV). In multivariate analysis,

Table IV: Univariate relationships of patient characteristics to death.

Ratio	Characteristic [95%CI's]	Odds p value
Adult (vs child)	1.07 [0.47, 2.45]	0.87
Male gender (vs female)	0.73 [0.32, 1.68]	0.45
HIV status (vs negative):		0.24
Positive	1.41 [0.51, 3.90]	
Unknown	0.61 [0.22, 1.69]	
Presence of comorbidities	1.24 [0.53, 2.90]	0.63
Route of herbal remedy (vs oral)		0.27
Enema	0.52 [0.17, 1.55]	
Unknown	1.31 [0.51, 3.35]	
Liver dysfunction	5.35 [1.99, 14.4]	0.0006
Renal dysfunction	5.10 [1.41, 18.5]	0.0077

liver dysfunction (OR 8.37, 95% CI 2.58 to 27.1) and renal dysfunction (OR 5.22, 95% CI 1.28 to 21.3) were significantly related to mortality. This model included adjustment for HIV status and route of administration, both of which met criteria as confounders. In secondary analysis, the odds of kidney dysfunction with oral route of administration was 1.93 (95% CIs 0.78 to 4.80). The odds of liver dysfunction with use of an enema preparation was 1.69 (95% CIs 0.69 to 4.10). Patients with missing data regarding presence of liver dysfunction were statistically more likely to be male and to have unknown HIV status than those without missing data. Patients with missing data had an odds ratio of death that was not statistically different from that of patients whose data on liver dysfunction were not missing. Similarly, there was no evidence that patients whose route of administration was unknown had significantly different odds of liver dysfunction, renal dysfunction, or death.

Discussion

Because of secrecy surrounding use of folk remedies we do not believe that all eligible patients were identified within the study period. It is, therefore, not possible to determine the true frequency of hospital admissions resulting from severe adverse reactions to folk remedies. Furthermore, because of the difficulty in confirming use of folk remedies, denial by a patient does not exclude use, therefore it was not possible to obtain a reliable control group of patients in order to compare outcomes in our setting. Despite these limitations, our series represents one of the largest single studies of this problem.

All 103 patients gave a definite history of recent use of a traditional folk remedy, which in most cases had been taken within a week prior to presentation. In a retrospective study it is impossible to prove that the folk remedies caused illness, but the temporal proximity of remedy use to subsequent onset of symptoms strongly suggests an association. The routes of folk remedy administration in this study are consistent with findings of other African studies,[7,17] with the exception that in the present study no patient reported administration *per vaginam*.[16] This likely

reflects a decreased need for abortifacients since abortion laws have been liberalised in South Africa.

Most patients fell into two age groups, below one year and above 15 years of age (Table I). This observation likely reflects the belief that folk remedies are helpful during periods of life associated with great stress, e.g. pregnancy, the neonatal period, puberty, and marriage.[24] In addition, infants below one year of age may be more susceptible than older children to overdosage or the harmful effects of traditional remedies or subsequent volume depletion. The administration of traditional remedies to children is a common practice in Africa and studies from several countries describe increases in childhood mortality associated with their use.[25-28] Males predominated in the two major age groups as has been reported previously.[7] The reason for this may lie in traditional roles. Males, as "heads" of households, have increased access to herbal remedies, male children need more "protection", and adult males take remedies for specific indications e.g. sexual potency. Most studies where females predominate have been in small groups where the remedies were used to induce abortion.[16]

The clinical presentation of patients in this series was similar to that reported by other authors (Table II).[7,11,16,17,29] The presence of three patients with unexpectedly high anion-gap metabolic acidosis is interesting. In a study of metabolic acidosis associated with folk remedy toxicity, Nkrumah *et al.* found that renal failure and/or lactic acidosis accounted for the elevated anion gap in 14 of 20 children with severe metabolic acidosis, but failed to find any evidence that a toxin or its metabolite had made a direct contribution.[4]

Folk remedies are frequently used for purposes other than clinical complaints. Some reasons include protection of the child, to "clean the stomach", removal of evil spirits, to get rich, infertility, impotence and prophylaxis against witchcraft.[11,16,17,24,30] Some patients do, however, seek folk remedies for physical symptoms. One third of patients presented here had concomitant clinical disorders that may have been the primary reason for visiting a traditional healer, and were unlikely to have been induced by a folk remedy (Table III). Although not frequently reported, Nyazema also found a 30% incidence of "other" disorders in patients presenting to hospital after use of folk remedies.[2] In such cases it is often not possible to determine the relative contributions of the underlying condition and the folk remedy to the patient's condition. More significantly, however, no identifiable cause of illness was found in two thirds of our patients, strongly implicating the recently used folk remedy. Whether the remedy exerts a direct effect through specific organ toxicity or an indirect or augmented effect e.g. through concomitant volume depletion, is not possible to determine here.

The wide spectrum of clinical presentations associated with traditional folk remedy use suggests that different remedies contain substances with selective toxicities. This is the case with several herbal remedies described thus far: pyrrolizidines, present in the plant genera *Senecio* and *Crotolaria*, cause hepatic veno-occlusive disease,[8] atractyloside, present in *Callilepis laureola*, has both liver and renal toxicity,[3,12,31] polycyclic hydrocarbons present in *Euphorbia ingens* are hepatotoxic;[2] methyl salicylate, present in *Securidaca longepedunculata* causes renal failure;[16] and aloesin and aloeresin A, present in Cape aloes have been found to be nephrotoxic.[15] Further work is necessary to identify other potentially toxic compounds and to elucidate their mechanisms of toxicity.

In the government hospitals in South Africa dialysis is not widely available and intensive care beds are scarce. Mortality in patients presenting with severe liver or renal dysfunction is often high. The overall mortality in this study was 34%, which is within the range reported by other African studies.[7,11,29] Morbidity was also high, with 76 % of patients having renal dysfunction and 48 % having liver dysfunction (Table I). ARF and liver dysfunction are frequent findings in patients presenting to hospital after use of traditional remedies.[2,7,11,29] In most studies renal dysfunction is more common than liver dysfunction, but as is the tendency here, liver dysfunction is associated with a poorer prognosis.[29] Possible reasons for this observation may include the fact that supportive care is more difficult in patients with liver failure than renal failure; remedies inducing liver dysfunction may have higher intrinsic toxicity; and the majority of renal dysfunction is pre-renal or ATN which tends to improve spontaneously with time.

In conclusion, we have reported clinical manifestations and outcomes in a large group of patients presenting to hospital after use of a traditional remedy, in whom morbidity and mortality were high. Significantly, most prior studies describing similar outcomes were published several years ago, suggesting that little progress has been made in understanding the nature of the remedies used in Africa, or in improving patient outcomes. The use of herbal medicines and other alternative practices has increased greatly in the United States and other western countries during the last decade.[32,33] Proponents of alternative medicine cite the prevalent use of folk remedies in many cultures as evidence of the efficacy and safety of these practices. However, belief in the safety of folk remedies is based on a lack of information and not on data. Despite the logistical and cultural obstacles to obtaining reliable data in medically underserved communities,[3-13,15,16] there is increasing information about the toxicity of folk remedies, but such reports from Africa have not received much attention in western journals. We certainly do not intend to imply that all folk remedies are harmful, and we are aware that their use is widespread and plays a significant role in the lives of most people in our community. We do believe, however, that collaboration between traditional health care practitioners and the medical community is urgently needed to identify potentially harmful compounds that are present in traditional remedies, and to modify their use in patients at greatest risk of complications. Many Africans now live in Europe and North America, and physicians practicing in these countries need to be aware of the widespread use of traditional remedies and to inquire about their use.

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