

Original Article

Progression rate of Chinese herb nephropathy: impact of *Aristolochia fangchi* ingested dose

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Abstract

Background. Renal failure after ingestion of Chinese herbs between 1990 and 1992 was related to the replacement of *Stephania tetrandra* by *Aristolochia fangchi* (*ST-AF*), containing nephrotoxic and carcinogenic aristolochic acids. However, the relationship between *ST-AF* and renal failure is still a matter of debate. We therefore tested the impact of the *ST-AF* ingested dose on the progression of renal function deterioration.

Methods. Analysis of medical charts and prescriptions between 1990 and 1992 was carried out to determine the presence of risk factors for kidney failure and the cumulative dose of pill components. Individual progression rate of renal impairment was studied by the time-course of the inverse of blood creatinine level ($1/P_{\text{creat}}$).

Results. Patients were divided into an end-stage renal disease (ESRD) group ($n = 44$) and a chronic renal failure (CRF) group ($n = 27$) according to their P_{creat} at the time of this study. The mean number of risk factors (\pm SD) was equally distributed within both groups (1.50 ± 0.18 vs 1.59 ± 0.17 , $P = 0.74$). Patients from the ESRD group ingested significantly higher cumulative doses of *ST-AF* (192 ± 13.1 g vs 138 ± 16.3 g), *Magnolia officinalis*, (80.1 ± 6.3 g vs 59.8 ± 11.7 g), diethylpropion (14.7 ± 1.4 g vs 10.0 ± 1.4 g) and fenfluramine (14.1 ± 1.6 g vs 8.7 ± 1.3 g). In the ESRD group, some patients who had received steroids had a slower progression to ESRD than the others. In multiple regression analysis, *ST-AF* emerged as the only significant drug predicting the slope of the progression of renal failure. Moreover, hypothesizing a linear dose–response relationship, the risk of developing ESRD linearly increased with *ST-AF* doses.

Conclusions. The relationship between the cumulative *ST-AF* dose and the renal failure progression rate

confirms that regular ingestion of *Aristolochia* sp. extracts is causally involved in the onset of chronic interstitial nephropathy leading to ESRD.

Keywords: *Aristolochia* species; Chinese herbs; chronic interstitial nephropathy; renal fibrosis; toxic nephropathy

Introduction

Chinese herb nephropathy (CHN), a progressive interstitial nephropathy, was reported for the first time in 1993 in a young women after the intake of a Chinese herb for slimming purposes, namely *Stephania tetrandra* (*ST*) [1]. One year later, the presence of aristolochic acids instead of tetrandrine in the pills ingested by the patients, confirmed the replacement of *ST* by another Chinese herb, *Aristolochia fangchi* [2]. Exposure to aristolochic acids (AA) was confirmed by the demonstration of AA-DNA adducts in kidney tissue [3,4]. Aristolochic acids are known for their nephrotoxic effects in rodents as well as for their carcinogenic and mutagenic properties [5,6]. Recently, a high prevalence of urothelial carcinoma was observed in our CHN patients in end-stage renal disease (ESRD) and treated by transplantation or currently dialysed. The cumulative dose of the so-called *ST* (actually *A. fangchi*; thus symbolized further by *ST-AF*) emerged as a significant risk factor for urinary tract carcinoma [4]. Such a direct negative impact of the total ingested dose has not yet been clearly demonstrated in relation to the severity of the renal disease. Moreover, some controversies still persist about the relationship between *Aristolochia* spp. and renal failure [7–9].

Therefore, the aims of the present study were to retrospectively determine the time-course of renal failure in our CHN patients and to identify the possible risk factors for the deterioration of renal function, especially regarding the cumulative dose of *ST-AF*.

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Subjects and methods

Patients

Until March 2001, 78 patients with a diagnosis of renal failure related to Chinese herb intake were followed in the Department of Nephrology, Hôpital Erasme. Among them, 48 ESRD patients have been treated with chronic dialysis ($n = 6$) or transplantation ($n = 42$), and 30 subjects have blood creatinine levels (P_{creat}) ranging from 1.2 to 6 mg/dl. Patients had been given pills containing powdered *ST-AF* prepared by a pharmacist from a medical prescription. The intake period was related to the period of distribution of the so-called *ST* in Belgium (from 1990 to 1992). Seven patients were excluded since no reliable data about quantitative evaluation of *ST-AF* intake were available (no medical prescriptions were available for four patients) and renal function parameters were insufficient to evaluate the progression rate of renal function (there were no serum creatinine levels high enough to calculate $1/P_{\text{creat}}$ for three patients). The present study therefore focuses on a total of 71 patients (44 ESRD and 27 chronic renal failure (CRF) patients). With the exception of one case, all patients were women whose mean age (\pm SD) was not different between one group and the other (46.7 ± 1.24 vs 44.8 ± 1.8 years; $P = 0.38$) (Table 1).

Seven of 27 CRF patients and 15 of 44 ESRD patients actually received corticotherapy [10]. These proportions do not differ significantly ($P = 0.60$).

The diagnosis of CHN was based on a history of *ST-AF* intake as well as the clinical presentation (normal serum creatinine levels before herb ingestion and progressive degradation of renal function after herb exposure). Diagnosis of CHN had been confirmed by histological data (namely tubular atrophy and paucicellular interstitial fibrosis) from renal biopsies [11] or pieces of nephrectomies in 50 cases (41 in the ESRD group and nine in the CRF group). No immune deposit had been found and electron microscopic studies were negative, leading us to rule out any underlying primary renal disease. Moreover, the prior exposure to *Aristolochia* spp. had been demonstrated in 39 cases by the detection of specific DNA adducts in

tissue samples from native kidneys removed in ESRD patients [4].

Identification of risk factors, except the slimming regimen

We retrospectively reviewed the medical charts of all patients in order to identify any pre-existing risk factor before Chinese herb intake that may have been responsible for renal dysfunction. Such factors included: age at the beginning of the regimen, whether the patient was overweight (body mass index (BMI) ≥ 30), high blood pressure according to the criteria used before 1990 (systolic and diastolic pressures ≥ 160 and ≥ 90 mmHg, respectively), dyslipidemia (total cholesterol blood level ≥ 200 mg/dl and triglyceridemia ≥ 180 mg/dl), diabetes as well as glucose intolerance, and regular alcohol consumption (> 3 drinks daily). The smoking status was also recorded as well as the regular use of non-steroidal anti-inflammatory drugs and/or analgesics (daily intake during a minimal time period of 6 months).

Evaluation of exposure to possible toxic agents linked to the slimming regimen

All the prescriptions delivered to the patients between 1990 and 1992 were directly obtained from the pharmacists and were carefully reviewed.

The usual treatment consisted of a mixture of Chinese herbs in variable concentrations (the suspected *ST-AF* and *Magnolia officinalis*), appetite suppressants ((dex)fenfluramine, diethylpropion, phentermine) and/or acetazolamide [1]. Individual cumulative doses of pill compounds (expressed in grams) were calculated, taking into account the total amount of pills prescribed and the usual frequency of intake reassessed by interviewing each patient.

Some patients also received mesotherapy (subcutaneous injections of artichoke extracts and/or euphyllin, known for their absence of any systemic toxic effect, performed every 2 weeks at low doses), which was also reassessed by interviewing each patient.

Retrospective analysis of renal function parameters

The progression rate of renal function was studied for each patient by the time-course of the inverse of plasma creatinine ($1/P_{\text{creat}}$), taking into account all data of $P_{\text{creat}} > 1.2$ mg/dl (at least three results) obtained at a minimal time interval of 1 month. From each linear regression analysis, the slope was determined. For the corticoid-treated patients, the slope has been calculated taking into account serum creatinine levels measured before and after treatment.

Statistical analysis

Cumulative doses of pill compounds were ln-converted due to their loggaussian distribution. Differences between proportions of categorical variables were tested using Fisher's exact test, and ANOVA with a posteriori Bonferroni-Dunn test was used for continuous variables. Multiple regression analysis was used to test the relationship between a continuous dependent variable and several continuous independent variables. A stepwise ascending method was used to enter these variables in the model, with an F value > 4 corresponding to a P value < 0.05 . Statview 5.0 statistical software was used for all analyses (Abacus Concepts, Inc., Berkeley, CA, USA).

Table 1. Risk factors pre-existing to Chinese herbs intake in end-stage renal disease (ESRD) and chronic renal failure (CRF) patient groups

		ESRD ($n = 44$)	CRF ($n = 27$)	P value
Gender F/M	n	43/1	27/0	> 0.99
Age (years)	Mean \pm SEM	46.7 ± 1.2	44.8 ± 1.8	0.38
BMI (kg/m^2)	Mean \pm SEM	24.9 ± 1.5	24.6 ± 0.7	0.73
Overweight				
$26.5 \geq \text{BMI} < 30$	n	9	2	0.19
$\text{BMI} \geq 30$	n	3	2	> 0.99
Hypertension	Yes/no	13/31	10/17	0.60
Hypercholesterolemia	Yes/no	24/20	16/11	0.81
Hypertriglyceridemia	Yes/no	4/40	0/27	0.29
Glucose intolerance	Yes/no	1/43	1/26	0.48
Tobacco use	Yes/no	14/30	7/20	0.79
Alcohol excess	Yes/no	10/34	7/20	0.78
Total No. of risk factors	$\leq 2 / > 2$	35/9	23/4	0.75

BMI, Body mass index.

The relationship between the cumulative doses of *ST-AF* and the risks of developing ESRD was assessed using the χ^2 test of linear tendency [12].

Results

For presentation purposes, patients were divided into two groups according to their renal status at the time of the present study: ESRD (ESRD group) and CRF (CRF group).

Identification of risk factors existing prior to the slimming regimen

No significant differences for several risk factors were observed between the CRF group and the ESRD group (Table 1). Except for one case (from the ESRD group), all patients were women, aged around 45 years. Except for five cases (three in the ESRD group and two in the CRF group), all patients were below the 30 BMI criterion of being overweight. One third of them had arterial hypertension and half of them dyslipidemia. Glucose intolerance was virtually absent in both groups. Active smokers were detected as being in a proportion of one-third in each group, whereas 25% of patients regularly consumed alcoholic beverages.

Taking into account those seven risk factors, the majority of patients were attributed none to two factors (35 out of 44 and 23 out of 27, respectively), suggesting that the patients might be considered healthy subjects at the initiation of the slimming regimen. The total number of risk factors per patient (mean \pm SEM) was equally distributed within both groups (1.59 ± 0.17 in the CRF group vs 1.50 ± 0.18 in the ESRD group, $P = 0.74$).

Characterization of drugs used in the slimming regimen

Almost all patients received *ST-AF* associated with *Magnolia officinalis*, and appetite suppressants, fenfluramine and diethylpropion. Only a few patients received other anorectic drugs (phentermine and dexfenfluramine). Moreover, 53 were additionally given acetazolamide, while 60 received concomitant mesotherapy. The concomitant intake of analgesics and/or non-steroidal anti-inflammatory drugs during the 1990–1992 period was not a prominent feature (Table 2). Eleven patients did not receive mesotherapy (eight in the ESRD group and three in the CRF group).

Patients from the ESRD group had ingested significantly higher cumulative doses of *ST-AF* than the CRF group (mean \pm SEM) (192 ± 13.1 g vs 138 ± 16.3 g), *Magnolia officinalis*, (80.1 ± 6.3 g vs 59.8 ± 11.7 g), diethylpropion (14.7 ± 1.4 g vs 10.0 ± 1.4 g) and fenfluramine (14.1 ± 1.6 g vs 8.7 ± 1.3 g), but the difference between both groups was greatest for *ST-AF* (Table 3). In contrast, the duration of *ST-AF* intake was not significantly longer in ESRD patients

Table 2. Characteristics of slimming regimen and concomitant treatments in ESRD and CRF patient groups

		ESRD (n = 44)	CRF (n = 27)	P value
<i>ST-AF</i>	Yes/no	44/0	27/0	> 0.99
<i>MG</i>	Yes/no/unknown	43/1/0	25/0/2	> 0.99
AC	Yes/no	32/12	21/6	0.78
DIETH	Yes/no	44/0	25/2	0.14
FEN	Yes/no	44/0	24/3	0.051
DEXF	Yes/no	19/25	8/19	0.32
PHEN	Yes/no	7/37	4/23	> 0.99
Mesotherapy	Yes/no	36/8	24/3	0.51
Analgesics	Yes/no	16/28	8/19	0.61
NSAID	Yes/no	12/32	7/20	> 0.99

ST-AF, *Stephania tetrandra* replaced by *Aristolochia fangchi*; *MG*, *Magnolia officinalis*; AC, acetazolamide; DIETH, diethylpropion; FEN, fenfluramine; DEXF, dexfenfluramine; PHEN, phentermine; NSAID, Non-steroidal anti-inflammatory drugs.

Table 3. Ln values of mean cumulative doses of pill compounds: comparison between ESRD and CRF groups

	Ln cumulative doses (mean \pm SEM)		
	ESRD (n = 44)	CRF (n = 27)	P value
<i>ST-AF</i>	5.15 ± 0.08	4.72 ± 0.14	0.0046
<i>MG</i>	4.26 ± 0.08	3.89 ± 0.16	0.0341
AC	3.28 ± 0.18	3.15 ± 0.15	0.60
DIETH	2.45 ± 0.12	1.93 ± 0.21	0.0203
FEN	2.34 ± 0.13	1.78 ± 0.21	0.0204
DEXF	1.23 ± 0.23	1.25 ± 0.30	0.95
PHEN	2.22 ± 0.36	1.32 ± 0.76	0.25

ST-AF, *Stephania tetrandra* replaced by *Aristolochia fangchi*; *MG*, *Magnolia officinalis*; AC, acetazolamide; DIETH, diethylpropion; FEN, fenfluramine; DEXF, dexfenfluramine; PHEN, phentermine.

than in CRF patients (13.6 ± 0.8 months vs 11.0 ± 1.2 months, $P = 0.07$).

Relationship between cumulative doses of ingested drugs and the slope of renal function deterioration

Ln-converted doses of *ST-AF*, *Magnolia officinalis*, diethylpropion and fenfluramine were entered in an ascending stepwise multiple regression analysis as independent variables potentially predicting the depending variable, the slope of renal function deterioration. F values to enter into the model were 5.59, 4.84, 3.34 and 2.03 for *ST-AF*, *Magnolia officinalis*, diethylpropion and fenfluramine, respectively. At the end of the stepwise process, only *ST-AF* had entered the model, whereas the F values for *Magnolia officinalis*, diethylpropion and fenfluramine were 0.96, 0.52 and 0.01, respectively, which are far from statistical significance. *ST-AF* is thus the only significant drug predicting the slope of renal function deterioration, according to the equation:

$$\text{Slope} = 0.027 - 0.009 \times \ln \text{dose (ST-AF dose)} \\ (P = 0.041).$$

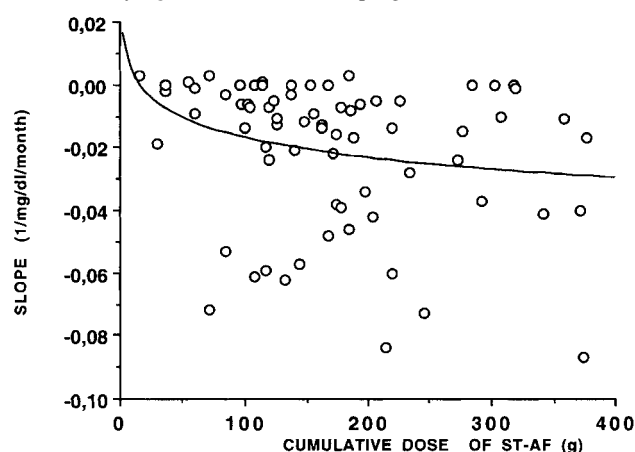


Fig. 1. Relationship between the slope of renal function deterioration (1/mg/dl/month) and the cumulative dose of ingested *ST-AF* (g, grams) in 71 CHN patients with ESRD ($n = 44$) and CRF ($n = 27$).

This relationship is illustrated in Figure 1. It should be noted that the slope quickly decreased with increasing cumulative *ST-AF* doses, but remained virtually constant for doses > 200 g.

Histological data were actually obtained from renal biopsy and/or nephrectomy samples in 50 out of 71 CHN patients. The calculated relationship between the slope of renal function deterioration and the cumulative dose of ingested *ST-AF* in this subgroup was the following:

$$\text{Slope} = 0.020 - 0.009 \times \ln(\text{ST-AF dose}).$$

According to these data, the relationship between the slope of renal function deterioration and the cumulative dose of *ST-AF* is similar between the whole group ($n = 71$) and the group with histological data ($n = 50$).

Additional data were obtained about a possible role of mesotherapy. The following relationship between the slope of renal function deterioration and the cumulative dose of *ST-AF* was found:

$$\text{Slope} = 0.023 - 0.009 \times \ln(\text{ST-AF dose}).$$

Thus, the relationship is similar in this group treated by mesotherapy ($n = 60$) to the whole group ($n = 71$).

Correlation between the cumulative dose of *ST-AF* and the risk of developing ESRD

The proportion of patients who reached ESRD after ingestion of *ST-AF* was correlated with its cumulative dose, categorized in four classes of equal *ST-AF* 100 g dose intervals (Table 4). The global difference between the four groups is nearly significant (χ^2 with 3 degrees of freedom (df) = 7.32, $P = 0.062$). If we hypothesize a linear dose-response relationship, then the χ^2 test of linear tendency with 1 df is significant ($P = 0.022$), suggesting that the risk of developing ESRD increased in a linear manner with *ST-AF* doses.

Table 4. Relationship between the cumulative doses of *ST-AF* and the risk of developing ESRD

Cumulative dose of <i>ST-AF</i> (g)	No. of patients with CRF	No. of patients with ESRD	Total No. of patients	Risk of ESRD (%)
0–99	9	4	13	30.8
100–199	13	24	37	64.9
200–299	3	9	12	75.0
300–399	2	7	9	77.8

ST-AF, *Stephania tetrandra* replaced by *Aristolochia fangchi*.

Relationship between the slope of renal function deterioration and the cumulative dose of ingested *ST-AF* according to the 'corticotherapy status'

An ANOVA test was performed to search for a possible difference in the total cumulative dose and the slope of renal function deterioration ($1/P_{\text{creat}}$ vs time) between corticoid-treated and untreated patients. No difference in the mean (\pm SEM) total cumulative dose could be found in either subgroup from the CRF group (124.9 ± 19.0 g vs 142.9 ± 21.1 g, $P = 0.64$) or from the ESRD group (215.4 ± 23.7 g vs 179.9 ± 15.4 g, $P = 0.20$). By contrast, a statistically significant difference was found in the mean (\pm SEM) slope among ESRD patients in favour of steroid-treated patients (-0.021 ± -0.06 vs -0.037 ± -0.004 , $P = 0.034$) but not among CRF patients (-0.0026 ± -0.003 vs 0.0031 ± -0.001 , $P = 0.84$). These data suggest that renal function in ESRD patients treated by corticotherapy deteriorated more slowly than those not treated with corticoids.

Discussion

The main finding from this study is that higher intake of *ST-AF* was associated with an increased risk of renal dysfunction in CHN patients. Moreover, these patients were found to be free of major risk factors before being exposed to the toxic agent.

This study is the first to quantify the risk of developing severe renal failure in CHN patients through a comprehensive quantitative determination of the total cumulative dose of *ST-AF*. This could be done as all patients, with the exception of one, obtained their slimming pills from medical prescriptions filled in by pharmacists. Copies of all these prescriptions were obtained from the pharmacists.

Statistically larger amounts of ingested *ST-AF* and anorectic drugs (diethylpropion and fenfluramine) were found in the group of ESRD patients in comparison with the group of CRF patients. The difficulties in clearly separating the respective roles of Chinese herbs on the one hand and anorectic drugs on the other can be easily explained by the fact that the

patients were given a relatively standardized prescription including both groups of compounds. Although the results of the multiple stepwise regression analysis strongly suggest the absence of any role for anorectic drugs in the development of renal failure, a possible potentiating effect of anorexigens cannot be ruled out. However, descriptions of a similar renal disease in clinical circumstances not associated with slimming regimens (Spain [13], UK [14], Japan [15,16], Taiwan [17]) indicate that the role of fenfluramine, if it exists, should not be strictly necessary to induce renal disease. Along these lines, histopathological lesions similar to the initial human CHN were recently reproduced by long-term intraperitoneal injections of aristolochic acids alone in New Zealand white rabbits [18]. Moreover, mesotherapy may be excluded since 11 of our patients were not given this treatment. Obviously, mesotherapy was not given to the patients reported in other countries [13–17]. In the present study, the relationship between the slope of renal function deterioration and the cumulative dose of *ST-AF* found in the group of 60 patients treated by mesotherapy was similar to that found in the whole group ($n = 71$), reasonably excluding the involvement of mesotherapy in the pathogenesis of CHN. In the same line, the relationship between the slope of renal function deterioration and the cumulative dose of *ST-AF* was similar in the group of patients with histological data obtained by renal biopsy and/or nephrectomy ($n = 50$) and in the whole group of patients ($n = 71$). Thus, limiting the study to patients with histological findings would not modify the conclusion.

In addition, our data also confirm a previous report [10] showing a beneficial effect of steroid therapy on the course of the renal disease, at least in patients suffering from ESRD at the time of the present study.

As the risk of developing ESRD was closely correlated with *ST-AF* dose, the hypothesis that *Aristolochia* sp. is causally involved in the onset of the renal disease is now clearly confirmed. Consequently, faced with a case of interstitial renal nephritis of unknown origin, all nephrologists should be encouraged to examine with the utmost care whether herbal remedies containing aristolochic acids as depicted by the Food and Drug Administration [19] can be genuinely ruled out.

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