Aristolochic Acid Nephropathy: The Hong Kong Perspective

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Aristolochic acid nephropathy (AAN) is a progressive tubulointerstitial nephropathy attributed to aristolochic acid (AA) toxicity. Five cases of AAN have been diagnosed in Hong Kong. Most were caused by the inadvertent substitution of innocuous herbs with Aristolochia species. Our findings contributed to the withdrawal of the AA-containing herbs and products in Hong Kong. This paper aims to review the topic of AAN from a Hong Kong perspective. [Hong Kong J Nephrol 2007;9(1):7–14]

Key words: aristolochic acid, Chinese medicine, herbs, nephropathy

Aristolochic Acid Nephropathy

Aristolochic acid nephropathy (AAN) is a unique nephropathy characterized by rapidly progressive interstitial fibrosis and urothelial cancer. It is related to the prolonged intake of Chinese herbal remedies containing the nephrotoxic and carcinogenic aristolochic acid (AA).

AAN was recognized and reported in the Chinese and English literature in the early 1960s. In 1963, Peters and Hedwall observed the loss of concentrating ability of the kidney as a result of intoxication with AA [1]. Ten cases of acute renal failure, caused by overdose of Caulis Aristolochiae Manshuriensis (馬兜鈴), were reported in China between 1964 and 1988 [2–5]. However, there has been a delay in the appreciation of these findings until the early 1990s [6].

In the early 1990s, a weight loss clinic in Belgium formulated a “slimming regimen” consisting of a cocktail of drugs and various herbal powders including Radix Stephaniae Tetrandrae (烏木蛇) and Cortex Magnoliæ Officinalis (厚朴). Between 1990 and 1992, about 1,700 users were exposed to the product. More than 100 patients subsequently developed severe renal failure, about half of whom required a renal transplant [7]. End-stage kidney failure occurred 3 months to 7 years after the patients had stopped taking the weight loss pills. Renal biopsy samples showed extensive interstitial fibrosis without glomerular lesions [8]. Urothelial malignancies were common [9]. Based on the clinical evidence and involvement of Chinese herbs, clinicians in Belgium coined the term, “Chinese herb nephropathy” to describe the phenomenon.

But was the first to suggest that one of the herbs, Radix Stephaniae Tetrandrae (烏木蛇), could have been inadvertently replaced by AA containing Aristolochiae Fangchi (馬兜鈴). Phytochemical analysis of 12 different samples of Radix Stephaniae Tetrandrae delivered to Belgium from 1990 to 1992 showed that only one sample corresponded to Stephania species, whereas the others were probably Aristolochia species [11]. The causal role of AA in the Belgian epidemic was established later by the detection of AA DNA adducts in kidneys removed from patients with Chinese herb nephropathy [12]. These adducts are specific markers of exposure to aristolochic acids [13,14]. Furthermore, AA given alone to rabbits induced similar renal and urothelial lesions [15]. The term AAN was proposed to replace Chinese herb nephropathy [16].

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Subsequently, more reports linking AA to nephrotoxicity were reported worldwide, resulting in the ban of AA-containing herbs and products in many countries [17–22].

AA-containing Herbs

AA includes a mixture of structurally related nitrophenanthrene carboxylic acids produced by the Aristolochiaceae family, with 8-methoxy-6-nitrophenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid (AAI) and its 8-desmethoxylated form (AAII) representing the major constituents of these plants [23]. Aristolochia plants and their extracts have been used in traditional Chinese medicine (TCM) to remove heat, relieve pain, dispel wind and promote diuresis [24]. Examples of frequently encountered AA-containing herbs include Caulis Aristolochiae Manshuriensis (關木通), Radix Aristolochiae Fangchi (重樓), Fructus Aristolochiae (馬兜鈴), Radix Aristolochiae (青木香) and Herba Aristolochiae (天仙藤). The amount of AA varies between species, and Caulis Aristolochiae Manshuriensis contains the highest amount [25]. Low levels of AA have also been reported in Herba Asari (細辛) [26].

Etiology and Pathology

Several studies have established that AA is strongly nephrotoxic [15,27–29], genotoxic [30,31], and carcinogenic in humans and rodents [9,13,32,33]. AAI was found to be more toxic than AAII, and other structural analogs either have less overall toxicity or no toxicity [34].

AAN is recognized as a separate entity of renal tubulointerstitial disease. The renal pathology is characterized by extensive interstitial fibrosis and tubular atrophy, which generally decreases in intensity from the outer to the inner cortex. The glomeruli are usually spared, but global or peripheral sclerosis of glomeruli, decreasing from the outer to the inner cortex, including the columns of Bertin has been reported. Immune deposits are not a feature. Endothelial cell swelling is often apparent with consequent thickening of interlobular and afferent arterioles [35–38]. Urothelial cancer of the upper urinary tract associated with urothelial atypia is frequently found in AAN [39].

The nephrotoxic effect of AA is dose dependent [28,40]. AA has been shown to be toxic to renal tubular epithelium and to induce apoptosis [41–43]. However, the underlying mechanism driving the progression of renal interstitial fibrosis remains unclear. There is markedly injured peritubular capillary in the renal interstitium from patients with acute AAN [44].

The subsequent ischemia and hypoxia may contribute to the fibrosis [45].

AA is among the most potent 2% of known carcinogens [46]. The cumulative dose of aristolochia was a significant risk factor for urothelial carcinoma [9]. Mutagenic and carcinogenic effects of AA are associated with the formation of AA-DNA adducts [47]. Metabolic activation of AA is essential to produce the DNA-binding species. AA is activated by different enzymes, including prostaglandin H synthase, the most abundant peroxidase present in the kidney and ureter [48]. Therefore, prostaglandin H synthase could be one of the most important activators of AA to toxic and carcinogenic metabolites in the target tissues of AAN patients [49]. On metabolic activation, AA binds covalently to the exocyclic amino group of DNA purine nucleotides, leading eventually to the formation of DNA adducts [50]. The most abundant adduct is the AA-I adenine adduct, which is a mutagenic lesion leading to A to T transversion in DNA during replication in vitro [14,51,52]. The specific DNA adduct remains in tissues for an extensive period and suggests non-reparable genomic lesions [9].

Urothelial carcinoma as well as urothelial atypia were associated with the overexpression of the p53 protein in Belgian AAN patients, suggesting that the p53 gene is mutated in AA-associated urothelial cancer [39]. This conclusion is further supported by the formation of AA-DNA adducts and the characteristic A to T transversion mutation in the human p53 gene [29,53].

It is interesting to note that only a small fraction of the patients who followed the slimming regimen in Belgium developed AAN [54]. A few cases with AAN showed familial aggregation [44]. Predisposition towards nephrotoxicity and carcinogenicity may be genetically determined [55]. The effect of the genetic polymorphism on AA metabolism remains to be evaluated.

When AAN is suspected, biopsy or per transplantation nephrectomy should be seriously considered: the histologic picture is highly suggestive and the detection of AA-DNA adducts is confirmatory [56]. The association of interstitial fibrosis with urothelial atypia and malignancy is also reminiscent of analgesic nephropathy. The hallmark of classic analgesic nephropathy is papillary necrosis with associated interstitial fibrosis and chronic inflammatory cell infiltrates, a feature that is absent in AAN [57].

Clinical Features

AAN has two distinctive clinical syndromes. The classical type is subacute renal failure associated with normal or mildly elevated blood pressure, low-grade proteinuria, glycosuria and insignificant urinary...
sediments. Anemia was more severe than expected for the degree of renal failure, probably as a result of early destruction of peritubular cells producing erythropoietin [58]. Renal function deteriorated rapidly and progressively in most patients despite discontinuation of the herbal medicines [59]. The rate of progression of renal failure is significantly related to the duration of AA-containing herb use and the cumulative dose [40, 58]. Corticosteroid therapy has been claimed to slow the progression of renal failure [60]. A recent study in rats revealed that angiotensin II receptor blocker shows a protective effect on renal interstitial fibrosis induced by AA-containing herbs [61].

The other variant, Fanconi’s syndrome, has been mostly reported in Asian countries [62–66]. It is characterized by proximal tubular dysfunction and slowly progressive renal insufficiency which is often reversible [67,68]. The aminoaciduria showed predominance of imino acid [69]. There was no subsequent development of urothelial carcinoma reported in association with the Fanconi’s syndrome variant [70]. The reason that AA causes two clinical syndromes remains elusive. The amount of ingested AA, difference in AA-containing constituents and racial differences are possible factors [62].

In addition to renal toxicity, AAN is also associated with the development of urothelial carcinomas in 40–46% of patients [9]. Urothelial cancer seems to be a late complication since most cases were detected in patients with end-stage renal failure. Nevertheless, invasive urothelial carcinoma after exposure to AA-containing herbs may occur without severe renal failure [38].

AA POISONINGS IN CHINA AND HONG KONG

Initially, there was a lack of consensus on the toxicity of AA-containing herbs in China. It was suggested that the renal disease described in Belgium was the result of inappropriate use of Chinese herbs by physicians who were not trained in TCM rather than the toxicity of Chinese herbs per se [71]. Nevertheless, renal toxicity occurred even when the herbs were used in accordance with TCM guidelines. Two series of 58 and 51 cases of AAN were reported in China in 2001; patients had taken different Chinese herbal medicines containing AA and developed nephropathy similar to the one reported in Belgium [72,73]. Many of them took the liver tonic Longdan Xieganwan (龍膽泻肝丸), a composite formula that contained Caulis Aristolochiae Manshurienisis (關木通) as the major ingredient. Presence of other ingredients in the formula did not prevent AA toxicity [74]. With more and more cases reported, control measures on the use of AA-containing herbs were introduced in China in 2003. Recently in China, more than 100 patients have launched legal action against the manufacturer of Longdan Xieganwan, arguing that they sold it despite knowledge of the dangers [75].

While AAN has been reported in many countries, there was no local case reported in Hong Kong until 2004 [76]. Five cases of AA poisoning have been identified (Table 1). Four of them were confirmed in our laboratory by the detection of AA in the herbal products concerned. One patient developed progressive renal failure and bladder cancer after taking the herbs for 6 months [77]. We found that the non-toxic Herba Solani Lyrati (白英) had been mixed up with the AA-containing Herba Aristolochia Mollissemame (馬兜鈴) and Herba Asari containing aristolochic acid should also be forbidden for use [83].

PREVENTION OF AA POISONINGS

Most AAN cases are associated with prolonged usage or acute overdose. Few patients got the disease after taking therapeutic dosage for a short period [72]. There is thus no consensus on what constitutes a safe dose [74]. Some advocate a total ban on all AA-containing herbs from the pharmaceutical market [78]. As expected, the scope and depth of control measures on AA-containing herbs vary among countries. Table 2 is a summary of the ban condition in China, Hong Kong, and Taiwan [79].

Since June 2004, the importation and sale of Aristolochia Linn (馬兜鈴) herbs and products have been prohibited in Hong Kong. Regarding the herb Herba Asari (細辛), only the root can be used [80].

According to TCM practice, Herba Asari alleviates pain and dispels cold winds. Therefore, it is a common ingredient in traditional formulae. There is a paucity of information on the toxicity of Herba Asari. According to a recent survey, nine species of Herba Asari in the market were found to contain variable amounts of AAI. In general, only small amounts of AA were present. Nevertheless, AA contents in some Asarum species were comparable to that of Caulis Aristolochiae Manshurienisis (關木通) [25,81]. Small amounts of AA are also present in the root of Herba Asari [82]. Recently, there was a report of AAN in a patient who had been taking patent herbal remedies containing Herba Asari for 4 months. It was suggested that Herba Asari containing aristolochic acid should also be forbidden for use [83].
CONCLUSION

AAN has been well documented in the past 10 years. Use of AA-containing herbs is prohibited in many countries. This action has no doubt reduced the incidence of AAN. However, the public may still be at risk. It was found that AA-containing products were still available in the market after the ban [84–87]. The risk is exemplified by the latest report of AAN associated with the use of Herba Asari. Despite the relatively small amounts of AA present, it is uncertain if cumulative toxicity could occur after prolonged or intermittent use of Herba Asari. More information and studies are required before the risk can be fully validated. Patients with underlying renal disease are particularly susceptible to AA toxicity [76,88,89]. It is prudent for renal patients to avoid AA-containing herbs. We believe that AAN will persist as long as AA-containing herbs are available for use. Unexplained renal failure together with interstitial fibrosis should alert a physician to the possibility of AAN. A multidisciplinary team of experts should be made available to provide advice to frontline healthcare professionals [90].

AAN is a terrible example of what can go wrong when quality control measures of herbal products are insufficient or not observed. It also highlights the importance of improving the nomenclature system of

Table 1. Local cases of aristolochic acid poisonings

<table>
<thead>
<tr>
<th>Patient details and adverse events</th>
<th>Final renal outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M/75 Acute renal failure complicating pre-existing focal segmental glomerulosclerosis after daily intake of herbs for 2 wk; renal biopsy confirmed a diagnosis of interstitial nephritis</td>
<td>Steroid treatment resulted in significant renal recovery</td>
<td>18 herbs in the prescription, including “fangi” and “mutong”; AAI and AAII were detected in the “fangi” but not “mutong” samples</td>
</tr>
<tr>
<td>2 M/60 Rapidly progressive renal failure and bladder cancer after taking herbs for 6 mo; renal biopsy showed hypocellular interstitial nephritis</td>
<td>End-stage renal failure</td>
<td>“Baiying” was prescribed but Herba Aristolochia Mollissemae was dispensed; AAI was detected in the “Baiying” sample submitted by the patient</td>
</tr>
<tr>
<td>3 F/55 Renal failure after taking herbs for 18 mo; renal biopsy showed interstitial fibrosis</td>
<td>End-stage renal failure</td>
<td>“Baiying” was prescribed but Herba Aristolochia Mollissemae was dispensed; AAI was detected in the “Baiying” sample submitted by the patient</td>
</tr>
<tr>
<td>4 F/41 Renal failure after taking herbs for 18 mo; renal biopsy showed hypocellular interstitial fibrosis</td>
<td>End-stage renal failure</td>
<td>“Baiying” was prescribed but Herba Aristolochia Mollissemae was dispensed</td>
</tr>
<tr>
<td>5 F/53 Underlying scleroderma and fibrosing alveolitis; normal plasma creatinine; several doses of herb taken over a period of 10 d before presentation with proteinuria (0.17 g/d); no renal biopsy performed</td>
<td>Transient proteinuria; creatinine remained within normal range throughout hospitalization</td>
<td>Fructus Aristolochiae was prescribed; AAI was detected in the herbal item</td>
</tr>
</tbody>
</table>

Table 2. Ban of aristolochic acid-containing herbs in China, Hong Kong and Taiwan

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Mainland China</th>
<th>Hong Kong</th>
<th>Taiwan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caulis Aristolochiae Manshuriensis (關木通)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Radix Aristolochiae Fangchi (地錢)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Radix Aristolochiae (青木香)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Fructus Aristolochiae (馬兜鈴)</td>
<td>✓*</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Herba Aristolochiae (天仙藤)</td>
<td>✓*</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Herba Aristolochia Mollissemae (尋骨風)</td>
<td>✓*</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Radix Aristolochiace Cinnabarina (朱砂蓮)</td>
<td>✓*</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>Herba Asari (番薯)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Should be used under the prescription of Chinese medicine practitioners; only the root of Herba Asari can be used.
Confusion in the nomenclature of Chinese herbs

<table>
<thead>
<tr>
<th>Common name</th>
<th>Latinized pharmaceutical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fang Ji (防己)</td>
<td>Radix Aristolochiae Fangchi (防己) *</td>
</tr>
<tr>
<td></td>
<td>Radix Stephaniea Tetrandrae (防己) *</td>
</tr>
<tr>
<td></td>
<td>Radix Aristolochiae Heterophyllae (漢中防己) *</td>
</tr>
<tr>
<td></td>
<td>Radix Cocculi Trilobi (木防己) *</td>
</tr>
<tr>
<td>Mu Tong (木通)</td>
<td>Caulis Aristolochiae Manshuriensis (關木通) *</td>
</tr>
<tr>
<td></td>
<td>Caulis Clematis Armandii (川木通) *</td>
</tr>
<tr>
<td></td>
<td>Caulis Akebiae (木通) *</td>
</tr>
<tr>
<td>Pak Mo Tang (白毛藤)</td>
<td>Herba Aristolochia Molissimae (尋骨風) *</td>
</tr>
<tr>
<td></td>
<td>Herba Solani Lyrati (白英) *</td>
</tr>
</tbody>
</table>

*Contains aristolochic acid.

There are different ways to name a herb: the common name, the latinized pharmaceutical name and the scientific name. Common names can be very loose (Table 3). The same name can be applied to several herbs and the same herb can have several names. This frequently leads to substitution of one herb by another with similar name and appearance. In China, most cases of AAN result from the substitution of AA-containing Caulis Aristolochiae Manshuriensis (關木通) for the herb Caulis Akebiae (木通). The substitution had become routine and accepted before the risk of AA-containing herbs was recognized [91–93]. In Hong Kong, the substitution of Herba Solani Lyrati (白英) with the A-A-containing Herba Aristolochia Molissimae (尋骨風) had been present for many years. We do not know how many people have been exposed and for how long. As the effect of poisoning can present much later, it will take time before the true impact to the Hong Kong community is known.

AA was known to be a carcinogen long before the Belgian incident [13], but it took years before the risk to the community was recognized. The AAN episode could have been avoided or detected earlier if surveillance programs had been more effective. Indeed, the importance of an effective surveillance system for adverse effects associated with herbal use, similar to the one for Western medicine, cannot be overemphasized. Enhancement on safety measures should go hand in hand with further developments in TCM or other herbal products in clinical practice.

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