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Regular use of nephrotoxic medications is an independent risk factor for chronic kidney disease—results from a Chinese population study

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Abstract

Background. Prescription drug abuse is an important global health concern. Our previous survey in Beijing indicates that nephrotoxic medication use is independently associated with chronic kidney disease (CKD).

Methods. In the present study, the study population consisted of participants from our previous survey with a confirmed history of nephrotoxic medication use. Nephrotoxic mediations included three antipyretic analgesics (58.2%) and three Chinese traditional medicines containing aristolochic acids (CTM-AAs, 47.3%). Prevalence of CKD (defined by presence of albuminuria and/or reduced estimated glomerular filtration rate) as well as markers of tubular injury was analysed, and compared with 109 age- and sex-matched controls.

Results. The prevalence of CKD was higher among medication users compared with controls, which was 18.3% and 8.5%, respectively. Among participants with medication use without CKD, markers of tubular injury including *N*-acetyl-β-D-glucosaminidase, transferrin and α_1-microglobulin, were present in 26.6%. CKD was associated with CTM-AA use (cumulative AA-I dose >0.5 g, OR = 5.625,

$P < 0.05$) and antipyretic analgesic use (cumulative dose >2.0 kg, OR = 3.848, P = 0.063) in a dose-dependent manner. Albuminuria and tubular injury persisted among CTM-AA users, but not among analgesic users after cessation of drug.

Conclusions. Our study suggests that education about rational analgesic use and CTM-AA banning may constitute an effective CKD prevention strategy.

Keywords: chronic kidney disease; nephrotoxic medication; screening

Introduction

Habitual analgesic use is common in developed countries, for example in 23.7% of adults in the USA [1]. In China, commonly used over-the-counter medications include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and Chinese traditional medicines containing aristolochic acids (CTM-AAs). Numerous clinical studies have reported the occurrence of analgesic nephropathy (AN) or aristolochic acid nephropathy (AAN) with excessive intake, which presented as acute or progressive chronic renal failure [2–4]. There is a consensus that chronic AN can be caused by habitual consumption of any mixture containing two analgesic components combined with caffeine and/or codeine [5]. Therefore, early detection of CKD among medication users and withdrawal of those medications might constitute an effective strategy to reduce the burden of CKD. However, most previous epidemiological studies have focused on end-stage renal disease but not on detection of early stage of CKD [6–10]. For example, based on the Australia and New Zealand Dialysis and Transplant registry data Chang *et al.* [11] reported that 10.2% of analgesic abusers received renal replacement therapy. Only a few recent cohort studies have reported an association between chronic analgesic intake and decreased estimated glomerular filtration rate (eGFR) [12,13], which was usually evaluated on information, indication, or protopathic and ingredient biases [14]. Two studies from Taiwan reported that regular herbal medication could increase the risk of developing CKD [13,15], but neither of them elaborate the responsible compound in the herbal medication. A recent study by Lai *et al.* [12] suggested that at a certain dosage of CTM-AAs (>30 g Mu-Tong or >60 g Fang-chi) was associated with increased risk of CKD. This is the first population-based study indicating that abuse of CTM-AAs might be related to a high incidence of CKD. In addition, a previous study from our group [16] also demonstrated a strong correlation between consumption of analgesics or CTM-AAs and the risk of CKD.

The present study was initiated to explore further the relationship between nephrotoxic medication use and CKD in the Chinese population, with the specific aims to characterize individuals with medication exposure, to investigate the effects of nephrotoxic medication use on kidney structure and function, and to explore factors which predispose participants to medication-related kidney injury.

Materials and methods

Study population

In our previous cross-sectional survey, a representative sample of 13 925 adults in Beijing were screened for CKD and associated risk factors (details are described elsewhere [16]). Among these, 343 persons studied (2.46%) reported a history of nephrotoxic medication use in their lifetime, who were distributed in 18 districts (50 subdistricts) of Beijing. The 172 participants from 26 subdistricts were chosen by a probability proportional to size method, in order to reduce the working load by sparse distribution of participants in geographic districts. Altogether, 129 participants (response rate 75.0%) responded to a second interview of detailed inquiry of medication use. Two designated nephrologists performed in-person interview to confirm and to collect details of the nephrotoxic medication intake. In the in-person interview, 109 participants verified a history of regular or sporadic use of pre-specified nephrotoxic medications (Figure 1). These participants were defined as the medication group. Furthermore, 109 age- and gender-matched controls selected from the previous survey, constituted the control group.

History of exposure to nephrotoxic medications

In Beijing, the most commonly used over-the-counter nephrotoxic medications included phenacetin-containing analgesic mixtures (Somedon and APC) combined with caffeine; ibuprofen, which is the most frequently used NSAID with a single active ingredient; and three different CTM-AAs in pill form. Every participant was asked about their lifetime consumption in detail, including the daily dosage, frequency, cumulative dosage and time course of administration.

The pattern of medication use was categorized into three types: regular use (>20 pills during lifetime, at least twice a week for >2 months), sporadic use (>20 pills during lifetime, but not regularly taken) and minimal use (<20 pills during lifetime) [6]. The antipyretic analgesic dosage was expressed as the real amount and graded as high or low dosage according to the average cumulative dosage. Heavy analgesic users were defined as those who took >2 kg in total [17]. The dosage of AA-I was calculated referring to content of AA-I measured by HPLC in the original medicines [17].

Albuminuria and reduced eGFR

Albumin and creatinine were measured from a morning spot urine sample by immunoturbidimetric methods (Audit Diagnostics, Cork, Ireland) and Jaffe's kinetic method, respectively. The albumin–creatinine ratio (ACR) was calculated in milligram per gram. Patients with an ACR from 17 to 250 mg/g (1.9–28.3 mg/mmol) for men and 25–355 mg/g (2.8–40.2 mg/mmol) for women were classified as having microalbuminuria.

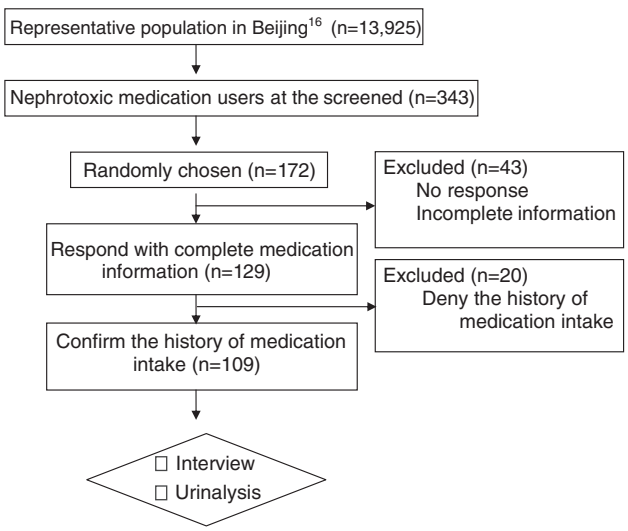

Fig. 1. Study flow diagram.

Table 1. Clinical features and prevalence of CKD in different groups

	n	Age (year)	Gender (M/F)	Hypertension (%)	DM (%)	History of CHD (%)	Nephrotoxic medication (%)	CKD (%)	Albuminuria (%)	Reduced eGFR (%)
Total	13 925	40.0 ± 0.8$^{\nabla}$	1.18:1$^{\nabla}$	30.2$^{\nabla}$	6.3$^{\nabla}$	2.2$^{\nabla}$	2.46	10.25$^{\nabla}$		
Medication group	109	54.9 ± 12.0$^{\nabla}$	0.58:1$^{\nabla}$	57.8$^{\nabla *}$	11.0$^{\nabla}$	4.6$^{\nabla *}$	100	18.3$^{\nabla *}$		
Only antipyretic analgesic	57	53.6 ± 10.8	0.36:1$^{\blacktriangle}$	49.1$^{\blacktriangle}$	7.0	3.5$^{\blacktriangle}$	/	12.3	3.5$^{\blacktriangle}$	10.6
Only CTM-AAs	46	56.8 ± 13.5	1.10:1$^{\blacktriangle}$	67.4$^{\blacktriangle}$	13.0	6.5$^{\blacktriangle}$	/	23.9	21.7$^{\blacktriangle}$	6.5
Control group	109	55.8 ± 11.9	0.58:1	39.4*	15.6	0*	0	8.3*		

$^{\nabla}$Significant difference between total and medication groups.
*Significant difference between control and medication groups.
$^{\blacktriangle}$Significant difference between antipyretic analgesic and CTM-AAs groups.

GFR was estimated using calibrated serum creatinine and a formula specifically for individuals from China [18]: eGFR (mL/min/1.73 m^2) = 175 × serum creatinine (mg/dL)$^{-1.234}$ × age (years)$^{-0.179}$ (women × 0.79).

CKD was defined by the presence of albuminuria and/or eGFR <60 mL/min/1.73 m^2 [19].

Urinary tubular injury markers

Urinary *N*-acetyl-β-D-glucosaminidase (NAG), transferrin (TRU), and α_1-microglobulin (α_1-MG) were measured as indicators of tubular injury. Urinary NAG was measured by the enzyme–substrate direct coloration assay, and TRU and α_1-MG were measured using an immunoturbidimetric method (Audit Diagnostics, Cork, Ireland). Results were compared with reference results from a local laboratory to determine if levels were elevated; NAG >21 U/L, TRU >2 U/L and α_1-MG >12 mg/L were regarded as abnormal.

Concomitant diseases

Hypertension was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg or a previous diagnosis of hypertension or use of antihypertensive medication(s). Diabetes was defined as a fasting plasma glucose level of ≥126 mg/dL (≥7.0 mmol/L) or a previous diagnosis of diabetes mellitus (DM). Coronary heart disease was determined by a positive record of coronary angiography or a history of myocardial infarction.

Statistical analysis

Continuous data were compared using *t*-tests or non-parametric tests. Chi-square test was used to compare the difference of categorical data. A difference was considered statistically significant if the P-value was <0.05. Logistic regression was used to investigate the effect of nephrotoxic medication use on CKD, before and after adjusting for other relevant covariates. Odds ratios (OR) with 95% confidence interval were reported. Nephrotoxic medication use was analysed as categorical variables: antipyretic analgesics, phenacetin-containing analgesics or ibuprofen, and low-dose and high-dose CTM-AAs. Covariates included age, gender and concomitant diseases [hypertension/DM/coronary heart disease (CHD)]. Statistical analyses were performed using SPSS (version 13.0).

Results

The participants in the medication group were older (54.9 ± 12.0 years vs. 40.0 ± 0.8 years), and had higher percentage of females (63% vs. 46%) compared with the control group. The female predominance was more prominent in the antipyretic analgesics subgroup (74%) (Table 1).

Spectrum and features of nephrotoxic medication intake

Among 109 medication users, 52.3% (*n* = 57) were antipyretic users only, and 42.2% (*n* = 46) were CTM-AA users only; 5.5% (*n* = 6) used both and were therefore excluded from further analysis. In the antipyretic analgesics subgroup, 65.6% had taken phenacetin-containing analgesics. Regular medicine use was reported by 62.5% of the antipyretic analgesics subgroup and 84.6% of the CTM-AAs subgroup. The major reasons for medication were chronic pain and headaches, arthralgia, palpitation, and chest pain. The duration of antipyretic analgesic administration varied from 1 to 50 years with a median cumulative dosage of 0.5 kg. Among antipyretic analgesics subgroup, 23.2% were heavy users. None of the ibuprofen users took medicine for >2 years, while nearly half of phenacetin users (21/43 = 48.8%) confirmed a chronic intake for >5 years. In the CTM-AAs subgroup, the median cumulative dosage was 0.5 g (range 0.027–9.72 g). Excessive intake of >2.0 g occurred in 15.4% of this subgroup.

In 2001, the Chinese government banned one of the major CTM-AAs called 'Guan-mu-tong'. Following this ban, 81.4% of CTM-AA users stopped using the drug over the next 5 years. The average time interval from cessation was 6.6 years. In contrast, all the phenacetin regular users still kept up habitual medication after the first screening when they were informed about the chronic nephrotoxic effect of analgesics.

Prevalence of CKD in nephrotoxic group

Microalbuminuria was detected in 12.8% of the medication group, and eGFR of <60 mL/min/1.73 m^2 was de-

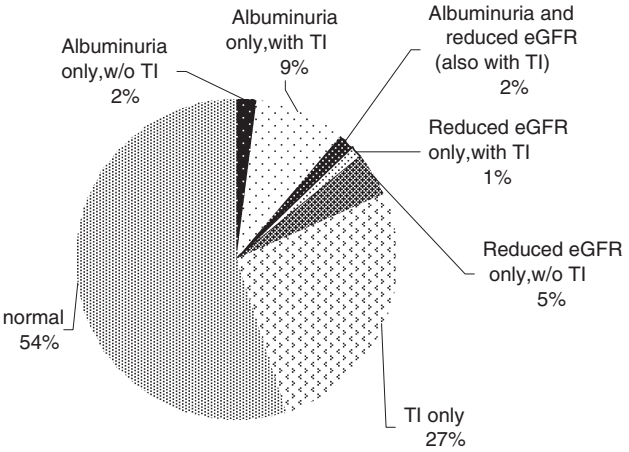

Fig. 2. Tubular injury (TI) detected in nephrotoxic medication users.

Table 2. The prevalence of CKD and medication cessation by the time of the second interview

	Cessation of antipyretic analgesic			Cessation of CTM-AAs		
Time interval▲	<1 year	1~5 years	>5 years	<1 year	1~5 years	>5 years
Albuminuria (%)	8/38 (21.1%)	1/7 (14.3%)	2/9 (22.2%)	6/9 (66.7%)	3/15 (20.0%)	4/22 (18.2%)
Tubular injury markers						
Transferrin	6/38 (15.8%)	0	0	1/9 (11.1%)	2/15 (13.3%)	2/22 (9.1%)
NAG	5/38 (13.2%)	0	0	2/9 (22.2%)	1/15 (6.7%)	3/22 (13.6%)
α_1-MG*	5/38 (13.2%)	0	0	6/9 (66.7%)	3/15 (20.0%)	3/22 (13.6%)

▲From medication withdrawal to the second interview.
*α_1-MG abnormality was defined as more than two times of the upper limits.

tected in 7.3% of the medication group. The prevalence of CKD in the medication group was higher than that of the control group (18.3% vs. 8.3%) (Table 1).

The prevalence of CKD in the CTM-AAs subgroup was higher than that in antipyretic analgesics subgroup (23.9% vs. 12.3%), but not statistically significant. The prevalence of microalbuminuria was significantly (P = 0.004) higher in the CTM-AAs subgroup compared with that in the antipyretic analgesics subgroup (21.7% vs. 3.5%). The prevalence of eGFR <60 mL/min/1.73 m^2 was not different between the antipyretic analgesics subgroup and CTM-AAs subgroup (10.6% vs. 6.5%, P = 0.261) (Table 1). Tubular dysfunction manifested by elevation of NAG, urine TRU or α_1-MG was detected in 38.5% (n = 42) of the medication group (42 cases). Among those 42 participants, 29 had neither albuminuria nor reduced eGFR (Figure 2). Tubular injury was no longer present in individuals stopping analgesic use, but persisted among some participants who stopped using CTM-AAs (Table 2).

Risk factors for nephrotoxic medication-related CKD

Demographic data and the status of hypertension, DM and CHD in the medication group and control group, and the representative sample of Beijing [16] inhabitants are listed in Table 1. Participants in the medication group were older and had higher prevalence of hypertension, DM and CHD compared with the general Beijing population. Table 3 lists crude and adjusted ORs for the presence of albuminuria. CTM-AA use was independently associated with presence of albuminuria (OR = 4.39, P = 0.002) and CKD (OR = 2.99, P = 0.012), and the OR was higher among high-dose users. There was no interaction effect between CTM-AA use and hypertension, DM or CHD. If participants with DM were excluded, CTM-AA use remained significantly associated with presence of albuminuria (OR = 6.40, P = 0.031) and CKD (OR = 5.28, P = 0.038). In the previous survey in Beijing [16], a history of hypertension persisted for more than 10 years and was independently associated with eGFR <60 mL/min/1.73 m^2, while such an association was not observed in the present analysis. Secondary analysis showed that among participants without a history of DM, hypertension and CHD, high-dose antipyretic analgesic intake was associated with increased risk of CKD (OR = 8.55, P = 0.056; Table 4), especially for habitual users of phenacetin-containing analgesics. No association was observed between ibuprofen use and albuminuria or reduced eGFR.

Discussion

Prescription drug abuse is an important global health concern [1]. Our previous cross-sectional survey in a representative sample of adults in Beijing suggested that the prevalence of nephrotoxic medication use was 2.46% [16]. Considering the large population in China, the public health implication of those medications might be considerable. Our study indicated that antipyretic analgesics were more frequently used than CTM-AAs in Beijing. Of the analgesics, the phenacetin-containing combination was the most popular, accounting for 65.4% of analgesic users.

There are several previous studies about nephrotoxic medication use among patients with chronic renal failure or end-stage renal disease [2–5]. However, the potential influence of nephrotoxic medication intake on the development of CKD in the general population has not been well

Table 3. Unadjusted and adjusted odds ratios (ORs) for the presence of albuminuria

Input variable	Unadjusted OR (95% CI)	P	Adjusted OR* (95% CI)	P
DM	5.13 (1.81–14.56)	0.002	3.66 (1.15–11.79)	0.028
Hypertension	3.54 (1.24–10.12)	0.018	2.11 (0.65–6.83)	0.212
CHD	7.07 (1.11–45.14)	0.039	2.88 (0.34–24.70)	0.335
Antipyretic analgesics	0.44 (0.12–1.54)	0.197	0.71 (0.16–3.11)	0.651
CTM-AAs	4.39 (1.70–11.32)	0.002		
CTM-AAs/low dose	/		2.10 (0.54–8.20)	0.284
CTM-AAs/high dose	/		5.94 (1.73–20.34)	0.005

*ORs adjusted for all the variables listed in the table.

Table 4. Unadjusted and adjusted odd ratios (ORs) for the presence of CKD

Input variable	Unadjusted OR (95% CI)	P	Unadjusted OR[#] (95% CI)	P	Adjusted OR[*] (95% CI)	P	Adjusted OR[**] (95% CI)	P	Adjusted OR[▲] (95% CI)	P	Adjusted OR[▲▲] (95% CI)	P
Diabetes	3.19 (1.22–8.33)	0.018	/		2.14 (0.73–6.29)	0.168	2.14 (0.73–6.29)	0.794	7.19 (0.60–86.50)	0.120	/	
Hypertension	2.85 (1.19–6.84)	0.019	/		1.89 (0.72–4.96)	0.197	1.89 (0.72–4.96)	0.113	17.48 (0.339–900.4)	0.155	/	
Coronary heart disease	11.56 (1.84–72.73)	0.009	/		5.22 (0.73–37.20)	0.099	5.22 (0.73–37.20)	0.198	3.96 (0.21–74.30)	0.358	/	
Antipyretic analgesics	1.12 (0.43–2.73)	0.798	12.35	0.028	1.49 (0.53–4.18)	0.448	/	/	/		9.05	0.063
Analgesics/ high dose	/	/	/		/	/	2.78 (0.43–17.90)	0.283	/		8.55	0.056
Phenacetin -containing	/		6.79	0.004	/		/		/		2.14	0.656
Ibuprofen	/		3.11	0.339	/		/		/		/	
CTM-AAs	2.99 (1.23–7.00)	0.012	0.00	0.999	/		/		/		/	
CTM-AAs/ low dose	/		/		1.60 (0.44–5.85)	0.480	/		/		/	
CTM-AAs/ high dose	/		/		5.07 (1.60–16.10)	0.006	/	/	14.52 (1.83–114.90)	0.011	/	
Age	/		1.07 (0.99–1.17)	0.084	/		1.11 (1.01–1.21)	0.030	1.013 (0.937–1.094)	0.748	1.07 (0.98–1.17)	0.130
Sex (M/F)	/		0.00	0.998	/		1.00 (0.89–11.40)	0.999	0.098 (0.011–0.878)	0.038	0.00	0.998

[*]ORs adjusted for all the variables listed in the table.
[#]ORs adjusted for all the variables listed in the table in users without hypertension, diabetes or coronary heart disease.
[**]ORs adjusted for all the variables listed in the table in antipyretic analgesic users.
[▲]ORs adjusted for all the variables listed in the table in CTM-AAs users.
[▲▲]ORs adjusted by age and sex in users without hypertension, diabetes or coronary heart disease.

established. A large population-based epidemiological study of the general population in Taiwan [15] found that regular users of Chinese herbal products (CHPs) had a 20% increased risk of developing CKD (OR = 1.2). As there are thousands of herbs used in the general practice of Chinese medicine and not all of them are nephrotoxic [12,20], that study was limited by being unable to clarify the responsible compounds in CHPs. Our study specifically looked at herbal products containing aristolochic acids (AAs), as these are regarded as the epitome of over-the-counter nephrotoxic CHPs and are widely used in the general population. The dosage of CTM-AAs was calculated as the dosage of aristolochic acid I (AA-1), which is the predominant component in *Aristolochia* and a pathogenic agent of AAN [2]. Proper grading of the cumulative dosage may also help to reduce recall bias by the uncertainty of exposure. Initial information of medication use was obtained by our previous cross-sectional survey [16]. Details of medication intake were collected through a second in-person interview by nephrologists, which ensured the reliability of information. The coincidence rate between the initial survey and second interview results was 84.5%. Besides CTM-AAs, three popular antipyretic analgesics in the Beijing area were investigated. These included the well-known phenacetin-combined analgesics Somedon and APC. Definite evidence for a nephrotoxic effect from non-phenacetin analgesics is controversial, and therefore, the renal effect of the single-ingredient analgesic ibuprofen was also observed.

In the medication group, the prevalence of CKD was 18.3%, and this was divided into 12.3% in the antipyretic subgroup and 23.9% in the CTM-AAs subgroup. The prevalence was higher than 10.3% observed in the general population [16] and 8.3% in control group. CTM-AAs and antipyretic analgesics all contributed to occurrence of CKD despite different patterns of effects. Nephrotoxic medication-induced CKD is mainly characterized by chronic tubulointerstitial nephritis (CTIN) [21]. The most practical biomarkers of CTIN are NAG, TRU and α_1-MG. Consequently, these biomarkers were included as evidence of kidney tubular injury, in addition to the urinary ACR and the eGFR. For those individuals who presented with tubular injury, 31% had microalbuminuria and/or reduced eGFR, and the remainder (69%) did not. The group without microalbuminuria or reduced eGFR composed of 26.6% of the total medication group. This is an alarmingly high prevalence for kidney injury, and prompts special attention for the early detection and prevention of nephrotoxic medication-induced CKD. We suggest that the CKD screening questionnaire in China, at least, includes evaluation of the history of nephrotoxic medication use. For participants with a positive history, examination for biomarkers of tubulointerstitial damage might be helpful.

Previous studies have indicated that all the nephrotoxic effects are dose-dependent, and persistent kidney injury is dependent on cumulative effects. McCredie and Stewart [22] investigated 91 patients with renal papillary necrosis from outpatient clinics. They found a greatly increased risk for patients consuming phenacetin ≥ 1 kg (OR = 19). Pommer *et al.* [23] also reported an increased risk (RR = 9.2) for >1 kg phenacetin users in 517 German ESRD patients. Steenland *et al.* [24] observed that risk increased with increasing duration of drug use. In the present study, a cumulative dosage of >0.5 g of AA-I from CTM-AAs was associated with increased risk of developing CKD (OR = 5.07, $P < 0.05$). For the antipyretic analgesics, especially the phenacetin-containing analgesics, the at-risk cumulative dosage was >2 kg (OR = 9.049, $P = 0.063$). However, it is obvious that medication dosage is not the only deciding factor. Rexrode *et al.* [25] followed up a large cohort of 11 032 initially healthy men (40~84 years old) without prior history of cardiovascular disease, current renal dysfunction or other major illness. Data obtained over an average of 14 years showed that the mean creatinine clearances were similar among men both without and with analgesic use, even with total intake of 2500 or more pills.

It is well known that age, hypertension, DM and cardiovascular disease are risk factors strongly correlated with CKD. In the case of the at-risk population in the current study, we could not rule out the potential effect of these factors. Increased susceptibility to nephrotoxic damage not only arises from genetic heterogeneity but also occurs in older age, and with hypertension and previous chronic renal failure, which is characterized by impaired autoregulation and chronic intrarenal hypoxia [26–28]. Such conditions should be considered as probable pathogenic causes of CKD in addition to the effects of nephrotoxic medication. Fored *et al.* [6] analysed acetaminophen and aspirin use in patients with newly diagnosed chronic renal failure and found that regular use of either drug in the absence of the other was associated with a 2.5 times greater CKD risk. In this high-risk population, nephrotoxic medication-related CKD developed as a linked result. Subanalysis of the Nutrition and Health Survey in Taiwan (NAHSIT; 1993–96) database showed that compared with individuals without CKD, participants with CKD were older and had more analgesic use, DM, hypertension and cardiovascular disease. Of the CKD patients, 10.7% were regular users of Chinese herbal medication [15]. In comparison, in our study, the prevalence of Chinese herbal medication use was only 1.67% in the CKD group.

Phenacetin-containing mixtures, usually combined with caffeine or codeine, create a psychological dependence resulting in chronic ingestion over several years. In the present investigation, almost half of the phenacetin-containing analgesic users had a history of use for >5 years. In comparison, the duration of ibuprofen use was <2 years. Discontinuation of similar medication has been recognized as an essential step for prevention and treatment of nephrotoxic medication-induced kidney diseases. We noticed that in the antipyretic analgesics subgroup, tubular dysfunction was not found in individuals who had stopped taking the drugs >1 year before. This indicates a reversible medication-induced reaction in this group of cases. The psychological dependence in phenacetin combination users may be an important factor for persistent kidney injury. For ibuprofen, the only non-phenacetin-containing analgesic included in this study, no correlation was found with kidney injury. A recent large-scale case–control study on analgesic nephropathy found that the continued use of non-phenacetin-combined or single-agent analgesics such as ASA or salicylates is associated with faster progression

of renal impairment and an increased risk of death or ESRD in patients with AN [29]. These results are controversial and require further study.

For the CTM-AAs subgroup, 81.4% of individuals had already stopped nephrotoxic medication use years before our interview. This might have been related to the intensive education campaign for the general public and clinicians on the nephrotoxic effect of herbs containing AAs, and the banning of the major product Guan-mu-tong by the Chinese government in 2001. Unfortunately, tubular injury persisted in quite a number of individuals who had discontinued drug use >1 year prior, although prevalence of albuminuria seemed to be relieved. The prolonged injury despite of drug cessation may partially be due to the unique pharmacokinetic characteristics of AA-I. AA-1 has a long-clearance half-time ($t_{1/2}$ β of 20.46 h), and using isotope-tracing method, it could be detected in the kidneys even after 40 days from administration [30]. The long-term existence of AA DNA adducts might also play a role in the continual kidney damage [29].

Our study had certain limitations. Markers of kidney injury were based on a single measurement, which could lead to an overestimation of the prevalence of CKD. It is usually difficult to avoid incidence–prevalence bias in a cross-sectional study. A rigorously designed cohort study would be helpful to evaluate the long-term outcomes of various types and combinations of medications. It has been recognized that abnormalities in urinalysis are indicators of kidney injury. We selected several urinary tubular injury markers for screening in consideration of the characteristics of nephrotoxic medication-associated kidney injury. However, the most appropriate biomarkers still need to be determined in respect of their clinical relevance, practical application and medical economics. There were unavoidable interactions between medications and co-morbid diseases, and the correlation and pathophysiology of these need to be further investigated.

In conclusion, the prevalence of CKD was higher in the nephrotoxic medication users, with a dose-dependent pattern in CTM-AA users. For those with a history of nephrotoxic medication use, indicators of kidney injury should be closely monitored, especially for patients with older age, or a history of cardiovascular disease, or metabolic disorder. The tubulointerstitial injury in CTM-AAs users was not recovered even after a long interval of drug withdrawal. Therefore, education on the banning of these medications would be the most effective measure for AA-induced CKD.

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Conflict of interest statement. None declared.

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A meta-analysis of the clinical remission rate and long-term efficacy of tonsillectomy in patients with IgA nephropathy

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Abstract

Background. We wished to evaluate the clinical remission rate and long-term efficacy of tonsillectomy for patients with IgA nephropathy.

Methods. We searched a number of databases, including PubMed, CNKI, Wanfang and others, for clinical case–control studies of tonsillectomy in patients with IgA nephropathy. We then performed a meta-analysis of these studies. After evaluating total clinical remission rates, we compared the remission rates for specific treatments: tonsillectomy plus steroid pulse, tonsillectomy plus normal-dose steroid, and general treatment using neither tonsillectomy nor steroids. We also compared the rates of end-stage renal failure (ESRF) at last follow-up to estimate the long-term renal survival rate associated with each treatment.

Results. Seven retrospective studies met the inclusion criteria and were included. These included a total of 858 patients, in which 534 underwent tonsillectomy and 324 did not. The total clinical remission rate was higher in the operative group, while the ESRF rate was higher in the non-operative group. The clinical remission rate in patients who underwent tonsillectomy remained higher than in the non-operative group at both 5- and 10-year follow-up. The clinical remission rate in patients who underwent tonsillectomy plus steroid pulse was higher than in those treated with steroid pulse alone, normal-dose steroids or general treatment alone ($P < 0.05$). However, the clinical remission rate of simple tonsillectomy was not higher than that of general treatment ($P > 0.05$).

Conclusions. Whereas neither tonsillectomy nor steroid treatment alone increased remission rates in patients with IgA nephropathy, tonsillectomy combined with either normal steroid or steroid pulse treatment resulted in higher remission rates with favourable long-term efficacy.

Keywords: clinical remission; IgA nephropathy; long-term efficacy; steroid; tonsillectomy

Introduction

Primary immunoglobulin A (IgA) nephropathy (IgAN) is an immune complex-mediated glomerulonephritis that is characterized pathologically by deposition of IgA–IgG immune complexes in the mesangium of the kidney. Although the incidence of IgAN varies among different ethnic groups, it is believed to be the most common form of primary glomerulonephritis worldwide. From 30 to 40% of individuals with IgAN progress to end-stage renal disease (ESRD) within 20 years. Many aspects of the pathogenesis of primary IgAN remain obscure, including the source of IgA and the mechanism underlying its deposition.

It has been noted that ~40% of IgAN patients exhibit grossly deteriorated urinary function or haematuria after