RISK FACTORS BETWEEN ANALGESIC USE AND CHRONIC NEPHROPATHY IN THAILAND

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Abstract. Analgesic abuse is common in Thailand. Heavy use of analgesic may also increase risk of chronic nephropathy. However, the extent of this risk remains unclear. We carried out a case-control study in three referral hospitals. A total of 84 patients with newly diagnosed of chronic tubulointerstitial nephritis were enrolled as cases. Two control groups were randomly selected, 192 from hospitalized patients who had no renal disease and serum creatinine below 1.2 mg/dl and 166 from relatives of friends visiting the hospitals. Both cases and controls were interviewed by a standardized pre-coded questionnaire to obtain histories of analgesic use before diagnosis of renal disease. On multiple logistic regression analysis, patients whose estimated lifetime use of acetaminophen of 1,000 g or more had an increased risk of chronic nephropathy compared with non-users, the odds ratio (OR) was 5.9 (95% confidence interval (CI) 1.3-25.6, hospital controls) and OR = 5.8 (95% CI 1.04-31.9, visitor controls). Also, uses of aspirin showed a similar relationship. Patients who used aspirin 1,000 g or more per lifetime had higher risk of chronic nephropathy when compared to non-users, the odds ratio were 7.1 (95% CI 2.0-25.8, hospital controls) and 20.4 (95% CI 2.4-174.2) for visitor controls. These data indicate that analgesic abuse increased risk of chronic nephropathy in Thailand.

INTRODUCTION

An association between excessive use of analgesics and chronic tubulointerstitial nephritis was first noted in 1953 (Spuhler and Zollinger, 1953). The occurence of analgesic nephropathy was reported from many countries and was a major cause of renal failure. The prevalence of analgesic nephropathy resulting in end-stage renal disease varies widely both from country to country and within individual countries from 1.2% to 25% (Disney and Row, 1974; Kincaid-Smith, 1978; Brynger *et al*, 1980; Buckalew and Schey, 1986). These differences maybe attributed to differences in patterns of analgesic use (Abel, 1971; Prescott, 1976; Kincaid-Smith, 1978; Murray and Goldberg, 1978; Buckalew and Schey, 1986) or from different criteria of diagnoses or other biases (Abel, 1971; Schwartz *et al*, 1984; Lanes *et al*, 1986). Despite these many reports, causal association cannot be yet established (Sorenson, 1966; Prescott, 1982; Lanes *et al*, 1986).

Analgesic abuse is rather common in Thailand, the prevalence of habitual analgesic consumption in rural areas varied from 8.0-9.5% in 1981 (Tirapat *et al*, 1982) to 9.3% in 1988 (Leeprasert, 1988). Because of a potential causative role of phenacetin in analgesic nephropathy (Burry, 1967; Kincaid-Smith, 1967; Gloor, 1978), it was removed from over-the-counter and prescription drug lists in 1984. Nevertheless, the mixture of aspirin or acetaminophen with caffeine is still commonly used among Thai laborers and farmers. Because of the additive effect of caffeine, it was removed from analgesic combination in 1991. This probably resulted in slight reduction in prevalence of habitual analgesic consumption to 7.4% (Department of Epidemiology, 1991). Because of high prevalence of analgesic abuse in Thailand and the inconclusive

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evidence of association with nephropathy, we therefore carried out a case-control study to figure out risk factors associated with chronic renal disease in Thai patients.

MATERIALS AND METHODS

Definitions of study groups and terms

We used a case-control design (Schlesselman and Stolley, 1982). Cases were patients aged 25 years old and over who had serum creatinine 2 mg/dl or above and newly diagnosed as chronic tubulointerstitial nephritis by any two out of three of the following criteria (modified criteria of Murray and Goldberg, 1975 a): 1) urinary sediment without cellular cast; 2) urinary protein excretion less than one gram per day or 2 + by Dipstick (Bayer Diagnostics, Mulgrave, Victoria, Australia); 3) an evidence of tubular dysfunction such as hyperchloremic acidosis, salt loss, etc. These cases were enrolled from renal outpatient clinics or those who were hospitalized in three referral centers, Ramathibodi Hospital (Bangkok), Srinagarind Hospital (Khon Kaen Province) and Maharat Nakhon Ratchasima Hospital (Nakhon Ratchasima Province). Patients, whose etiology of renal disease was known *eg* diabetic nephropathy, lupus nephritis, amyloidosis, obstructive uropathy, ureterovesical reflux, nephro-lithiasis, hereditary kidney disease, renal artery stenosis, glomerulonephritis, were excluded.

Controls were subjects who had no condition which was an indication for or contraindication to analgesic use, for example, chronic arthritis, cancer, cerebrovascular disease, ischemic heart disease, neuropsychiatric disorder, peptic ulcer and bleeding tendency, etc. These controls were randomly selected from 2 groups. Control group 1 (hospital controls) were patients in either an outpatient clinic or a medical ward who had no renal disease and had serum creatinine of 1.2 mg/dl or lower. Control group 2 (visitor controls) were relatives or friends of the patients who visited that hospital. These two difference choices of controls offer us the possibility to detect any selection bias that may arise in the case-control comparison.

The estimated lifetime cumulative dose was calculated using the average amount and frequency and duration in years of regular drug use. Analgesic abuse was defined when estimated lifetime cumulative dose of one or more analgesic drugs is more than 1 kg (Pommer *et al*, 1989). This study was approved by the Ethical Commitee of Ramathibodi Hospital (Document number 016/1992).

Study variables

Both cases and controls were interviewed by a standardized pre-coded questionnaire using trained interviewers who were blinded against study hypothesis and the case-control status. History of analgesic use including types, its composition, dosage, frequency, duration and indication of analgesic use were recorded. To ensure that drug histories were as complete as possible, patients were first asked about indications. With regards to analgesic use, they were questioned about the indication of use for general pain, headache, backache, toothache, menstrual cramps, muscle relaxation, muscle spasm, arthritis, gout, colds, influenza and other infections. Samples of common analgesic drugs sold in local markets were shown to both cases and controls.

Data on potential confounding variables were: use of other drugs history, demographic variables, occupation, and income. We defined persons with income less than 6,000 baht per month and education less than 9 years as low socioeconomic and low education people. Since analgesic abuse is common in farmers and laborers in rural area, we included both groups as laborers in this study. History of lead exposure was also obtained in order to exclude chronic lead nephropathy (Batuman *et al*, 1981, Ritz *et al*, 1988). Information on the clinical course of the illness was recorded by physicians.

Sample size consideration

We assumed that the prevalence of analgesic use among the controls was 8% (Tirapat *et al*, 1982; Leeprasert, 1988), also assuming 5% α-error, 20% β-error, the smallest detectable relative risks will be 0.36, 1.87 for 84 cases and 192 hospital controls; and 0.33, 1.96 for 84 cases and 166 visitor controls (Walter, 1977).

Data management and analysis

Data were entered twice into the computer using Epi Info version 5.01b (Dean *et al*, 1991) and then

were checked and edited for errors and inconsistencies. We used odds ratio (OR) and its confidence interval (CI) to estimate the strength of association (Fleiss, 1981). We used an unconditional multiple logistic-regression model (Breslow and Day, 1980) with forward stepwise approach (Krzanowski, 1988) to simultaneously adjust for potential confounders and to assess any interaction between covariables. We used Epi Info version 5.01b and EGRET (EGRET, 1993) statistical packages for appropriate data analyses.

RESULTS

There were 84 cases, 192 hospital controls and 166 visitor controls in the study (Table 1). Visitor controls were younger (mean age 48.1, 95% CI 46.2-50.0 years) when compared with cases (mean age 53.9, 95% CI 50.8-57.0 years) or hospital controls (mean age 53.3, 95% CI 51.1-55.5 years). On bivariable analysis, there was no association between cases and any controls with regards to sex, and marital status. But associations between cases and any controls could be found with respect to being laborers, having monthly income of 6,000

Table 1

Bivariable comparisons of case and control characteristics[a].

Variables	Cases	Hospital controls	Visitor controls	OR (95% CI)[b]	OR (95% CI)[c]
Sex					
Female[d]	46	92	93	1.0	1.0
Male	38	100	73	0.8 (0.4-1.3)	1.1 (0.6-1.9)
Marital status					
Ever[d]	84	183	159	1.0	
Never	0	9	7	0.0 (0.0-1.1)	0.0 (0.0-1.4)
Laborers					
No[d]	55	150	132	1.0	1.0
Yes	29	42	34	1.9 (1.0-3.5)	2.2 (1.1-3.9)
Monthly income (Baht, 1 US$ = 25 baht approximately)					
> 6,000[d]	32	112	98	1.0	1.0
≤ 6,000	52	80	68	2.3 (1.3-4.0)	2.3 (1.3-4.2)
Education					
≥ 9 yrs[d]	19	62	66	1.0	1.0
< 9 yrs	64	129	97	1.62 (0.86-3.07)	2.29 (1.21-4.37)
Estimated life time use of acetaminophen (grams)					
0[d]	32	60	33	1.0	1.0
0.1-99.9	20	96	86	0.4 (0.2-0.8)	0.2 (0.1-0.5)
100-999.9	19	25	37	1.4 (0.6-3.2)	0.5 (0.2-1.2)
≥ 1,000	7	3	2	4.4 (0.9-27.6)	3.6 (0.6-37.6)
Estimated lifetime use of aspirin (grams)					
0[d]	36	112	114	1.0	1.0
0.1-99.9	20	52	35	1.2 (0.6-2.4)	1.8 (0.9-3.7)
100-999.9	12	16	8	2.3 (0.9-5.8)	4.8 (1.6-14.0)
≥ 1,000	10	4	1	7.8 (2.1-35.2)	31.7 (4.2-1,385.8)

[a] Totals vary because of missing values
[b] Odds ratio of cases compared with hospital controls
[c] Odds ratio of cases compared with visitor controls
[d] Reference

Table 2

Logistic regression analysis between cases and controls.

Variables	Hospital controls OR (95% CI)	Visitor controls OR (95% CI)	Combined controls OR (95% CI)
Estimated life time use of acetaminophen (grams)			
0[a]	1.0	1.0	1.0
0.1-99.9	0.5 (0.3-1.01)	0.4 (0.2-0.9)	0.5 (0.3-1.0)
100-999.9	1.9 (0.9-4.1)	0.8 (0.4-1.8)	1.3 (0.7-2.7)
≥ 1,000	5.9 (1.3-25.6)	5.8 (1.04-31.9)	6.2 (1.7-22.5)
Estimated lifetime use of aspirin (grams)			
0[a]	1.0	1.0	1.0
0.1-99.9	1.1 (0.6-2.2)	1.9 (1.0-3.7)	1.5 (0.8-2.8)
100-999.9	2.1 (0.9-5.2)	3.7 (1.3-10.3)	2.7 (1.2-6.3)
≥ 1,000	7.1 (2.0-25.8)	20.4 (2.4-174.2)	10.9 (3.3-36.0)

[a] Reference

baht (US$240) or less, and estimated lifetime use of acetaminophen or aspirin of 1,000 g or more ($p < 0.05$, Table 1). Using multiple logistic regression, only estimated lifetime use of acetaminophen and aspirin were the only two significant variables in the model (Table 2), regardless of the type of controls. Patients whose estimated lifetime use of acetaminophen of 1,000 g or more had about a 5-6 fold higher risk of chronic nephropathy compared with non-users. Uses of aspirin showed a dose-response relationship. Patients who used aspirin 1,000 g or more per lifetime had a 7-20 fold higher risk of chronic nephropathy when compared with non-users. Because of comparison between cases with both controls was similar, a comparison of cases with the combined controls was made. The results also showed significant risks associated with heavy use of both drugs. Regarding medication use, the cases were more likely than both hospital and visitor controls to report taking analgesics for as stimulants to laborious work (11% *vs* 3.8% and 3.0% respectively, $p = 0.008$). These drugs were claimed by cases to enable them more cheerful (9.2% *vs* 2.7% and 0.6% respectively, $p = 0.001$). They were also claimed to prevent sleepiness (11.8% *vs* 1.6% and 1.3% respectively, $p < 0.001$), although they did not differ in the use of such medications for other symptoms.

DISCUSSION

In this study, we found an increased risk of chronic renal disease in association with heavy use of analgesics: aspirin and acetaminophen. In addition, the risk tends to increase with larger cumulative dose, which is similar to those found by others (Pommer *et al*, 1989; Sandler *et al*, 1989; Morlans *et al*, 1990) except that of Murray (Murray *et al*, 1983). The association observed in our study may be explained by the cumulative toxicity of both drugs to renal tubular cells. Acetaminophen, the major metabolite of phenacetin, is concentrated in renal papillae and had direct toxicity to tubular cells (Mudge *et al*, 1978; McMurtry *et al*, 1978). In addition, aspirin can cause glutathione depletion by inhibiting hexose monophosphate shunt (Murray and Goldberg, 1975 b). This will increase toxicity of acetaminophen. Finally, aspirin can cause renal ischemia by inhibiting vasodilator prostaglandin production especially in the risk patients who are elderly, dehydrated and suffering from heart disease and renal insufficiency (Patrono, 1986).

Retrospective histories of analgesic use may be subject to bias in reporting. In this study, we selected two control groups from hospitalized patients and visitors in order to detect selection bias

because hospitalized patients tend to report analgesic use more than visitors who are generally healthy and less motivated to report medication histories. Nevertheless, we found the similar results regardless of any comparison we made (Table 2). Moreover, this may explain higher risk of nephropathy associated with analgesic use when compared cases with visitor controls than with hospital controls.

Regarding indications of drug use, cases were more likely to report taking analgesic as stimulant believing that it will produce powerful work. This might be an effect of caffeine ingredient in analgesic mixture before its removal from drug composition in the market. In addition, psychological dependence may play some role because prevalence of habitual analgesic use in Thailand is still high even though caffeine is no longer used in analgesic mixtures (Department of Epidemiology, 1991).

Analgesic use could be the result rather than the cause of renal disease. Therefore we included only patients with newly diagnosed chronic renal disease and patients were asked about their medication use before diagnosis. Nevertheless, patients with renal disease may have vague symptoms for which they take analgesic for a long period of time before a diagnosis is made, but we found no difference in their reporting of analgesic use for symptoms of back pain, headache, malaise and others between cases and both controls, except for indication of CNS stimulants as mentioned earlier.

In conclusion, heavy use of analgesics, aspirin and acetaminophen, or both, increased risk of chronic nephropathy. The strategies to prevent overuse of these drugs including public education and restriction of over-the-counter drug may cause a decrease in prevalence of analgesic associated nephropathy in Thailand.

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