ANALGESIC NEPHROPATHY AS A CAUSE OF END-STAGE RENAL DISEASE IN MALAYSIA

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SUMMARY

We questioned 180 patients with end-stage renal disease on maintenance haemodialysis, chronic ambulatory peritoneal dialysis and those who had undergone renal transplantation at the Department of Nephrology, General Hospital, Kuala Lumpur. Twelve patients (6.7%) had consumed excessive quantities of analgesics prior to the institution of long-term dialysis or transplantation. Primary renal disease was considered to be analgesic nephropathy in seven patients (3.9%); in five patients (2.8%), analgesic abuse could have been a contributory factor to end-stage renal failure. Analgesic nephropathy is hence an uncommon cause of end-stage renal disease in Malaysia. However, it is important to be aware of the problem and to institute preventive measures as the cost of treatment for end-stage renal disease is prohibitive.

INTRODUCTION

Analgesic nephropathy (AN) is an important cause of renal failure in many countries. However there is marked geographical variation in the prevalence of AN between countries and even between different areas within the same country. The reported figures for AN causing terminal renal failure requiring dialysis and transplantation vary from 2.5% in Canada,[1] 4.8% in Scotland,[2] 2–10% in the United States,[3] 9.6% in Sweden, 14% in Denmark, 16.7% in Switzerland,[4] 21.5% in Australia,[5] and as high as 44% in Belgium.[6]

In the United States, the proportion of patients with end-stage renal disease (ESRD) with the diagnosis of AN varies considerably from region to region, the figures ranging from 2% in California,[3] 6.25% in the Philadelphia region[7] and 10% in North Carolina.[8] In a retrospective study of analgesic intake, it was demonstrated that 2.8% of patients with ESRD receiving maintenance haemodialysis in the Washington, D.C. area had consumed excessive quantities of analgesic compounds prior to institution of dialysis.[9] Likewise in Australia, there is marked regional variation in the prevalence of AN, with Queensland and New South Wales having a higher proportion than the other states.[10]

No work has been done in any Asian country to determine the proportion of patients with ESRD caused by AN. The present study was therefore undertaken to determine the pattern of analgesic consumption in patients with ESRD requiring dialysis and transplantation in Malaysia.

MATERIALS AND METHODS

The study population consisted of patients with ESRD on maintenance haemodialysis, chronic ambulatory peritoneal dialysis (CAPD) and those who had undergone renal transplantation at the Department of Nephrology, General Hospital, Kuala Lumpur. Data on analgesic consumption by the patients in this study were obtained by interview using standardised questionnaires by the authors.

Patient charts were also reviewed to determine the cause of renal failure, urographic abnormalities, renal biopsy findings and other relevant investigations performed. Significant analgesic abuse was defined as "a minimum total of 2 kg of aspirin, phenacetin, paracetamol and other compounds alone, or in combination prior to the institution of long-term dialysis or transplantation".

RESULTS

Glomerular disease was considered to be the cause of end-stage renal failure in 56 (31.1%), tubulointerstitial disease in 25 (13.9%), vascular disease in nine (5.0%), systemic disease in 12 (6.7%), and "unknown" in 78 (43.3%)(Table I). The high incidence of "unknown" aetiology in our study is due to the late presentation of many patients when diagnostic procedures cannot be performed. One patient was diagnosed as having AN on the basis of a history of excessive consumption of analgesics (paracetamol) and the demonstration of renal papillary necrosis on intravenous urogram.

Significant analgesic abuse was noted in 12 patients (6.6%) (Table I). There were seven males and five females with an age range of 31 to 61

TABLE I

DIAGNOSIS OF PATIENTS WITH END-STAGE RENAL FAILURE

Classification	Frequency
Glomerulonephritides (GN)	56 (31.1%)
Chronic GN	33
Membraneous GN	4
Focal glomerulosclerosis	6
Rapidly progressive GN	5
Mesangiocapillary GN	6
Post-streptococcal GN	2
Tubulointerstitial Nephropathies	25 (13.9%)
Analgesic nephropathy	1
Chronic pyelonephritis	3
Vesico-ureteric reflux	4
Polycystic kidney disease	4
Chronic urate nephropathy	7
Obstructive nephropathy	6
Vascular Nephropathies	9 (5.0%)
Nephrosclerosis	9
Systemic Diseases	12 (6.7%)
Diabetes mellitus	8
Systemic lupus erythematosus	4
Unknown	78 (43.3%)
Total	180 (100.0%)

years (mean 39.2 years). Paracetamol is the commonest analgesic consumed, seven having consumed paracetamol singly (2,100 to 6,600 g) and one having consumed paracetamol (1,500 g) in combination with *Chap Harimau* (Tiger Brand) (1,400 g) which is the local proprietary compound analgesic containing aspirin, phenacetin and caffeine (Table II). One patient had consumed only Indomethacin (7,300 capsules). Two patients were unable to specify the amount of analgesics they had had consumed but they did state that they have been consuming analgesics excessively, one for nine years and the other for 28 years. The major reasons for consuming analgesics were headache for seven patients, and arthritis in three patients.

Primary renal disease was considered to be AN in seven patients (3.9%) on clinical grounds. In five patients (2.8%) of whom two had renal calculi, two had chronic glomerulonephritis and one had polycystic kidney disease, analgesic abuse could have been a contributory factor in the development of end-stage renal failure.

DISCUSSION

Previous studies have shown that analgesic abuse, renal papillary necrosis and AN are prevalent in the Malaysian population. In a survey conducted on three different groups of population, it was found that 0.5 – 2.0% of the people surveyed had consumed more than 2 kg of analgesics, an amount sufficient to cause renal damage.[11] In a retrospective radiological study of the 1,011 intravenous urograms done at the Department of Nephrology, General Hospital, Kuala Lumpur from 1968 to 1981, 20 had renal papillary necrosis of which two were due to diabetes mellitus and the rest due to AN.[12]

TABLE II

AMOUNT OF ANALGESICS CONSUMED

Amount (kg)	No.	Percentage of total population
0 – 0.25	16	8.9
0.26 – 0.50	15	8.3
0.51 – 1.0	7	3.9
1.1 – 2.0	5	2.8
2.1 – 5.0	4	2.2
> 5.1	4	2.2
Excessive	4*	2.2

* Unidentified (5,100 tab) – 1; Indomethacin (7,300 cap) – 1; Unable to remember – 2.

In a prospective study performed on patients admitted to the medical and renal wards of General Hospital, Kuala Lumpur, from January 1982 to February 1983, 12 new cases of AN were documented.[13] Since then a further 13 cases have been documented.[14]

This study has demonstrated that 6.7% of patients with ESRD receiving maintenance dialysis or transplantation in Malaysia consumed excessive quantities of analgesic compounds prior to the institution of dialysis or transplantation. Primary renal disease was considered to be AN in 3.9% of patients, and in 2.8% of patients, consumption of analgesic compound may have contributed to further renal deterioration. In Malaysia, analgesic consumption would appear to be an uncommon cause of ESRD. These figures however may not reflect the true percentage of patients with ESRD due to AN as it is well known that many patients with AN will deny analgesic abuse.[15]

There is considerable international and regional variation in the apparent incidence of AN. One of the most likely causes for this is the variation in the consumption of analgesics.[16] There is however a problem in attempting to define the incidence of AN as there is no common agreement on the definitions of abuse and use of analgesics, while the actual drugs taken and the various combinations used vary widely, even in different parts of the same country.

Authors employ different criteria concerning the frequency of analgesic intake such as daily, several times a day, at least twice weekly, etc., and some surveys are carried out on a community

TABLE III

CLINICAL CHARACTERISTICS OF PATIENTS WITH EXCESSIVE ANALGESIC CONSUMPTION

Patient's age (yr.) and sex*	Cause of end-stage renal disease	Analgesics consumed	Reason	Amount (g)	Dose	Duration of dialysis/ transplantation
38 / M	AN	Paracetamol	Asthma	2,100	8/wk, 10 yrs	11 mths
38 / M	AN	Paracetamol+ *Chap Harimau*	Headache	2,900	2/day, 4 yrs	1.5 yrs
30 / F	AN	Paracetamol	Headache, backache	4,400	6-8/day, 3 yrs	4.5 yrs
34 / M	AN	Paracetamol	Headache	5,500	10/day, 3 yrs	6.5 yrs
32 / F	AN	Paracetamol	Headache	5,700	2-3/day, 14 yrs	2.5 yrs
61 / M	AN	Unidentified	Gout	5,100 (tab)	2/day, 7 yrs	6 mths
42 / M	AN	Unidentified	Headache	Excessive	28 yrs	5 mths
34 / M	Calculi	Paracetamol	Headache	2,400	4/wk, 23 yrs	11 mths
31 / F	Chronic Glomerulonephritis	Paracetamol	Giddiness	6,600	2-6/day, 9 yrs	4 yrs
44 / F	Chronic Glomerulonephritis	Paracetamol	Headache	5,100	2/day, 14 yrs	2.5 yrs
31 / M	Calculi, gout	Indomethacin	Gout	7,300 (cap)	2/day, 10 yrs	5 mths
4 55 / F	Polycystic kidney	Paracetamol	Arthralgia	Excessive	9 yrs	8 yrs

*M – Male; F – Female.

basis, while others have been conducted in highly selected groups of individuals such as factory and office workers or hospital patients.[16] The variation in the consumption of analgesics might be determined by local, social, cultural factors as well as the role played by advertising.[16]

Variation in factors which modify susceptibility to the nephrotoxicity might also account for the geographical variation in the true incidence of AN.[16]

Recognition of the disease and awareness of analgesic abuse is a very important factor accounting for the variation in the incidence of AN. AN is often not recognised and this is underlined by the recent "discovery" of the condition in a number of countries where it was formerly considered to be rare.[16] The conclusion of many authors is remarkably similar in that they all acknowledge that AN is a major problem which has not been appreciated previously.[16]

We conclude that analgesic abuse and AN do exist in Malaysia. Significant consumption of analgesics occurred in 6.6% of our patients with

ESRD requiring dialysis or transplantation. In 3.9% of the patients the primary renal disease was considered to be AN whilst in 2.8% of the patients analgesic abuse could have been a contributory factor in the development of end-stage renal failure. Although analgesic consumption is an uncommon cause of ESRD its significance cannot be underestimated. AN is essentially a preventable disease and the long-term outlook is optimistic if patients stop analgesic abuse as renal function will improve with the cessation of drug consumption.[17] Thus it is important to be aware of the existence of analgesic abuse and to institute preventive measures as well as to advise patients to stop the regular use of analgesics as the cost of definitive treatment for ESRD is prohibitive.

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REFERENCES

[1] Gault M H, Wilson D R. Analgesic nephropathy in Canada: clinical syndrome, management and outcome. *Kidney Int* 1978; 13 : 58–63.

[2] Pendreigh D M, Heasman M H, Howitt L F, *et. al.* Survey of chronic renal failure in Scotland. *Lancet* 1972; 1 : 304.

[3] De Palma J, Wassanmiller J, Akuburah A. Phenacetin/aspirin nephritis as a cause of chronic renal failure. Abstracts of the Western Dialysis Transplant Meeting, Las Vegas, 1975.

[4] Bengtsson U. Prevention of renal disease. *Proc EDTA* 1979; 16 : 466–471.

[5] Disney A P S, Correll R L. Report of the Australia and New Zealand Combined Dialysis and Transplant Registry. *Med J Aust* 1981; 1 : 117–122.

[6] Lornoy W, Morelle V, Becaus I, *et. al.* Analgesic nephropathy. *N Engl J Med* 1979; 300 : 319–320.

[7] Murray T G. Analgesic use and kidney disease. *Arch Intern Med* 1981; 141 : 423 – 424.

[8] Gonwa T A, Hamilton B W, Buckalew V M. Chronic renal failure and end-stage renal disease in north-west North Carolina. Importance of analgesic-associated nephropathy. *Arch Intern Med* 1981; 141: 462–465.

[9] McAnally J F, Winchester J F, Schreiner G E. Analgesic nephropathy: an uncommon cause of end-stage renal disease. *Arch Intern Med* 1983; 143 : 1897 – 1899.

[10] Stewart J H. Analgesic abuse and renal failure in Australia. *Kidney Int* 1978; 13 : 72–78.

[11] Segasothy M. Analgesic use and abuse – a study in threee selected population groups in Peninsular Malaysia. *Med J Malaysia* 1983; 38 : 282–287.

[12] Segasothy M, Kamal A, Abu Bakar Suleiman. Renal papillary necrosis: Retrospective radiological study. *S'pore Med J* 1984; 25 : 254–258.

[13] Segasothy M, Kong B C T, Kamal A, Murad Z, Abu Bakar Suleiman. Analgesic nephropathy – a prospective study. *Med J Malaysia* 1983; 38 : 315–319.

[14] Segasothy M, Kong B C T, Murad Z, Abu Bakar Suleiman, Cheong I, Kamal A, Fatimah Y. Analgesic nephropathy – a four-year experience in Kuala Lumpur. Abstracts of the Sixth Asian Colloquium in Nephrology, Kuala Lumpur, Malaysia 1985.

[15] Murray R M. The origins of analgesic nephropathy. *Brit J Psychiat* 1973; 123 : 99–106.

[16] Prescott L F. Analgesic nephropathy: the international experience. *Aust NZ J Med* 1976; 6 : 44–48.

[17] Kincaid-Smith P, Nanra R S, Fairley K F. Analgesic nephropathy: A recoverable form of chronic renal failure. In Kincaid–Smith P, Fairley K F, (eds). *Renal Infection and Renal Scarring.* Melbourne: Mercedes Press, 1970 : 385–400.