Nephrol Dial Transplant (2004) 19: 840–843
DOI: 10.1093/ndt/gfh040

Nephrology
Dialysis
Transplantation

Original Article

Analgesic nephropathy in Hungary: the HANS study

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Abstract

Background. The diagnosis of analgesic nephropathy has improved significantly with modern imaging techniques. We reviewed a large portion of the Hungarian dialysis population to obtain additional insight into the problem.

Methods. Twenty-two participating dialysis units enrolled 1400 patients on renal replacement therapy between 1 January 1995 and 1 January 1998. Patients with no known aetiology ($n = 284$) were interviewed and studied with renal imaging. We assessed the presence of decreased renal mass combined with either bumpy contours, papillary calcification, or both. The subjects studied were interrogated extensively.

Results. Our survey suggested analgesic nephropathy in 47 of 1400 patients (3.3%), 3-fold higher than the EDTA database estimate for Hungary. The analgesics most commonly abused were phenacetin-containing mixtures. The driving symptoms were mainly headache and joint pain. Cardiovascular complications were more common than in the rest of the dialysis population, independent of smoking and lipid values ($P < 0.01$).

Conclusions. Phenacetin should be banned. Our study results support the need for longitudinal cohort and case–control studies in Hungary.

Keywords: analgesic nephropathy; Hungary; renal replacement therapy

Introduction

Analgesic nephropathy (ANP) commonly occurs after prolonged and excessive consumption of analgesic mixtures containing mainly phenacetin [1]. In some studies, analgesic mixtures containing two other analgesics, such as salicylic acid–pyrazolones, salicylic acid–paracetamol, paracetamol–pyrazolones or two pyrazolones combined with potentially addictive substances such as caffeine and/or codeine, were implicated [2–4]. However, other publications cast doubt on a significant role of non-phenacetin mixed analgesics in the genesis of ANP [5,6]. Australia and New Zealand Dialysis Registry data showed a progressive decrease in ANP after phenacetin was banned [1,4]. At the same time, unexpectedly high incidences were identified recently in the Czech and Slovak Republics [7]. In Hungary, the ERA-EDTA Registry estimated the prevalence of ANP at ~1% in new patients starting renal replacement therapy between 1991 and 1995. They relied on information supplied by the centres. However, the survey lacked uniform diagnostic criteria. The incidence in Hungary could be higher since phenacetin-containing analgesics and other mixtures combined with caffeine and/or codeine are on the market and available without prescription. Our aim

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was to estimate the frequency of ANP among patients starting dialysis by using modern imaging to support the diagnosis [8–10].

Subjects and methods

The study was designed on the basis of the Belgian [8] and European Multicenter Collaborative Study, the ANNE (Analgesic Nephropathy Network Europe) Study [9], with minor modifications. In the 22 participating dialysis units (the total number of eligible units was 52), all of the adult (>20 years) patients with newly initiated renal replacement therapy were invited to participate over 3 years (between 1 January 1995 and 1 January 1998). The study was duly approved and informed consent was obtained. The participating dialysis units were evenly distributed throughout the country. Three of the four large University centres participated. Furthermore, four large centres were located in Budapest and another four in cities with 100 000–200 000 inhabitants. The remaining centres were situated in smaller cities. The distribution of participating dialysis centres was roughly proportional to urban and rural regions and to the density of the population.

Patients with established glomerulonephritis, polycystic kidney disease, diabetic nephropathy, other systemic diseases (systemic lupus erythematosus, Henoch–Schönlein syndrome and other vasculitis), hypertensive nephrosclerosis or clinically confirmed chronic pyelonephritis/chronic interstitial nephritis were excluded. We also excluded patients with incomplete data, those who died before examinations were completed, and those who refused to participate. All other patients with renal disease of unknown aetiology comprised the study cohort.

We defined analgesic abuse as daily use of analgesics for at least 5 years before the start of dialysis. We conducted an interview on the basis of a questionnaire focusing on the name(s) of analgesics, the frequency (daily, weekly, less) of use, number of units of drugs/day or week, number of years of consumption and the indication for analgesic use. We prepared a book containing a photograph of each common generic and brand name analgesic sold on the market between 1970 and 1995, which was shown to the patients. A computed tomography (CT) scan without contrast and/or renal ultrasonography was used for the imaging diagnosis. On CT scan, the renal mass was examined by measuring the anteroposterior (vertical) and medio-lateral (horizontal) dimensions at the level of the renal vessels on both sides [10]. On renal sonography, the lengthwise axis of both kidneys was measured [11]. The kidney contours were classified as smooth, lobular or bumpy (diffuse indentation). Calcifications on the papillary line were described according to Weber *et al.* [12]. ANP was accepted or rejected on the basis of renal imaging criteria developed in Belgium demonstrating a decreased renal mass combined with bumpy contours and/or papillary calcification [8–10]. The method used to diagnose analgesic nephropathy was validated at the Nephrological Center, University of Pécs and at the First Department of Internal Medicine, University of Debrecen. A sensitivity of 83.8% and a specificity of 82.4% were found for bilateral decrease in length together with bumpy contours and/or renal papillary calcification.

Statistical analysis

Data were collected on lipid levels, blood pressure and smoking habits, as well as on the presence of cardiovascular and cerebrovascular complications (acute myocardial infarction and stroke).The data were analysed with the use of the SPSS 8.0 statistical package. Data are given as the mean $\pm$ SD.

Results

During the 3-year study period, 1400 adult patients started renal replacement therapy in the 22 participating dialysis centres. Out of 1400, 284 patients (124 men, 160 women, mean age $\pm$ SD $= 61.1 \pm 12.7$ years) with unknown aetiology were included in the detailed examinations for ANP. A total of 1116 patients were excluded from the study, 999 (89%) because they had established renal disease, and 117 (11%) because of incomplete data collection, death before all examinations were performed, or failure to participate. The most common renal diagnoses were chronic interstitial/chronic pyelonephritis 25.7%, diabetic nephropathy 22.7%, chronic glomerulonephritis (clinically diagnosed and/or confirmed by biopsy) 15.9%, and hypertensive renal disease 11.5%. Other diagnoses were present in $<10\%$ of the patients.

The 284 patients comprised three groups. Group I ($n=39$) were those patients who ingested analgesic mixtures daily for at least 5 years. Group II ($n=62$) were patients who ingested analgesics regularly (but not daily) for >5 years or those who ingested analgesis daily but for <5 years. Group III ($n=183$) were patients who denied taking any analgesics. Group I patients were 80% women and were aged 66 ± 8 years, making them the oldest patients. Group II were 60% women and 40% men. They were aged 61 ± 13 years. Group III were 50% men and women. Their age was 59 ± 15 years.

Table 1 summarizes the six most frequently used combined analgesics in Hungary between 1990 and 1997 and the percentage of ANP patients admitting to having taken them regularly. Most of the patients took more than one product. There was one single analgesic containing amidazophene, which was also commonly consumed (25%) but always together with combined analgesics, except in two patients. The ANP patients consuming combination products generally selected those containing caffeine. Notably, five of six preparations contain phenacetin. Imaging basically corroborated the historical information. Positive CT and ultrasound studies were obtained in 24 of the 39 group I patients, 18 of 62 group II patients, and only five of 183 group III patients.

The indication for analgesic consumption was mainly chronic headache or chronic joint pain. Significantly more women than men took analgesics because of headache ($P<0.01$), as shown in Figure 1. The cardiovascular and cerebrovascular complications (acute myocardial infarction and stroke) are summarized in Figure 2. There were significantly more acute myocardial infarctions in classical (group I) and

Table 1. The most frequently used combined analgesics in group I

	Phenacetin (mg)	Salicylic acid (mg)	Aminophenazon (mg)	Caffeine (mg)	Codeine (mg)	%[a]
T, Antineuralgica	300	–	200	50	–	46.0
P, Combinatus	–	500	350	50	–	37.5
T, Karil	300	–	150	100	–	16.0
T, Salvador	150	–	150	80	–	16.0
P, Antidolor	500	500	–	50	20	12.5
P, Analgeticus	200	–	300	70	–	8.3

T = tablet; P = powder.
[a]Percentage of total number of patients who regularly ingested different combined analgesics in group I.

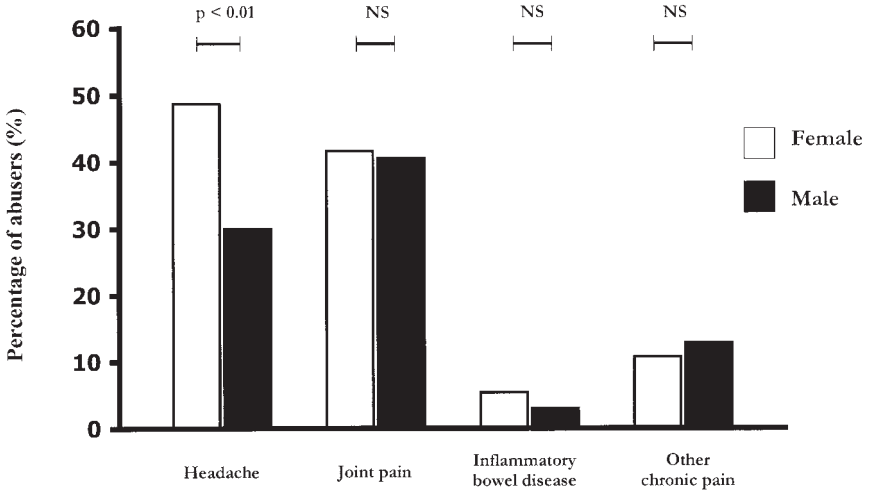

Fig. 1. Indications for use of analgesics in groups I and II.

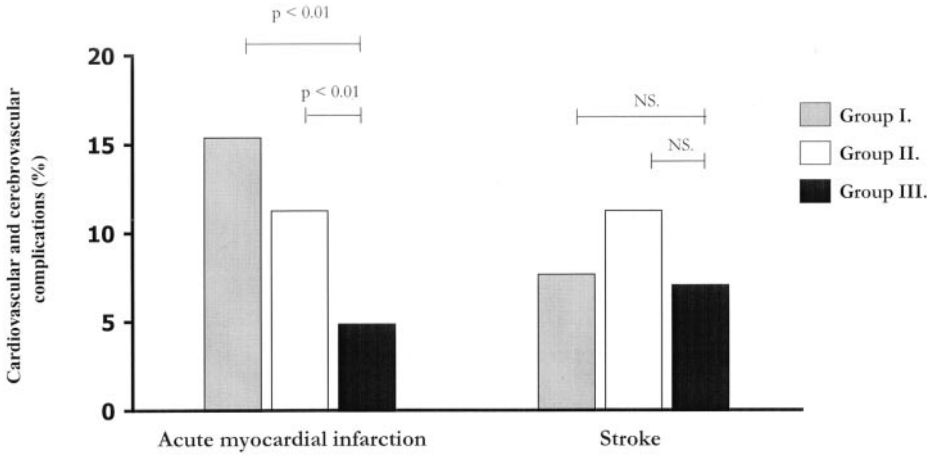

Fig. 2. Cardiovascular and cerebrovascular complications and analgesic abuse in group I.

regular, but not daily (group II) analgesic abusers than in non-abusers (group III) ($P < 0.01$). At the same time, there was no significant difference among the groups in terms of important confounders, including dyslipidaemia, hypertension and smoking.

Discussion

There are two important findings from our survey. First, ANP is probably 3-fold more common in Hungary than believed on the basis of EDTA database estimates. Secondly, our findings suggest that at least 100 Hungarians are on dialysis who do not need to be. Our study has clear limitations. We performed a preliminary survey and we only studied those patients in whom no renal diagnosis had been made. Nevertheless, we subjected our patients to careful interrogation and to imaging studies. We probably underestimated the impact of ANP in Hungary. Patients with renal tumours and those with clinically diagnosed chronic interstitial nephritis/pyelonephritis

were not included. The latter is a 'waste basket' diagnosis that may harbour many ANP patients. In one of our participating centres, the clinicians found that after carefully imaging all patients who started renal replacement therapy, the ANP incidence was 13% in 1996 [13]. Finally, it may very well be that analgesics accelerate chronic renal disease of any cause. Chronic kidney patients commonly have pain and discomfort. In Hungary, they have ready, over-the-counter access to phenacetin to hasten the progression of their disease.

The most important indication of ANP was, and still is, a history of regular analgesic abuse in the absence of any other aetiology of chronic renal insufficiency. However, we and others observed that patients 'play down' their analgesic consumption [3,14,15]. We used the diagnostic criteria of De Broe *et al.*, who relied on a renal imaging technique for the diagnosis of ANP [8–10]. Renal imaging is a very helpful tool for diagnostic confirmation. Knowing who has the condition is important, above and beyond prevention for others. These patients need careful monitoring for atherosclerosis, as documented here, and for possible tumour complications [16,17]. Sometimes, psychological counselling is helpful in giving the patients insight into their condition. Pain experts may also be helpful.

The European and Australian experience suggested that by the withdrawal of phenacetin and by limiting the 'over-the-counter' sale of mixtures containing two analgesic components combined with caffeine and/or codeine, the incidence of the disease significantly decreased and, in some countries, almost disappeared [18–20]. However, many of these studies have design limitations. The *ad hoc* Committee of the International Study Group on analgesics and nephropathy [5], as well as Michielsen and de Schepper [6], have raised critical comments. We cannot resolve this issue. Nor can we draw conclusions about non-phenacetin-containing compounds. We believe that phenacetin clearly should be banned in Hungary. Moreover, our survey gives us a reason to perform a more sophisticated long-term study.

Acknowledgements. We thank Marc De Broe and Monique Elseviers for their help, as well as all the collaborating nephrologists and radiologists.

Conflict of interest statement. None declared.

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Received for publication: 24.6.02
Accepted in revised form: 20.11.03