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End-stage renal disease and non-narcotic analgesics: a case-control study

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1 To assess the risk of end-stage renal disease (ESRD) associated with the regular use of three classes of non-narcotic analgesics, we performed a case-control study of 340 patients with ESRD on a haemodialysis maintenance program and 673 hospital controls.
2 The overall odds ratio estimate for non-narcotic analgesics taken at least every other day for 30 days or longer before the first symptom of renal disease was 2.89 (95% CI, 1.78 to 4.68).
3 The risk increased in relation to the use duration.
4 The previous regular consumption of combinations containing phenacetin was strongly associated with ESRD (odds ratio, 19.05; 95% CI, 2.31 to 157.4). The odds ratio for previous regular consumption of salicylates was 2.54 (95% CI, 1.24 to 5.20) and for pyrazolones 2.16 (95% CI, 0.87 to 5.32).
5 An analysis for possible confounding by a history of repeated headaches, arthritis, kidney stones, hypertension, and diabetes did not alter the results.
6 The odds ratio estimates for different pathological subgroups of ESRD patients in relation to previous use of any non-narcotic analgesic were glomerulonephritis, 10.57 (95% CI, 1.25 to 89.0), interstitial nephritis, 3.33 (95% CI, 1.21 to 9.17), cystic kidney disease, 0.71 (95% CI, 0.25 to 1.97), and unknown, 5.15 (95% CI, 2.29–11.57).
7 The results of this study suggest that the regular consumption of analgesics should be routinely considered as a risk factor for any non-congenital cause of chronic renal failure. They also suggest that the risk of ESRD associated with the regular consumption of phenacetin is much higher than the risk associated with other non-narcotic analgesics.

Keywords analgesics aspirin kidney failure, chronic nephritis, interstitial pyrazolones

Introduction

In 1950 an increasing incidence of chronic interstitial nephritis of unknown aetiology was observed in autopsies carried out in Zurich. Some of the patients had a history of long-term consumption of large amounts of analgesic mixtures. The authors were unable to establish whether abuse preceded or followed the onset of renal disease (Spühler & Zollinger, 1953). There is ample experimental and clinical evidence linking analgesic abuse with chronic renal disease, but the large majority of reports have incriminated analgesics—and phenacetin in particular—solely on the basis of association and circumstantial evidence (Prescott, 1982).

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Several aspects of this disease are still ill-defined. Firstly, generally agreed diagnostic criteria include a history of heavy use of analgesics, which may in itself bias any causal association (International Committee for Nomenclature and Nosology of Renal Disease, 1975). Secondly, its real incidence is a matter of controversy, and striking geographic differences as a cause of end-stage renal disease (ESRD) have been recorded (Brunner *et al.*, 1989; Brynger *et al.*, 1980; Gault & Wilson, 1978; Gonwa *et al.*, 1981; Murray & Goldberg, 1978; Vanherweghem & Even-Adin, 1982), Spain showing the lowest figure in Europe (Anonymous, 1981). Thirdly, the few epidemiological studies published to date have yielded conflicting results. A cohort study carried out in Basel, in which heavy users of analgesics were selected because of phenacetin metabolites in their urine, has shown a higher incidence of both abnormal kidney function and kidney-related mortality in this group compared with occasional users and non-users after a 10-year follow-up (Dubach *et al.*, 1983). On the other hand, a case-control study, conducted among patients on haemodialysis because of ESRD, was unable to demonstrate an increased risk of ESRD associated with past analgesic use (Murray *et al.*, 1983). These results contrast with those of two recent case control studies. In one of them, conducted in the USA and including patients with newly diagnosed kidney disease, an excess risk of renal disease in daily users of analgesic mixtures was shown (Sandler *et al.*, 1989). Another study from West Germany, including patients with ESRD, has shown a dose-dependent increase in risk with the cumulative use of more than 1 kg of analgesic mixtures (Pommer *et al.*, 1989a,b). Fourthly, the possible aetiological role of analgesics other than phenacetin—and particularly aspirin and the pyrazolones—has not been clearly established. Finally, there is little information on the association between analgesic use and the risk for specific types of renal disease other than interstitial disease (Bennett & DeBroe, 1989; Sandler, 1985).

We therefore undertook a case-control study to determine the risk, if any, of different forms of ESRD associated with the use of different analgesics.

Methods

The methods were similar to those employed in a previous investigation carried out in Pennsylvania and New Jersey (Murray *et al.*, 1983).

Briefly, the cases consisted of a randomly selected sample of patients with ESRD maintained on centre haemodialysis in the Metropolitan Area of Barcelona. Cases were selected using random number tables aiming for at least 50% of each dialysis unit; when the study was started, there were 632 patients undergoing dialysis in 10 units. When patients refused the interview ($n = 70$) or were found ineligible [because of disorientation, deafness, etc; ($n = 8$)], they were replaced by the next non-selected patient in tl.e unit's list.

For every case, two hospitalized controls, matched to the case by age (within ± 5 years) and sex, were randomly selected from hospital admission lists, after excluding admissions to obstetrics, oncology, psychiatry, and radiation therapy.

Three hundred and fifty-two cases and 673 controls were interviewed between September 1980 and March 1983 by a trained nurse, who was not aware of the diagnosis of the disease leading to ESRD. Twelve cases were completely 'unmatched' and seven cases were only matched with one control, and therefore 340 cases and 673 controls were left for analysis.

When approaching potential participants for recruitment, past use of analgesics was not mentioned as the primary investigation of the interview. Analgesic use was elicited by means of a standardized structured questionnaire including a 'life-history' review of ailments that might lead to analgesic intake (e.g. headache) and a list of analgesic brand names and samples of packages based on past marketing data. The questions were phrased in a non-judgemental tone. If there were any data suggesting that the case or the control had used an analgesic product daily or every other day for 30 days or longer, the patient was classified as a 'user'. Data collected on potential confounding factors included, in addition to the drug history, demographic information such as age and years of education, and detailed medical information such as a history of major illnesses.

The use of analgesics was only considered when it occurred prior to the date of entry into haemodialysis and to the date of the first evidence of kidney disease. To fulfill this aim, an 'index date' was established by the nephrologist from the answers to some of the questions (e.g. have you ever had haematuria? if yes, when?; have you ever had albuminuria? if yes, when?; had the doctor told you the name of the disease?). The 'index date' for controls was the same as for their matched cases.

In addition, the dialysis unit record and the medical record from the hospital where the

renal failure was diagnosed were abstracted whenever possible. This information was used to classify the ESRD cases according to their previous renal disease with an objective set of criteria initially developed by Murray & Goldberg (1975) and later applied in a case-control study (Murray *et al.*, 1983). Thus, 251 patients with ESRD could be classified in five diagnostic categories: interstitial nephritis (IN), glomerulonephritis (GN), cystic kidney disease (CKD), indeterminate (IND) (that is to say impairment of glomerulus and interstitium) and unknown (UNK). This last category included those patients with no information available before creatinine blood levels rose above 8 mg dl^{-1}. IN and GN patients were also classified as 'definite', 'probable', or 'possible' using the same objective set of criteria; the definition of IN was made with no knowledge of analgesic use. Patients with certain systemic diseases (such as diabetes mellitus or amyloidosis) are thus obviously distributed among these different groups according to the predominant renal lesion.

Estimates of the odds ratio (OR) were calculated using a conditional logistic model including age and sex (Rothman, 1986; Schlesselman, 1982). Potential confounding factors such as the history of recurrent headaches, arthritis, kidney stones, hypertension, and diabetes, were included in the model; four additional variables, corresponding to the use of four categories of analgesics (ASA, pyrazolones, phenacetin, any combination) were also included in the model when OR estimates for particular groups of analgesics were calculated. The strength of the association between previous use of analgesics and ESRD was not materially affected by the inclusion of these four variables. The exposure to caffeine-containing combination analgesics was also considered; only eight cases and nine controls had used these medicines, and the strength of the association between previous use of analgesics and ESRD was not affected by the inclusion of this variable. A trend test was performed treating the categorical variables as continuous in the model (Breslow & Day, 1980).

Results

Two hundred and seven men (60.9%) and 133 women (39.1%) were included in the study, this sex distribution being very close to that recorded among the ESRD population at that time in the study region. One hundred and forty-one patients (41.5%) were 15–44 years-old at the time of the interview, 178 (52.3%) were 45–64 years old, and 21 (6.2%) were over 65 years. Age and sex distribution (which were matched) and smoking and drinking habits among controls did not differ from those among cases. Although the proportion of cases having secondary and university education was higher than that of controls (26.2% *vs* 11.9%, $\chi^2 = 36.18$; $P < 10^{-6}$), no association was found between educational level and analgesic use ($\chi^2 = 0.30$; $P = 0.58$).

The use of analgesics in three subsets of controls was 10.5% among those with acute respiratory conditions ($n = 200$), 9.6% among those with digestive conditions ($n = 187$), and 7.0% among those with other conditions ($n = 286$).

Seventy cases (20.6%) and 59 controls (8.8%) reported analgesic use (at least one period of every other day use lasting 30 days or longer). The main reasons for analgesic use were headache (68% of cases and 47% of controls) and musculo-skeletal and joint pain (23% of cases and 38% of controls). The OR for ESRD development associated with overall analgesic exposure was 2.89 (95% CI, 1.78–4.68). The OR estimate increased with increasing duration of use. The effect of cumulated dose was difficult to evaluate due to the low numbers of cases and controls exposed to the higher doses (Table 1).

The OR of ESRD was particularly increased among patients with a history of previous use of combinations containing phenacetin (19.05, 2.31–157.4). The OR for salicylates was also significantly increased (2.54, 1.24–5.20), and for pyrazolones the increase was not statistically significant (2.16, 0.87–5.32). The OR for all other combinations (not containing phenacetin, but containing salicylates or pyrazolones) was 2.80 (1.07–7.33).

In the final model the association between potential confounding factors (see Methods) and ESRD was evaluated. A statistically significant association between previous history of hypertension and ESRD (5.48, 2.23–13.46) was found. The association of ESRD with a previous history of kidney stones was not statistically significant (3.50, 0.95–12.92). The crude estimate of the association between previous headaches and ESRD was 2.49 (1.52–4.10), but it was reduced to 1.38 (0.69–2.75) when the previous use of analgesics was also included in the model.

Out of 340 cases, the records of 251 could be traced and abstracted. Of these, 50 (19.9%) were classified as GN (43 definite, 6 probable, and 1 possible); in 43 of these patients the

Table 1 OR end-stage renal disease associated with the use of analgesics. Duration and type of analgesic exposure

	Number of cases (n=340)	*Number of controls (n=673)*	*Relative risk*	*95% CI*
Non-users	270	614	1.0	(Reference class)
Users	70	59	2.89	(1.78 – 4.68)
Duration				
< 1 year	18	21	2.15	(1.12 – 4.12)
1–5 years	15	13	3.43	(1.49 – 7.89)
> 5 years	35	25	3.44	(1.98 – 5.95)
Trend test				$P < 0.01$
Cumulated dose				
< 1 kg	35	26	3.09	(1.77 – 5.41)
1–3 kg	7	6	3.20	(1.00 – 10.26)
> 3 kg	5	3	2.01	(0.39 – 10.28)
Analgesics				
Pyrazolones	15	13	2.16	(0.87 – 5.32)
Salicylates	23	21	2.54	(1.24 – 5.20)
Phenacetin-containing combinations	9	1	19.05	(2.31 – 157.4)
Combinations, other[a]	20	9	2.80	(1.07 – 7.33)

[a] Containing ASA and pyrazolones, but not phenacetin.

Table 2 OR of ESRD according to the specific renal disease in 251 patients whose clinical records could be abstracted, and in their respective controls.

Diagnosis[a] (number of patients)	*Number (%) of exposed cases*	*Number (%) of exposed controls*	*Relative risk*	*(95% CI)*
GN (50)	6 (12.0)	2 (2.0)	10.57	(1.25 – 89.00)
IN (49)	10 (20.4)	6 (6.2)	3.33	(1.21 – 9.17)
IND (9)	1 (11.1)	1 (5.6)	2.00	(0.13 – 31.97)
CKD (41)	6 (14.6)	16 (19.5)	0.71	(0.25 – 1.97)
UNK (102)	25 (24.5)	15 (7.4)	5.15	(2.29 – 11.57)

[a] GN = glomerulonephritis; IN = interstitial nephritis; IND = indeterminate; CKD = cystic kidney disease; UNK = patients with unknown diagnosis because there was no information available before creatinine blood concentrations rose above 8 mg dl^{-1}.

diagnosis was based on biopsy. Forty-nine patients (19.5%) were diagnosed as IN (39 definite, 5 probable, and 5 possible); of these, 29 were diagnosed by intravenous pyelography, and 10 by renal biopsy. Forty-one patients (16.3%) were diagnosed as CKD, 9 (3.6%) as IND, and 102 (40.7%) as UNK; in this category biopsy was not available before creatinine blood levels rose above 8 mg dl^{-1}. Table 2 shows the estimates of risks for each one of these five diagnostic categories.

Discussion

This case-control study confirms previous reports concerning the risk of ESRD associated with the use of analgesics, particularly phenacetin (Pommer *et al.*, 1989a,b; Sandler *et al.*, 1989). In addition, it gives estimates of the risk associated with different classes of non-narcotic analgesics.

Although many publications have linked analgesic abuse to ESRD, the majority con-

sist of case reports and case series. These reports do not usually include data on analgesic use of a matched control group, fail to define clinical end-points such as 'reduced renal function' (Gonwa *et al.*, 1981), or, when referring to phenacetin, do not mention any of the other drugs which have almost invariably been taken with it (Prescott, 1982).

In Spain the diagnosis of 'analgesic nephropathy' is rare compared with that of other European countries (Anonymous, 1981), while the consumption of analgesics is relatively high—according to IMS data from different European countries, in 1982 34 defined daily doses (DDD) of minor analgesics per 1,000 inhabitants per day were consumed (i.e. a mean of 34 out of every 1,000 individuals in the general population took an analgesic daily during this year), compared with 20 DDDs in Italy and 30 DDDs in West Germany. Only 2.8 of those 34 DDDs corresponded to paracetamol; this, and the fact that our study sought after the past use of analgesics, explains why paracetamol-associated risk could not be analyzed.

We chose a low threshold of analgesic consumption because we wanted to avoid the prejudice that analgesic-related renal dysfunction is only seen in patients who have consumed large quantities during long periods of time.

It is unlikely that the results were materially affected by bias. The observed association might have occurred if nephrologists had tended to admit patients who had previously used analgesics to the haemodialysis program more often than patients who had not used analgesics. This was not the case, because admitting renal patients to maintenance haemodialysis depends on their clinical condition rather than on their previous history of analgesic use. Moreover, the checking of the clinical records showed that not a single patient had been diagnosed as 'analgesic abuse ESRD' before entering the maintenance program.

All the potential controls were successfully interviewed. It was reassuring that the distributions of past analgesic use were generally similar across the major diagnostic categories. The choice of hospital controls may have resulted in an underestimation of relative risks, because patients admitted to a hospital might be more liable to ingest analgesics than the general population. Therefore, the presented relative risks may be conservative estimates.

A particular feature of the study enables us to reasonably exclude information bias—the interviewer was unaware of the primary renal disease leading to ESRD. The cause of ESRD was congenital in 41 (16.3%) patients with cystic kidney disease (CKD), and no association was found between the use of analgesics and CKD, suggesting that the associations found with non-congenital diseases are valid.

The results were not explained by potentially confounding factors including age, sex, or a history of recurrent headache, arthritis, kidney stones, hypertension, or diabetes.

We found a slightly increased statistically significant risk of ESRD associated with previous use of salicylates (OR = 2.54; 1.24–5.20). Acute and chronic effects of salicylates on the kidney have been recognized for a long time, both from the results of animal experiments and clinical findings. Prescott (1982) records 88 cases of papillary necrosis due to acetylsalicylic acid (ASA) alone and a further 63 in patients taking ASA with other analgesics (but excluding phenacetin). In two recent case-control studies the use of ASA as a single agent, either daily (Sandler *et al.*, 1989) or every other day for at least 1 year (Pommer *et al.*, 1989a,b), did not increase the risk of renal disease. However, in the US study the level of drug exposure was characterized according to the pattern of use of the drug taken most often in each class, and this may have underestimated the total consumption by patients who took more than one drug (Sandler *et al.*, 1989). In the German study out-patients from clinics of departments of a University medical centre were used as controls (Pommer *et al.*, 1989a,b), and this population may use more analgesics than our control group.

The risk associated with previous use of pyrazolones was not statistically significant, perhaps due to the low numbers of patients exposed to these drugs for long periods of time, perhaps because there is no risk. Pyrazolone-induced renal damage has also been described, both experimentally (Brown & Hardy, 1968) and clinically. Out of the 44 patients originally described by Spühler and Zollinger, 14 had taken a combination containing phenacetin, amidopyrine, isopropylantipyrine, caffeine, and piritildione. Other case reports of pyrazolone-induced kidney damage refer to overdosage (Lachmann, 1977; Nelson & Berry, 1967) or to other acute effects, apparently hypersensitivity reactions (Eknoyan & Matson, 1964; Ortuño & Botella, 1973), and we are aware of only one report of severe renal impairment with papillary necrosis after taking an estimated 10 kg antipyrine over 12 years (Alexsson, 1958). An association between chronic use of metamizole (but not other

pyrazolones) and the risk of ESRD has been recently found in the German study quoted above (Pommer *et al.*, 1989a,b).

We did not find any association of ESRD with previous use of caffeine-containing drugs. This association was described in the German study (Pommer *et al.*, 1989a,b). This difference may be due to the fact that the proportion of caffeine-containing combination analgesics might be lower in Spain than in Germany: while in the German study 88% of the study subjects with regular analgesic intake and ESRD had taken caffeine, in our study this proportion was only 2.4%.

Disagreements between hospitals in establishing a uniform definition of chronic renal failure have been described (Modan *et al.*, 1975; Sandler, 1985). There are also wide interpatient differences in the length of the clinical course leading to ESRD, which may depend on the primary renal disease. These considerations led us to define cases by their need for maintenance dialysis. However, the selection of this high cut-point for case definition prevents knowledge of the primary renal disease in a proportion of the cases. Out of 251 patients whose clinical record could be traced and abstracted, in 102 (40.7%) no relevant clinical information was available before plasma creatinine level rose above 8 mg dl^{-1}. In these patients the primary renal disease diagnosis leading to ESRD was classified as 'unknown'. Even when renal biopsy is performed, if the damage is severe and extensive the specimen may be impossible to interpret.

The diagnosis of IN is difficult to make without a biopsy, a procedure that, in our series, was performed in 67 out of 340 patients (19.7%), a proportion which is higher than that of the US case-control study (Sandler *et al.*, 1989) (6%). Furthermore, at late stages of the renal disease the diagnosis of IN becomes indistinguishable from that of GN, even when a biopsy is done, as the tissue is already too scarred. Interstitial disease may be asymptomatic in the early stages and may develop slowly, so that these patients tend to be underrepresented among renal cases referred for dialysis, and particularly among those who do have a biopsy. Therefore, a substantial proportion of the patients whose diagnosis was classified as 'unknown' might actually have an interstitial primary renal disease which would have gone undetected before full deterioration of renal function developed because of a slower clinical course. The high risk associated with GN may have arisen by chance, despite statistical significance, the figure in Table 2 being based only on two exposed controls out of 92.

The prevalence of treated ESRD in the Metropolitan Area of Barcelona is 684 per million population (Registre de Malalts Renals de Catalunya, 1987). In Catalonia the figure in 1984 was 415 (Registre de Malalts Renals de Catalunya, 1985), compared with 304 in Belgium, 265 in Switzerland, 190 in the Netherlands, and 153 in the UK (Broyer *et al.*, 1984). On the other hand, Spain (and also Catalonia) has been cited as the country with the lowest European figure with regard to the proportion of cases attributed to 'analgesic nephropathy' (Anonymous, 1981). This situation conflicts with the figures of analgesic consumption quoted above. The results of this study suggest that ESRD may be due to more than one single factor, and that classification of renal diseases according to their presumed aetiology may introduce some confusion from an epidemiological point of view. In addition, analgesics should routinely be considered in clinical practice as one of the various known risk factors for developing ESRD.

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