Chronic analgesic nephropathy (AN) is a slowly progressive renal disease resulting from daily use for many years of mixtures containing at least two analgesics and caffeine or dependence-inducing drugs. Computed tomography scan can accurately diagnose this disease even in the absence of reliable information on previous analgesic use. The occasion to moderate regular use of aspirin and nonsteroidal anti-inflammatory drugs is without renal risk when renal function is normal. Paracetamol use is less clear although the risk is not great. The continued use of non–phenacetin-combined analgesics with or without nonsteroidal anti-inflammatory drugs is associated with faster progression toward renal impairment. As long as high-risk analgesic mixtures are available over the counter, analgesic nephropathy will continue to be a problem.


Chronic analgesic nephropathy, particularly chronic interstitial nephritis and renal papillary necrosis, results from daily use for many years of mixtures containing at least two analgesics (e.g., aspirin, paracetamol, pyrazolones, phenacetin) and caffeine, codeine, and/or barbiturates, which may lead to psychological dependence and overuse. The disease is characterized by capillary sclerosis, renal cortical atrophy, chronic interstitial nephritis, and papillary necrosis/calcifications. In a number of cases, not related to the progression or stage of renal failure, the uroepithelia can develop transitional cell carcinoma.1,2

The lack of reliable validated criteria, the high prevalence of AN in 1980 through 1990 in Belgium (>15% of the dialysis population), and the underestimation of the disease in Europe led us to perform studies defining and validating the criteria for AN. On the basis of the results of three multicenter multinational studies, computed tomography (CT) scanning without contrast medium turned out to be a valuable and validated test to diagnose or rule out AN as a possible cause of renal disease in patients with ESRD as well as in patients with stages 3 to 4 chronic kidney disease (CKD), even in the absence of reliable information on the use of combined analgesics (Figure 1).3

Known causes of renal papillary necrosis/calcifications other than combined analgesic use are diabetes, sickle cell disease, and pyelonephritis, the differential diagnosis of the two first conditions being straightforward. Chronic pyelonephritis is associated with progressive renal scarring, in the context of intrarenal reflux of infected urine. Calcified papillary necrosis observed in the majority of the papilla in both kidneys of patients with AN is not seen in chronic pyelonephritis.

Several studies using this validated diagnostic test showed either the absence or low prevalence of AN, whereas others confirmed the underestimation of AN in their country and showed a substantial number of patients with AN exist in the cohort of patients with unknown cause or chronic interstitial nephritis. Still, other investigators have used this validated diagnostic test in an epidemiologic study related to late referral of patients with severe renal failure toward renal units.

A study of patients with ESRD (National Analgesic Nephropathy Study [NANS]) in the United States evaluated the value of the non–contrast-enhanced CT as diagnostic test for AN.4 It turns out that in comparison with previous studies, the sensitivity of the noncontrast CT scan for the detection of analgesic-associated kidney injury was too low to be used as a routine test; that is, a specificity of >95%, comparable with the earlier reports, was found. The low prevalence of AN (clearly <5%) found in the United States, however, precluded calculating the clinically relevant sensitivity of the test.

WHAT KIND OF ANALGESICS ARE INVOLVED IN THE GENERATION OF AN?

Phenacetin was present in all products used by patients described in the early reports of AN. This finding is the sole argument to support the generally accepted “phenacetin kidney” concept. Ex-
Experimental studies revealed, however, that aspirin and phenazone derivatives—the drugs invariably taken with phenacetin—all produce experimental nephrotoxicity more readily than phenacetin. Whether phenacetin is the sole responsible ingredient causing AN still is a matter of intense debate. Phenacetin believers argue it was the ban of phenacetin that caused the decline in AN incidence observed in Switzerland and in other countries. In contrast, researchers in the field of AN have joined forces to identify the nephrotoxic potential of all analgesic mixtures with or without phenacetin. In 1995, the ad hoc committee of the National Kidney Foundation in the United States examined the available information from hundreds of peer-reviewed articles and stated that habitual consumption of both phenacetin-containing mixtures and non–phenacetin-containing mixtures is associated with AN. One year later, European nephrologists proffered a similar viewpoint, asking for the prohibition of over-the-counter sales of any analgesic mixtures containing two analgesic components combined with caffeine and/or codeine.

Clinical observations performed within the framework of the diagnostic criteria of AN document the nephrotoxicity of the combinations of salicylic acid with paracetamol, pyrazolones, paracetamol-pyrazolones, or two pyrazolones associated with dependence-producing drugs. Additional data from Australia and Belgium support the suggestion that withdrawal of phenacetin is not solely responsible for the decline in AN. Only after the drastic decrease in the sales of all analgesic mixtures was a substantial decline in the incidence of AN observed.

Many epidemiologic studies have investigated the risk for renal failure related to the prolonged excessive consumption of analgesics (Figure 2). In case-control studies, the overall risk after any analgesic consumption ranged from 1.02 (95% confidence interval 0.80 to 1.30) to 17.20 (95% confidence interval 8.50 to 34.70). The studies of Sandler et al., Pommer et al., and Morlans et al. resulted in comparable odds ratios (ORs) between 2 and 3, despite differences in study design. McCredie’s study showed a considerably higher OR by using the more specific lesion of renal papillary necrosis as the primary identifier of disease.

A solid demonstration of the association between analgesic use and renal failure is also provided by two prospective, controlled, cohort studies performed of patients with excessive use of analgesic mixtures in Switzerland and Belgium with a follow-up of 10 and 6 yr, respectively. Although both studies differed substantially with respect to study populations, analgesics consumed, and length of follow-up, the increased ORs were remarkably similar. In contrast, the observational studies of Kurth et al. and Curhan et al. could not demonstrate an increased risk after the (nonexcessive) consumption of any analgesic in a population of healthy US male physicians or female nurses, respectively.

It is inherent to the case-control design that the observed association between
CKD and analgesic consumption does not establish cause and effect. Moreover, serious flaws in study design or analysis of data have to be considered and were discussed in several reviews (Table 1). Most case-control studies suffer from selection bias. Lack of randomization of the control population and significant differences in gender and race between case patients and control subjects can seriously influenced results. Moreover, most heavy users tend to deny their analgesic consumption. Retrospective investigation of a precise history of analgesic consumption is difficult to obtain, necessitating the use of special interview techniques. Interviews by telephone or written self-reports of analgesic consumption in the past were not the methods of choice to detect hidden consumption of analgesics (information bias). Half of the case-control studies as well as all of the cohort studies also suffer from indication (protopathic) bias; that is, not being able to distinguish between analgesic consumption preceding de novo development of renal disease and the analgesic consumption because of symptoms of other diseases (e.g., diabetes) that predispose patients to renal failure. Finally, it is well established that patients with AN used analgesics on a daily basis and at least for a period of 5 yr, resulting in a total analgesic consumption of at least 1500 U. As shown in Figure 2, several studies suffered from dosage bias because they used a total amount that was far below the minimum consumption described in patients with AN.

The epidemiologic literature concerning the role of different substances that cause AN is limited and controversial. Substances combined in analgesic mixtures are invariably taken together. Most case-control studies suffer from ingredient bias because they present risk ratios based on analyses without making a distinction between analgesics used as single ingredient or in combination. Mainly because of ingredient bias, the potential nephrotoxicity of paracetamol remains a matter of debate, with six studies showing an increased risk and three studies not (Figure 3). The safety of aspirin used as a single ingredient is easier to evaluate. From seven case-control studies, only three showed an increased risk. In addition, two robust, observational cohort studies reported even slightly decreased OR for the use of aspirin (Figure 3). In both studies, calculated ORs were based on hundreds of regular users of aspirin, used as a single-ingredient analgesic.

**DOES ANALGESIC USE EXACERBATE THE PROGRESSION OF CKD?**

Some epidemiologic studies generate the hypothesis that habitual analgesic use in-
Table 1. Sources of bias in the epidemiologic studies

<table>
<thead>
<tr>
<th>Bias</th>
<th>Studies</th>
<th>Selection Bias</th>
<th>Information Bias</th>
<th>Indication or Protopathic Bias</th>
<th>Ingredient Bias</th>
<th>Dosage Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control studies</td>
<td>McCredie et al.,11 Australia, 1982</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<td></td>
<td>Murray et al.,12 United States, 1983</td>
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<td></td>
<td>Sandler et al.,13,14 United States, 1989 and 1991</td>
<td>No</td>
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<tr>
<td></td>
<td>Pommer et al.,15 West Berlin, 1989</td>
<td>No</td>
<td>No</td>
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<td></td>
<td>Morlans et al.,16 Barcelona, 1990</td>
<td>Yes</td>
<td>No</td>
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<td></td>
<td>Perneger et al.,17 United States,1994</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td></td>
<td>Fored et al.,18 Sweden, 2001</td>
<td>No</td>
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<td></td>
<td>Ibanez et al.,19 Barcelona, 2005</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<td></td>
<td>Van der Woude et al.,20 Austria, Germany, 2007</td>
<td>Yes</td>
<td>No</td>
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<td>Prospective controlled cohort studies</td>
<td>Dubach et al.,21 Switzerland, 1983</td>
<td>No</td>
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<td></td>
<td>Elseviers and De Broe,22 Belgium, 1995</td>
<td>No</td>
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<td>Observational cohort studies</td>
<td>Kurth et al.,23 United States, 2004</td>
<td>No</td>
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<td></td>
<td>Curham et al.,24 United States, 2004</td>
<td>No</td>
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</table>

*Selection bias, random selection of controls failed or the chosen control population is biased; information bias, methods used to obtain information about analgesic consumption are doubtful; indication or protopathic bias, failure to control for analgesic intake preceding the development of renal failure; ingredient bias, failure to entangle the use of particular ingredients either as single analgesic or as one of the ingredients of analgesic mixtures; dosage bias, definition of analgesic use far below the amount consumed by patients with analgesic nephropathy.

fluenences the progression of CKD. Fored et al.18 performed a carefully designed study of patients with moderate to severe renal failure. They tried to exclude several biases, including indication bias. Indeed, the use of analgesics and the risk for CKD was not consistently stronger among patients with underlying diseases causing frequent aches and pain.18 They analyzed their results on the basis of three different periods of exposure, trying to separate analgesic use as a causal factor from the possibility that renal diseases or their prodromal symptoms initiated analgesic use (protopathic bias). In addition, they avoided the previously described excess risk for ESRD to be greater in those whose paracetamol use occurred within a 5-yr period closest to the initiation of treatment for ESRD, explained by the advice of their physicians to avoid taking nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin. All of these analyses result in only minor reduction in estimates of relative risk. Nevertheless, caution is still required because, as the authors pointed out, “it is impossible to rule out bias caused by consumption of these analgesics for symptoms of the condition that predispose patients to renal failure,” the latency time between the exposure to analgesics and CKD being unknown.

To evaluate a possible effect of analgesics on the progression of CKD, one needs at least two time points of renal function measurement after randomization of patients with incipient or moderate degrees of renal failure and documented pronounced analgesic use and groupings into those who stopped analgesic intake and those who maintained a substantial consumption of analgesics. The study that realized the best possible approach toward this important design issue is that of Mackinnon et al.25 The authors studied patients with CKD of undetermined cause associated with important use of analgesics in which the stoppage or ongoing analgesic use was registered regularly along with several measurements of renal function of a median follow-up period of 58 mo. Patients were considered to have AN when they had a history of analgesic ingestion on a daily basis (excluding low-dosage aspirin as an antiplatelet agent) for at least 3 yr and no other explanation for their renal impairment could be found. NSAIDs, analgesic mixtures, and paracetamol, all or not in combination, were used. No patient gave a history of phenacetin ingestion. During follow-up, 27 patients were judged to have ceased all analgesic intake, whereas the remaining 51 continued using one or more of the preparations listed.

There were no significant differences between the two groups in terms of racial background, gender, age, or proteinuria at presentation. The proportion of patients in each group with a history of smoking, hypertension, or vascular disease was not significantly different, either. Despite these similarities, the renal function of those who continued to take analgesics declined 3.5 ml/min per yr faster than the patients who stopped taking all analgesics. In addition, continuing analgesics conferred a six-fold increase in the risk for death or progression to ESRD. Despite some flaws in this study, it supports the contention that the continued use of non-phenacetin-combined or single-agent analgesics is associated with faster progression of renal impairment and an increased risk for reaching a combined end point of death or ESRD in patients with AN.

IS THE PROLONGED USE OF NSAIDS ASSOCIATED WITH RENAL PAPILLARY NECROSIS OR CKD?

The most common renal disorder associated with NSAIDs is acute kidney injury, largely reversible, as a result of the inhibition of renal vasodilatory prosta-
glandins in the clinical setting of a stimulated renin-angiotensin system. Older age, hypertension, comitant use of diuretics or aspirin, preexisting renal failure, diabetes, and plasma-volume contraction are known risk factors for renal failure after the ingestion of NSAIDs. Rarely, NSAIDs cause acute interstitial nephritis (AIN) with proteinuria.

A retrospective study of all cases of AIN (reviewing 1068 renal biopsies from 1968 to 1997) noted analgesics, particularly NSAIDs, as risk factors for sustained renal insufficiency. AIN was found in 6.5% of all biopsies; infection-induced in 10%, idiopathic in 4%, and drug-induced in 85% of the cases (antibiotics in 13 cases, analgesics in 17, NSAIDs in 16, diuretics in five, and various other drugs in seven). Renal insufficiency was reversible in 69% and permanent in 31% (12% partially reversible, 19% irreversible). Drug-related AIN turned out to be a main cause of permanent renal insufficiency in 36% with a maximum of 56% in NSAID-induced cases.26

In contrast to the well-characterized acute effects of NSAIDs on the kidney, chronic effects are less well documented. Renal papillary necrosis has been induced experimentally by NSAIDs in animals; the severity of the effects varies from one product to another and increases with caffeine. Although renal papillary necrosis and chronic renal failure can occur after the prolonged use of NSAIDs, the actual risk for these serious complications in humans is not known.

CONCLUSIONS

AN is a slowly progressive renal disease resulting from the daily use, heavy or not, for many years of preparations containing at least two analgesics (aspirin, paracetamol, phenacetin, pyrazolones) and central-acting dependence-inducing substances (caffeine, codeine, and/or barbiturates). AN is a well-defined clinicopathologic entity, characterized by chronic interstitial nephritis and renal papillary necrosis and calcifications. This disease can be accurately diagnosed or excluded, at any stage of CKD, by CT scanning without contrast medium, a simple validated test, even in the absence of reliable information on previous analgesic use.

AN is invariably caused by compound analgesic mixtures containing dependent-inducing substances regardless of the presence or absence of phenacetin as one of the active ingredients. In healthy individuals with normal renal function, the occasional to moderate regular use of aspirin and NSAIDs is without renal risk. The case with paracetamol is less clear, although the described risk is at the most modest. The acute renal effects of NSAIDs and the frequent irreversibility of the NSAID-induced AIN are now well documented. How much the chronic use of NSAIDs may induce renal papillary necrosis, hence evolution toward ESRD, is far from clear.

The continued use of non–phenacetin–combined analgesics with or without NSAIDs is associated with faster progression of renal impairment and increased risk for reaching ESRD.

In patients with stages 3 to 4 CKD and ESRD, paracetamol is the analgesic of choice in the short-term treatment of mild to moderate pain. NSAIDs may be used for short-term management, taking into account the list of widely known risk factors for acute, frequently irreversible, deterioration of renal function. Regular renal function monitoring is mandatory. As long as analgesic mixtures containing more than one ingredient associated with centrally acting, dependence-inducing drugs are available over the counter, AN will continue to be a problem.

DISCLOSURES

None.

REFERENCES


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