

Analgesic use and chronic renal failure: A critical review of the epidemiologic literature

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Analgesic use and chronic renal failure: A critical review of the epidemiologic literature. Heavy use of analgesics, particularly over-the-counter (OTC) products, has long been associated with chronic renal failure. Most of the earlier reports implicated phenacetin-containing analgesics as the risk factor. Since the early 1980s, several case-control studies have reported associations between chronic renal failure and use of other forms of analgesics, including acetaminophen, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). Findings from these studies, however, should be interpreted with caution because of a number of inherent limitations and potential biases in the study design and data collection procedures. These limitations include: failure to identify patients early enough in the natural history of their disease to collect reliable information on analgesic use at an etiologically relevant time period; selection bias due to incomplete identification of subjects or low response rates; selection of cases and controls from different population bases; failure to employ survey techniques to improve reliability of recall of analgesic use; failure to collect detailed information on analgesic use such as year started and ended and reasons for switching analgesics; lack of standardization in the definition of regular analgesic use; and failure to adjust for phenacetin use and other confounding factors when assessing associations with analgesics other than those containing phenacetin. It is our hope that this review of study design limitations will lead to improvements in future studies of chronic renal failure risk. Since use of analgesics is widespread and new OTC products are introduced frequently, the potential impact of these drugs on the development of chronic renal failure may be significant, thus warranting continued evaluation of these products for any renal toxicity.

Abuse of analgesics has long been associated with the development of chronic renal failure. The clinically well-defined entity of classic analgesic nephropathy is a slowly progressing disease resulting from the daily consumption over several years of mixtures containing at least two

antipyretic analgesics, usually combined with caffeine and/or codeine, both creating a psychological dependence. It is characterized by renal papillary necrosis and chronic interstitial nephritis [1, 2], which once established tend to progress to end-stage renal disease (ESRD). Efforts to halt or even slow the progression have for the most part been unsuccessful [3, 4]. The incidence of ESRD and expenditures related to its treatment have been increasing consistently in the United States [5]; in 1989, an estimated 200,000 persons received treatment for ESRD and the direct costs of such therapy amounted to \$6 billion [5]. The progressive nature of chronic renal disease and the high costs of its treatment underscore the importance of identifying preventable causes of this disease. In particular, given the extensive worldwide market for analgesics and the general acceptance of their safety, detailed evaluation of the potential renal toxicity of these drugs is warranted.

Since the association between abuse or long-term heavy use of analgesics and chronic interstitial nephritis was first recognized more than four decades ago [6], numerous cases of analgesic-associated nephropathy have been documented [7], but a causal association has not been conclusively established. The majority of reports have implicated heavy consumption of analgesic mixtures containing phenacetin as the responsible agent [7–10]. By the late 1960s phenacetin was removed from the market in Scandinavia and by the 1970s was subsequently removed in many industrialized countries [7, 11]. In the United States, all phenacetin preparations were required after 1964 to bear a warning about possible kidney damage [12], and the drug was banned from the market in 1983 [13].

Several large analytic epidemiologic studies have more recently raised concern that chronic renal failure may be linked to heavy use of not only phenacetin, but also of a number of commonly used analgesics such as aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen [14–16]. In the United States, NSAID prescriptions increased rapidly from 27.5 million in 1973 to 66.7 million in 1983, although use of prescribed NSAIDs has stabilized since then. This phenomenon may be explained

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in part by the increased awareness among physicians of the gastrointestinal side effects of excessive NSAID use, as well as by approval of various NSAIDs for over-the-counter (OTC) sales [17, 18]. Since the 1980s, the stagnant market share of prescription NSAIDs has been replaced by increasing sales of acetaminophen and of former prescription-only NSAIDs such as ibuprofen, which now account for about one third of the OTC analgesic market share. As early as 1980, aspirin substitutes (primarily acetaminophen) accounted for \$300 million of the then \$1.2 billion spent on analgesic medication in the United States [19].

Of the OTC analgesics, acetaminophen has generated the greatest concern with respect to renal disease because it is the major metabolite of phenacetin [20, 21], although not the only metabolite [22, 23], and because acetaminophen-induced renal necrosis has been observed in susceptible laboratory animals [24–27]. However, the collective epidemiologic evidence with respect to acetaminophen as a single product is inconclusive. The majority of reports of chronic renal disease associated with acetaminophen use have been case series [7, 28, 29].

Most of the analytic epidemiologic data on analgesic use and chronic renal failure are derived from case-control studies [9, 14–16, 30–33]. To our knowledge, only two cohort studies [34, 35] have linked analgesic use to elevated risk of chronic renal failure, with similar risk estimates. Elseviers and De Broe [35] reported a significant sixfold increase in risk of decreased renal function among abusers of any type of analgesic compared to controls; their estimate, however, was based on only 12 exposed cases. In the 10-year follow-up study by Dubach, Rosner and Pfister [34], heavy use by young women of phenacetin-containing products was associated with an eightfold increased risk of developing renal failure, as measured by serum creatinine levels, but the absolute incidence of abnormal kidney function remained relatively small even among heavy users. Increased risk of mortality from urologic or renal disease was also reported in this study among heavy users of phenacetin [36]. Another small cohort study demonstrated a nonsignificant positive association between high analgesic use and papillary calcification [21]. By contrast, increased risks associated with acetaminophen use have been reported in several [15, 16, 30, 31], but not all [9], case-control studies of chronic renal disease, with aspirin and other NSAIDs often implicated as well [14–16, 31, 32].

Inherent methodologic limitations and potential biases in study design and data collection, however, hamper the interpretation of associations between analgesic use and chronic renal failure or ESRD observed in case-control studies. The purpose of this review is to critically evaluate the existing epidemiologic evidence that use of analgesics may increase the risk of chronic renal failure, and to suggest methods for improving the design of future studies of this issue.

CASE-CONTROL STUDIES OF ANALGESIC USE AND CHRONIC RENAL DISEASE

To date, the results of at least seven case-control studies of chronic renal failure have been reported in the United States and Europe (Table 1). All but one [33] were designed specifically to evaluate the role of analgesic use, but the studies varied according to case and control selection criteria, definition of analgesic use, and method of data collection. Many were based on relatively small numbers of users of large amounts of analgesics, making it difficult to meaningfully evaluate the role of these drugs in the etiology of renal failure. In one study, for instance, only 1.2% of controls and 0.6% of patients ever used acetaminophen in a single ingredient product [30]. The characteristics of these studies, as summarized in Table 1, will be reviewed below, with particular attention to methodologic strengths and weaknesses that could influence the interpretation of results.

Case identification and selection

The diagnostic criteria for defining cases of chronic renal disease varied across studies. In fact, only two studies [9, 15] have specified objective diagnostic criteria, and in the remaining studies it is difficult to rule out subjective diagnosis by physicians who were aware of the patients' analgesic use history. Moreover, most studies enrolled patients undergoing dialysis for ESRD, most likely as a result of the difficulty of diagnosing renal disease during the early stages. Thus, a critical limitation is the failure to identify and recruit chronic renal failure patients early enough in the natural course of their disease to insure that analgesic exposure information pertains to an etiologically relevant period prior to the development of the disease. Only in the study by Sandler et al [14, 15] were cases patients with kidney disease newly diagnosed based on serum creatinine levels. In the other six studies, cases were patients drawn from hemodialysis or renal transplant centers [30–32], registries of patients with ESRD [16, 33], or outpatient clinics [9]. Once diagnosed with chronic renal insufficiency, patients are often advised to discontinue use of aspirin and other NSAIDs as these drugs increase the risk of bleeding, interfere with renal potassium excretion and may further compromise their glomerular filtration rate [37–39]. As an alternative, these patients are often advised to use acetaminophen for pain relief following their diagnosis.

Patients with ESRD or those identified from hemodialysis units are likely to be prevalent cases in the final stages of their illness; they do not necessarily represent the population with non-terminal kidney disease in terms of patterns of analgesic use. It is the incidence of chronic renal failure, rather than the prevalence of ESRD, that is the more etiologically relevant outcome, since studies based on prevalent cases yield associations that may reflect determinants of duration and course of disease as much as the

Table 1. Case-control studies of analgesic use and chronic renal failure

Author, Year	Location	Study period	Study population	Data collection	Analgesic Data	Results
Murray et al., 1983 ³¹	Pennsylvania New Jersey	10/78–8/79	527 ESRD ¹ patients in dialysis units; 1,047 matched hospital controls	Personal interview	Life history of conditions likely to be treated with analgesics; Review of list of analgesics in use from 1920 to 1979; Detailed history for analgesics used daily or every other day for 30 days or more	No consistent association with ever use, duration of use or dose of aspirin, acetaminophen or phenacetin, alone or in combination products; <i>Compared to nonusers of any analgesic:</i> RR = 2.55 (1.07–6.11) for ≥3 years of phenacetin use; RR = 4.59 (1.59–13.28), 0.33 (0.10–1.07), and 2.00 (0.59–6.74) for <1 year, 1–<3 years, and ≥3 years of acetaminophen use, respectively
McCredie and Stewart, 1988 ⁹	Australia	1978–1980	91 cases of renal papillary necrosis from outpatient clinics; 120 clinic controls with other kidney diseases	Personal interview	Lifetime consumption of analgesics up to the year of diagnosis	<i>Compared to <1 kg:</i> OR = 19 (10–37) for ≥1 kg phenacetin; OR = 0.5 (0.1–1.9) for ≥1 kg paracetamol <i>Compared to <0.1 kg:</i> OR = 15 (8–28) for ≥0.1 kg phenacetin; OR = 0.7 (0.3–1.9) for ≥0.1 kg paracetamol ⁴
Sandler et al., 1989, 1991 ^{14,15}	North Carolina	9/80–8/82	554 patients newly diagnosed with CRF ² and with serum creatinine levels consistently ≥130 μmol/liter; 516 population-based controls, identified through random digit dialing or Social Security lists	Telephone interview	Life history of conditions likely to be treated with analgesics; Review of lists of generic and brand-name analgesics, sold OTC or by prescription in the 1960s and 1970s according to North Carolina pharmacy survey; Detailed history for analgesics used 10 or more times	<i>Compared to infrequent use:</i> OR for daily use of any analgesic = 2.79 (1.85–4.21), for phenacetin-containing analgesic = 5.11 (1.70–14.9), for acetaminophen = 3.21 (1.05–9.80), for aspirin = 1.32 (0.69–2.51); OR for daily use of NSAIDs = 4.6 (1.5–14.0) in men and 1.1 (0.4–2.7) in women, with increased risk in men restricted to men >65 years of age ⁴
Pommer et al., 1989 ³²	Germany	1984–10/86	517 ESRD ¹ patients in dialysis units or undergoing renal replacement therapy; 517 matched clinic controls	Personal interview	Detailed history among regular users, defined as users of 15 or more doses per month for one year or longer	<i>Compared to no regular intake:</i> RR for regular intake of any analgesic = 2.44 (1.77–3.39); RR for regular intake of combination drugs = 2.65 (1.91–3.67); RR = 9.20 (2.06–39.87) for >1 kg phenacetin in lifetime; RR = 4.06 (1.32–12.43) for >1 kg acetaminophen in lifetime
Morlans et al., 1990 ³³	Spain	9/80–9/83	340 ESRD ¹ patients in dialysis units; 673 matched hospital controls	Personal interview	Life history of conditions likely to be treated with analgesics; List of analgesics by brand names and sample packages; Detailed history for analgesics used daily or every other day for 30 days or more; No assessment of acetaminophen	No assessment of acetaminophen; OR = 2.89 (1.78–4.68) for regular use of analgesics; OR = 19.05 (2.31–157.4) for regular use of phenacetin; OR = 2.54 (1.24–5.20) for regular use of salicylates ⁴
Steenland et al., 1990 ³⁵	Michigan	1976–1984	325 ESRD ¹ patients identified from a registry; 325 matched population-based controls, identified through random digit dialing	Telephone interview	Regular pain pill use defined as more than one pill per week for two years or more; Acetaminophen grouped with phenacetin	OR for phenacetin/acetaminophen use = 2.66 (1.04–6.82); trend of increasing risk with increasing duration of use
Perneger et al., 1994 ¹⁶	Maryland Virginia West Virginia Washington, DC	1/91–7/91	716 ESRD ¹ patients identified from a registry; 361 population-based controls identified through random digit dialing	Telephone interview	Lifetime exposure to 5 groups of analgesics; Review of lists of brand-name NSAIDs ³ , according to 1990 Baltimore pharmacy survey; Review of lists of non-NSAID ³ analgesics, according to North Carolina pharmacy survey (Sandler et al. 1989); Detailed history of use for analgesics taken 10 or more times in a lifetime	<i>Compared to average intake of 0–104 pills/year:</i> OR for intake of 105–365 pills/year = 1.4 (0.8–2.4) for acetaminophen, 0.8 (0.5–1.3) for aspirin, 0.8 (0.4–1.5) for NSAIDs; OR for intake ≥366 pills/year = 2.1 (1.1–3.7) for acetaminophen, 1.1 (0.7–1.9) for aspirin, 1.0 (0.5–2.0) for NSAIDs ⁴

¹ ESRD: end-stage renal disease² CRF: chronic renal failure³ NSAID: non-steroidal anti-inflammatory drug⁴ mutual adjustment among types of analgesics

causes of disease. Thus, whether cases come from selected facilities or from a defined population, they should be limited to those newly diagnosed within a specified time period. Additional selection biases may be introduced when registries of patients with ESRD are used as a source for case identification, if case registration is incomplete or reporting of cases to the registry is selective [16, 33]. For instance, among cases identified from the Mid-Atlantic Renal Coalition in the study by Perneger, Whelton and Klag [16], 54% were blacks. Analyses of the data as presented would indicate that blacks have a sevenfold increased risk for ESRD compared with whites, a relative risk that is clearly overestimated based on the descriptive epidemiology of the disease. The substantially higher percentage of blacks suggests differential referral and registration by race. When cases are recruited only from selected area clinics and dialysis units or, alternatively, when patients referred from outside the study area are not excluded from the study, the primary study base that gave rise to the cases, and therefore the comparability of controls, is difficult to define. Finally, the representativeness of the case population may be limited by a low response rate or selective non-response among patients. In one study [33], for instance, only 53% of the eligible cases identified from a registry were eventually interviewed, and the non-respondents were more likely to be black and living in inner cities than study participants. In another study [15], white patients again were more likely than black patients to participate. The true relationship between analgesic use and chronic renal failure could be distorted in these studies if non-response is selective with respect to exposure, that is, if black patients or those living in inner cities have unusually high or low use of analgesics.

Control identification and selection

In order to have valid comparisons between groups in case-control studies, controls must be drawn from the same source population that gave rise to the cases [40]. Patients identified from population-based registries or from all clinics serving a well-defined geographic area [14–16, 33] should be compared with controls selected from the same general populations from which those cases were drawn. A number of investigations of analgesic use and renal disease have violated this fundamental epidemiologic principle, and comparability between cases and controls is therefore questionable. For instance, in a study conducted in the Mid-Atlantic region of the United States [16], the majority of the cases were male (58%) and black (54%), while the controls were predominantly female (65%) and white (86%). The overrepresentation of females among controls identified through random digit dialing suggests a selection bias with respect to socioeconomic status, whereby women more likely to be at home (housewives) are more likely to be selected. In another study [15], cases were significantly poorer and less educated than controls. Since patterns of

analgesic use vary substantially by demographic characteristics [41, 42], only an appropriately stratified analysis controlling for the selection factors (that is, race, gender, socioeconomic status) will eliminate the associated selection bias for all *other* variables, including analgesic use. In general, a selection bias will be introduced when controls are chosen through a process that is associated with the exposure under consideration, in this case analgesic use. Controlling for the suspected selection factors in the analysis of the data may reduce (but not necessarily eliminate) this problem, provided the selection factors can be correctly identified and accurately measured. In most studies, however, these factors were not appropriately identified or controlled for in the analysis (see below).

For the studies in which cases were identified from certain clinics or dialysis units, the controls have been selected from among patients treated for other conditions in the same hospitals or clinics or from those treated at different hospitals near the residence of the patient [30, 32]. Under such circumstances, the comparability of the two groups can be ensured only if the catchment area for the different hospitals and clinics is the same and patients residing outside the catchment area are excluded [40], criteria that clearly are not fulfilled in several studies. Moreover, hospital controls with conditions requiring extensive pain relief should be excluded since their patterns of analgesic use do not represent the exposure distribution in the source population for the cases. In fact, hospital patients in general are believed to have atypical patterns of analgesic use. In one study [30], approximately 40% of controls had either gastrointestinal tract, musculoskeletal and joint, urinary tract or neurologic disease, most of which may have been associated with or caused by analgesic consumption. A higher analgesic use among these controls compared to the source population would tend to bias the effect estimates to the null, and could explain in part the lack of association between analgesics and ESRD in this study. An additional selection bias may be introduced as a result of the low response rates among controls in a number of case-control studies [30, 33].

It is of interest that to date, only one study has undertaken analytic procedures to increase confidence in the comparability of the case and control series [32]. This can be done by: (a) comparing cases and controls with respect to the frequency of reporting of exposures or characteristics unlikely to be relevant to the etiology of the study disease; or (b) examining a group of patients not expected to share the etiologic background of the true cases, although they went through the same study procedures as the cases. Morlans et al evaluated 41 patients with ESRD caused by cystic kidney disease, a congenital condition, and found no association with analgesic use [32]; this finding serves to increase our confidence in the validity of the associations found with non-congenital ESRD.

Assessment of analgesic use

What is of particular concern in reviewing the relevant studies is the enormous potential for information bias given the various methods of assessing analgesic use, as well as the different perceptions among cases and controls about the problem under study. A complete history of analgesic use, particularly OTC drug use, is difficult to obtain reliably under the best of circumstances. It is especially doubtful whether such drug exposures can be accurately assessed through short telephone interviews or without visual recall aids [14–16, 33]. In no study was self-reported analgesic use, obtained through either telephone or in-person interview, validated. Furthermore, only one case-control study used photographs of the products and their packaging to facilitate recall of analgesics used [32], despite the fact that such visual aids have been shown to improve the reliability of recall in other areas of survey research [43].

The structure of the questionnaire varied greatly across studies and could have important consequences with respect to the accuracy and completeness of information elicited, and also to interpretation and comparison of findings from different studies. For instance, the definition of a regular user, for whom detailed history of analgesic use was collected, ranged from more than one pill per week for two or more years [33], to analgesics taken 10 or more times in a lifetime [14–16], to users of 15 or more doses per month for one year or longer [31], to use daily or every other day for 30 days or more [30, 32]. Such diversity in the definition of exposure and non-exposure may account for the large discrepancies in percentages of “regular” analgesic users among controls, which ranged from 2% to 30% in different studies. As a result, the magnitude of risk estimates could be greatly affected and direct comparison of findings from different studies is not possible.

The types of questions designed to elicit information on past analgesic use and the methods used to enhance recall also vary among studies. Investigators asked about history of drug use prior to the start of hemodialysis or renal transplantaton [16, 30, 31], prior to the appearance of symptoms of kidney disease [32], up to the year of diagnosis [9], or during the year before the start of the study [14, 15]. Even as such, the reference period for analgesic use was not clearly defined and is likely to include more than the relevant time window. The reference period is critically important as an indication of when in the natural history of the disease the analgesic exposure information is collected. Given the removal of phenacetin from the market, the more recent introduction of other types of analgesics, and the documented changes in use patterns following disease onset, it would also be useful to note the dates started and ended for each type of analgesic and reasons for changes in patterns of analgesic use. Unfortunately, only one study provides this type of detailed information [31].

While failure to ensure that analgesic use preceded the

onset of kidney disease is not critical in assessing the role of analgesics in the progression of established renal disease, it becomes an important limitation in studies of the etiology of the condition. The change in patterns of analgesic use after the onset of renal disease may bias the recall and the reporting of long-term analgesic use among ESRD patients, generating both false-positive (with respect to acetaminophen) and false-negative (with respect to aspirin) errors that could significantly bias the effect estimates. The potential for bias is further enhanced when the time reference for analgesic use as specified in the questionnaire is prior to starting dialysis; this approach would most likely capture the most recent use pattern rather than use during the etiologically significant time period long before the onset of renal dialysis. Indeed, the reporting of analgesic use patterns before the start of renal dialysis but after the initial onset of the disease, when patients often abstain from using aspirin, may account in part for the reduction in risk associated with moderate use of aspirin and increase in risk associated with acetaminophen use in at least one of the case-control studies [16]. Even studies that attempt to collect from prevalent cases data about analgesic use prior to the onset of kidney disease [32] cannot guarantee that the etiologically relevant time period is being reflected. This is of particular concern given the variable and often long time window between diagnosis and data collection for prevalent cases, since reports by subjects on exposures in the distant past tend to reflect the current exposure pattern [43, 44].

In addition to asking direct questions about use patterns, some [14, 15, 30, 32], but not all, investigators attempted to enhance recall by asking about past medical conditions likely to be treated with analgesics or providing a list of analgesic products in use during certain time periods. This type of probing, provided it was applied equally to both cases and controls, may have generated more accurate and complete data on analgesic use among study participants. However, in the study by Pommer et al, interviewers were not blinded with respect to case-control status, and non-standardized probing intended to stimulate recall of analgesic use could introduce information bias [31]. If in fact cases were probed more than controls, this would lead to an overestimation of the effect of analgesics on ESRD and could explain the high relative risks observed in this study. Finally, several investigators have addressed the issue of underreporting by cases as a potential source of bias that could attenuate risk estimates, and they have described probing methods intended to minimize denial or underreporting of use. However, an equally important source of bias that is often overlooked is the more likely problem of overreporting by cases. Given the perceptions of patients and physicians about the nephrotoxicity of analgesics, overreporting by cases is likely and could lead to false

positive associations, which could explain in part the increased relative risks for analgesic use seen in several studies.

A final issue encountered in some of these studies is the collection of drug history and other information from surrogate informants, rather than through direct interviews with the patients or controls themselves, which raises concern about the quality of the data as well as their comparability to those obtained directly from living subjects. While next-of-kin may provide reasonably reliable data with respect to certain lifestyle factors, such as consumption of tobacco, alcohol and coffee, their knowledge regarding the subjects' patterns of analgesic use, a relatively private habit, may be less accurate [45, 46]. The potential for bias appears to be greatest when data for one group, such as cases, are obtained from surrogates, whereas data for another, such as controls, are obtained from the index subjects. The direction of information bias has not been well-documented and might plausibly be in either a positive or a negative direction. In one study [14, 15], data on analgesic use were provided by next-of-kin respondents for 55% of the cases but only 10% of the controls, and a higher level of analgesic use was consistently reported by next-of-kin informants relative to self-respondents. It is possible that the higher levels of analgesic use reported by surrogates compared to directly interviewed cases reflects a survival bias whereby those patients who consume more analgesics actually have shorter survival times. However, it appears more likely that proxy respondents in general tend to overreport subjects' analgesic use, since an excess of analgesic use was also reported by the proxy controls than by directly interviewed controls. A number of other studies [16, 30, 33], excluded cases who could not be interviewed directly, due to either death or refusal. If cases who died of chronic renal failure, however, were more or less likely to be heavy, long-term users of analgesics than those cases who survived, exclusion of deceased subjects may lead to an underestimation or overestimation, respectively, of the association of analgesic use with chronic renal failure.

DATA ANALYSIS AND INTERPRETATION

Failure to adequately adjust for the confounding effects of phenacetin is a major limitation of most previous case-control studies of acetaminophen and other analgesics in relation to chronic renal disease. Phenacetin was widely used in combination analgesics in the United States and other countries from the early part of this century until the 1970s and even until the 1980s in some European countries. In contrast, use of acetaminophen and some NSAIDs as single analgesics did not become popular until the late 1970s to early 1980s. Thus, for most subjects identified during the time period covered by the published studies, the analgesic exposure of etiologic significance is primarily phenacetin-containing products, and unadjusted positive associations between ESRD and other analgesics are likely

to be overestimated due to confounding by earlier phenacetin use. For example, in the study conducted in North Carolina [15], the numbers of cases (31) and controls (5) who reported daily use of phenacetin were almost identical to the numbers who reported daily use of acetaminophen (30 cases and 5 controls), suggesting that they are the same subjects. Moreover, with only 5 controls it is impossible to adequately adjust for the effect of phenacetin or other confounding factors in assessing the risk associated with acetaminophen use. In order to meaningfully evaluate the association between acetaminophen and chronic renal failure, it is necessary to study users of acetaminophen exclusively. Such a population, with no prior use of phenacetin, may not be possible to identify with confidence for a decade or longer in the United States, with a shorter period for those countries that banned phenacetin sooner. Inadequate adjustment, or lack of adjustment for phenacetin altogether, limits the validity of reported associations between renal failure and non-phenacetin analgesics in other studies as well [16, 31, 32]. Residual confounding by phenacetin use cannot be excluded even in studies which claim to adjust for it, given that the exposure is self-reported and subject to major information bias, as described above.

Furthermore, significant differences between cases and controls were often evident with respect to a number of variables not accounted for in the analysis. These included race, sex, proxy response status, use of other medications, and socioeconomic status, all factors with potential for aggregate confounding that cannot be discounted on the basis of single factor evaluation [47]. For instance, in the study by Murray et al [30], the level of education, a marker of socioeconomic status, was significantly lower among cases than among controls and was not accounted for in the analysis.

Finally, as discussed above, it is necessary to analyze each type of analgesic in relation to date started and ended and to identify reasons for discontinuation or switching. For studies that included cases at various stages of renal failure, it would be useful to analyze risk associated with analgesic use by stage of disease. Such detailed analyses of type and timing of analgesic use have not been presented in any published study and may be precluded by the small numbers of users.

SUMMARY AND RECOMMENDATIONS

As the incidence of chronic renal failure continues to increase, as indicated by rising ESRD rates, and in the absence of effective treatment, prevention remains an important strategy for the control of this disease. The widespread use of analgesics calls for detailed evaluation of these drugs as potential risk factors for chronic renal disease. Several epidemiologic studies have attempted to examine the association between analgesic use and chronic renal failure; while the aggregate data suggest a relation

between heavy habitual use (particularly of products containing phenacetin) and chronic renal failure, the specific ingredient(s) responsible, as well as the duration of use and cumulative consumption required to produce the lesion, are less clear. Furthermore, it is unlikely that this issue can be resolved through a case-control study of patients late in the natural history of chronic renal failure. Etiologic inferences that can be drawn from the collective evidence to date are limited by numerous methodological flaws, the most serious of which is the inclusion of ESRD patients, whose patterns and reporting of analgesic use are likely to be affected by their illness, and by the failure to mutually adjust for the confounding effects of different analgesics. The cohort study approach minimizes problems of recall and several other potential biases, but is difficult to implement because of the rarity of chronic renal failure in the general population [3].

In designing future studies of analgesic use and chronic renal failure, we suggest that the following steps be attempted. (1) Include cases diagnosed at the earliest stage of disease. This is difficult since little is known about early stage disease and the identification of such patients [37, 38, 48], although recent work suggests highly predictive diagnostic performance of computed tomography scan in early stage renal failure [49]. Such an approach will minimize recall or reporting biases due to post-diagnostic changes in analgesic use patterns or lengthy time periods between disease diagnosis and interview. (2) Detailed information should be collected on date started and ended, and reasons for discontinuation or switching. (3) Interviews should be conducted in person, with visual aids of analgesic brand names and packaging if possible. Ideally, one would validate prescription analgesic use data through pharmacy records, if possible. (4) Population-based studies, with patients and comparison subjects drawn from the same source population, are preferable to hospital-based studies. (5) Finally, the number of study participants should be large enough to adjust for the mutually confounding effects of different analgesic types as well as the potential confounding effects of other risk factors.

In summary, the case-control studies of analgesic use and renal failure suffer from serious selection, information and confounding biases operating in different directions and generating both false positive and false negative associations. Thus, while the collective evidence suggests that habitual analgesic use may be associated with the development of chronic renal failure, it does not conclusively establish a causal link between use of specific analgesics, particularly acetaminophen, and chronic renal failure. However, because of the widespread use of analgesics, the recent introduction of new products, and the potential impact of these drugs on renal failure, the continued evaluation of any renal toxicity is a major research and public health priority.

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