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PERSPECTIVES IN RENAL MEDICINE

Relationship between nonphenacetin combined analgesics and nephropathy: A review

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Relationship between nonphenacetin combined analgesics and nephropathy: A review.

Background. The debate on the association between nonphenacetin-containing combined analgesics and renal disease has lasted for several years.

Method. A peer review committee of scientists, selected jointly by the regulatory authorities of Germany, Switzerland, and Austria and the pharmaceutical industry was asked to critically review data on the relationship between nonphenacetin combined analgesics and nephropathy.

Results. The committee regarded epidemiologic evidence on nonphenacetin combined analgesics as inconclusive because of sparse information and substantial methodological problems. The committee also noted that a diagnosis of analgesic-associated nephropathy (AAN) in clinical practice usually depends on information about exposure before or in the early stages of the disease and is seldom accompanied by specific histologic evidence. The morphologic finding of papillary calcification can arise from other conditions and is not specific for AAN. For these reasons, the identification criteria for AAN should be reappraised with scientific methods to validate the diagnostic procedure. In the limited amount of experimental pharmacological data in humans and animals, the committee found no convincing evidence to confirm or refute the hypothesis that nonphenacetin combined analgesics are more nephrotoxic than single formulations. For caffeine taken with combined analgesics, the currently available information is not sufficient to postulate a harmful toxicological effect.

Conclusion. The committee's two main conclusions were that sufficient evidence is absent to associate nonphenacetin combined analgesics with nephropathy and that new studies should be done to provide appropriate data for resolving the question.

Key words: end-stage renal failure, analgesic-associated nephropathy, combined analgesics, nonphenacetin analgesics, renal toxicity.

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The association between nonphenacetin-containing combined analgesics and renal disease has been debated for several years. In previous studies of humans, the main focus was on end-stage renal disease (ESRD), and no analytical study has examined analgesic-associated nephropathy (AAN) specifically or analyzed it separately regarding nonphenacetin-containing combined analgesics.

Despite considerable clinical, pathological, and epidemiological research, many open questions remain. Although the association with phenacetin is established, the primary question today is whether the modern, nonphenacetin-containing analgesics are also associated with ESRD or AAN or whether any apparent associations are caused by past use of phenacetin.

These questions have recently evoked considerable media attention in Germany, Austria, and Switzerland, where various groups have demanded protective regulatory action. As a result, the Federal Drug Authorities of those countries asked the pertinent members of the pharmaceutical industry to support a special ad hoc review of the available literature and evidence. The members of the review committee were chosen jointly by

the authorities and the industry. The industry gave an unconditional grant to the organizers to prepare and execute the meeting, which occurred on June 28–29, 1999, in Potsdam, Germany. The meeting was also attended by observers from the regulatory authorities and from the industry.

Objectives

The main question to be answered was whether the literature contained sufficient evidence to conclude that combined nonphenacetin-containing analgesics cause nephropathy. A subsidiary question was whether scientific evidence exists to show that the combination of analgesic drugs with caffeine increases nephrotoxicity or contributes to habituation and abuse of analgesic drugs.

A secondary objective of the meeting was to identify additional pertinent questions and to make recommendations for further research, if appropriate.

METHODS

The committee reviewed information from different sources: peer-reviewed papers, editorials, abstracts, and any other pertinent publications, including those in books and supplements to journals. The particular scientific issues considered during the appraisal were as follows: (*1*) quality of the diagnostic criteria for "analgesic nephropathy" in pathological and radiological manifestations, (*2*) objectivity and accuracy of the identification of past exposure to analgesics, (*3*) objectivity and accuracy of the selection and definition of cases of "nephropathy," and (*4*) appropriateness of the data analyses.

RESULTS

Epidemiologic studies

The available epidemiologic research could be divided into analytic (cohort or case control) and ecologic studies.

Analytic studies. In a thorough literature search before the committee meeting, only nine analytic epidemiologic studies could be identified that contained original research dealing with the association between nephropathy and use of various analgesics. Table 1 shows the analgesic agents examined in those nine studies [1–9]. The review committee concluded that only four [1, 3–5] of these studies were pertinent for estimating the effects of combined nonphenacetin analgesics, because the other studies did not specifically analyze the effect of analgesic formulations containing more than one ingredient.

The cohort study by Elseviers and De Broe followed a group of 200 abusers of various analgesic formulations and 200 nonanalgesic-using controls for seven years to see differences in renal function [1]. At the end of the observation period, a significant decrease of renal function was found in 12 abusers versus 2 controls. The study, however, has some important methodological problems. Unfortunately, the investigators identified the commercial combinations by brand names only, without distinguishing the changing ingredients of each brand during the period before 1983. Because the analyses did not account for the fact that brand-name products generally contained phenacetin before 1983, it is difficult or impossible to differentiate the actual constituents of the combined agents and to separate the effects of phenacetin and nonphenacetin combinations. The review committee also noted several other methodological weaknesses, such as the possible noncomparability of the exposed and unexposed cohorts at baseline, problems in identifying the duration and time since first use of analgesics, and the lack of information on the history of comorbidity and comedication and on indications for use of analgesics. For example, no information was given about preexisting renal diseases with normal renal function (or relevant therapy) that might differ among the exposed and unexposed groups, thereby explaining subsequent differences in results.

Because of the methodological weaknesses, the committee disagreed with the authors' conclusion that "all the cases developing renal impairment abused analgesic mixtures of varying composition suggesting once more that only by limiting the availability of all kinds of analgesic mixtures a decrease in the occurrence of this disease can be obtained" [1]. The committee concluded that all of the drug abusers cited by Elseviers and De Broe may have used phenacetin at some time in their history, and therefore, the data presented do not address the question of whether nonphenacetin-containing combined analgesics are associated with a higher risk of renal failure.

In the case-control study of Pommer et al, done in 1984 through 1986, 517 cases (patients on renal replacement therapy in whom a careful history of analgesic intake was collected) were matched to the same number of controls [3]. An increased risk of ESRD was found to be associated with the use of more than 0.1 kg phenacetin-containing analgesic substances, with an increasing risk for increasing dose. In general, an increased risk of nephropathy was found with intakes of >0.5 kg analgesic substances in most of the combination drugs. The odds ratio was 4.83 (95% CI, 2.70 to 8.76) for 60 analgesic doses—including phenacetin—taken monthly for more than five years. The pertinent exposures occurred in 65 cases and 18 controls.

One strength of the Pommer et al study is that the brand names of all analgesics were recorded and that the contents of different ingredients were identified at different periods in time. The case selection, however, seemed to include a nonhomogeneous group of prevalent (longer history of end-stage renal failure) and incident (newly developed end-stage renal failure) cases, and the investigators did not report evidence to show

Table 1. Analytic epidemiologic studies of nephropathy and diverse analgesics[a]

First author	Measure of association estimated for			
	Phenacetin	Nonphenacetin combinations	Other analgesics	NSAIDs
Cohort studies				
Elseviers [1]	?	?	Not specified	−
Dubach [2]	+	−	ASA	−
Case-control studies				
Pommer [3]	+	+	Multiple	−
Morlans [4]	+	+	PYR, ASA	−
Murray [5]	+	+	ACET, ASA	−
McCredie [6]	+	−	ACET	−
Sandler [7]	+	−	ACET, ASA	+
Steenland [8]	+	−	—	−
Perneger [9]	−	−	ACET., ASA	+

Symbols are: +, included in the study; −, not investigated; ?, could not be determined, for reasons cited in the accompanying text. Abbreviations are: ASA, acetylsalicylic acid, aspirin; ACET, acetaminophen, paracetamol; NSAIDs, nonsteroidal anti-inflammatory drugs; PYR, pyrazolone.

[a] For more details, see critical reviews by Delzell E, Shapiro S: A review of epidemiologic studies on nonnarcotic analgesics and chronic renal disease. *Medicine* 77:102–121, 1998; and McLaughlin JK, Lipworth L, Wong-Ho C, Blot WJ: Analgesic use and chronic renal failure: A critical review of the epidemiologic literature. *Kidney Int* 54:679–686, 1998.

that the risk estimates from the prevalent and incident cases are similar enough to permit their pooling. An additional problem is that the control group contained an ill-defined collection of university clinic patients, usually a highly selected group, which may not represent the same population from which the cases emerged. A separate problem was the study's low statistical power to evaluate the independent risk of nonphenacetin-containing combined analgesics. The number of persons who regularly used combined analgesics without past use of phenacetin was small: 54 cases and 59 controls (28 and 24 with a relevant dose of >0.5 kg analgesic substance). The results do not indicate, but cannot rule out, a significantly increased risk of nephropathy in the absence of phenacetin use.

In bivariate analyses, the use of combined analgesics coformulated with caffeine (irrespective of past use of phenacetin) showed an increasing risk of ESRD with increasing dose of analgesic substance. The peak odds ratio of 52.56 (95% CI, 6.83 to 402.78) was reached for an intake of 1.25 kg caffeine in the combinations. These high odds ratios are difficult to evaluate, however, because the investigators did not check for the possibility of confounding. The elevated odds ratios for combinations containing higher doses of caffeine could be explained by high doses of analgesics being associated with high doses of caffeine and past use of phenacetin.

Pommer et al concluded that "over-the-counter mixed-compound analgesics, particularly those that contain caffeine, should be banned or at least no longer made available without a prescription. Over-the-counter sales should be restricted to single-ingredient analgesics in small packages only" [3]. The committee disagreed with this conclusion, which did not seem appropriately supported by the data.

In one of the other two pertinent case-control studies, Morlans et al found that the risk for ESRD development was significantly increased with overall analgesic exposure (OR 2.89, 95% CI, 1.78 to 4.68), markedly increased with phenacetin-containing combinations (OR 19.05, 95% CI, 2.31 to 157.4), significantly increased for users of acetylsalicylic acid (OR 2.54, 95% CI, 1.24 to 5.20), and nonsignificantly elevated for pyrazolones (OR 2.16, 95% CI, 0.87 to 5.32) [4]. No estimates of risk were presented for the aspirin-paracetamol combination.

On the other hand, Murray et al did not find an elevated risk that was statistically significant for either combined analgesics or for phenacetin [5]. The odds ratios and 95% confidence intervals for all combinations, combinations of aspirin/paracetamol, and aspirin/phenacetin were, respectively: 1.32 (95% CI, 0.8 to 2.1), 1.86 (95% CI, 0.8 to 4.6), and 1.01 (95% CI, 0.6 to 1.7). No combination was found to be significantly related to ESRD development. The study, however, had small numbers of cases and controls who used the aspirin-paracetamol combination, and the data for this combination were not analyzed for a dose–response relationship. A significantly increasing trend in risk with the increasing dose (or duration of use) could indicate an increased risk, even if results for the individual dose categories are nonsignificant. Such trends were shown, however, only for phenacetin in cumulative doses or combinations.

Ecologic studies. In ecologic studies, individual subjects are not examined. Instead, general population data for the prevalence or incidence of a disease are correlated across regions with data for sales or general use of a suspected etiologic agent. Although often used to generate hypotheses, ecologic studies provide, at best, weak evidence on causation. In contrast to analytic epidemiological studies, no information is available about the disease, exposure (suspected agent), and important confounders in individual persons.

The ecologic study by Elseviers and De Broe found an apparently high correlation between the "prevalence" of analgesic nephropathy in dialysis units and the associated local sales of combined analgesics [10]. What was called "prevalence," however, was the proportion of AAN among dialysis patients, not in the general population. These "prevalence" data were correlated with the combined sales of three different analgesics: Perdolan, Mann, and Witte Kruis. All three had contained phenacetin. The correlations were not adjusted for the duration in which phenacetin had remained in each formulation.

The ecologic results can equally be explained by changes in the occurrence of AAN after withdrawal of phenacetin from the market, and not by regulation of the over-the-counter (OTC) availability of nonphenacetin-containing mixed analgesics. The underlying problem arises because regulatory withdrawal of a drug from the OTC market will reduce the number of newly exposed subjects without immediately altering the already exposed population, which enlarges with time. A long lag time between exposure and occurrence of the disease could be demonstrated with only age-stratified analyses over a series of time periods (the expectation would be declining incidence in younger age groups and more stable incidence of AAN with increasing age). Such data, however, were not provided and discussed.

In reviews in the *New England Journal of Medicine* [11] and the *American Journal of Kidney Disease* [12], patients not taking phenacetin were said to have developed AAN, but the information used in the reviews seems to have come from uncontrolled case series; our committee was unable to find the original data for those two reviews reported either consistently or in peer-reviewed journals.

In a separate report, Michielsen and De Schepper presented data showing similar time trends for the proportion of incident cases of AAN among patients starting dialysis in Australia (where combined analgesics were banned from the OTC market in 1979) and Belgium (where combined analgesics are still available as OTC drugs) between 1970 and 1998 [13]. At the meeting of our committee, Michielsen also showed currently unpublished data on time trends of AAN occurrence in patients starting dialysis and in the population of Flanders (Belgium) and in New South Wales (Australia). In these two regions with an apparently high occurrence of AAN, the trends per million population were almost identical, and they showed, despite different legislation regarding the availability of nonphenacetin combination analgesics, a similar decline in the overall proportions (1970–1998) and in the age-specific incidence per million population of AAN among patients admitted to dialysis (1984–1997). The age-specific incidences declined in patients under 55 years and were less altered in patients over 65. This would be the expected change if the AAN is caused mainly by past exposure to phenacetin. Although these data have not yet been published, the committee nevertheless regarded the results as reassuring since they revealed no worsening evolution of new cases of analgesic nephropathy in a country with free OTC sales of phenacetin-free combination analgesics.

From the currently available epidemiological evidence, the committee decided that both the analytic and ecologic types of studies are inconclusive about the relationship between combined nonphenacetin analgesics and the occurrence of nephropathy. No epidemiological data were found to support or refute the hypothesis that combined nonphenacetin analgesics, when coformulated with caffeine, elevate the risk of nephropathy. Finally, the epidemiological studies contained very little useful information on abusers of analgesics.

Methodologic issues

The committee's methodological discussion focused on temporal changes in the indications for dialysis, on the reliability of histories of drug use, and on the accuracy of the clinical diagnosis of analgesic nephropathy.

Temporal changes in the indication for dialysis are crucial in understanding the results of the ecologic studies. An increasing proportion of dialysis patients in higher age groups would also increase the number of patients with apparent AAN, and they would have been exposed long before any regulatory measures were taken.

Because the indications for dialysis have substantially changed during the past few decades, trend analyses of crude prevalence rates for AAN among dialysis patients are difficult to interpret. At the very least, they should be presented and appraised as age-specific proportions of AAN among those admitted for treatment. The possible multifactorial etiology of ESRD attributed to AAN requires that the analyses of analgesic use consider a lifelong history of onset, duration (dose), and types of analgesic as well as coexposures, medical conditions, and many other potential confounding variables. These factors have not been adequately considered in previous analytical studies.

In clinical practice, a specific diagnosis of AAN is almost never accompanied by histologic evidence and is usually based on information about exposure before or in the early stages of the disease. Papillary calcification may occur as a result of other conditions and is not specific for AAN [14]. Thus, identification criteria for AAN should be reappraised with scientific methods that validate the diagnostic tests, independently of exposure information.

In addition, having recently published on morphological issues in analgesic nephropathy [15], Mihatsch, Brunner, and Gloor pointed out that a specific morphological lesion—suburothelial capillary sclerosis—is present only for phenacetin-related nephropathy. Although Mihatsch,

Table 2. Unresolved issues

• Comparative nephrotoxicity of specific analgesic agents, other than those containing phenacetin.
• Dose-response relationships.
• Types of renal disease possibly caused by analgesics.
• Cofactors (including caffeine) possibly related both to analgesic use and to the development of chronic renal disease.
• Pathological mechanisms of analgesic-induced chronic renal disease in humans.

Brunner, and Gloor had not observed such a lesion in patients who abuse paracetamol, they included paracetamol in their list of potential causes of capillary sclerosis because Nanra, in a personal communication, said he had seen such patients. Mihatsch, Brunner, and Gloor also confirmed that capillary sclerosis has not yet been reproduced in animal studies and that animals seem inadequate as models for the AAN seen in humans.

The committee recognized that papillary necrosis has causes other than analgesic abuse and that if it is diagnosed by ultrasound or computed tomography scan, the result is consistent with AAN but lacks specificity. Mihatsch emphasized that early forms of papillary necrosis are often undiagnosed until calcification appears. In an autopsy study 20 years ago, they found that only 50% of the AAN cases were clinically suspected, but 137 of 141 patients had capillary sclerosis at a time when phenacetin was commonly used (abstracts; Mihatsch et al, *Kidney Int* 17:412 and 859, 1980). A modern repetition of this autopsy study would be desirable.

Several unresolved issues were identified during the discussion (Table 2). These issues should be kept in mind when new epidemiological studies are designed or planned.

EXPERIMENTAL PHARMACOLOGIC EVIDENCE

The generally accepted hypothesis for the mechanism of acute hepatic and renal cortical toxicity is that paracetamol is oxidized by an enzyme system that is not present in the medulla [16]. Therefore, this mechanism is not applicable as a cause of AAN. For medullary toxicity of paracetamol, the other hypotheses involve mainly co-oxidation during the reduction of arachidonic acid-derived hydroperoxides [17, 18]. These hypotheses essentially depend on data (some unpublished) obtained in vitro in cell-free systems in the absence of cell compartmentalization, competing enzymes, and substrates and in the presence of high concentrations of externally added substrates or inhibitors that do not exist in vivo. Thus, the hypotheses for the medullary toxicity of paracetamol and its increased toxicity in the presence of salicylate are largely unverified extrapolations to humans from artificial in vitro systems.

The essential cofactor of a suggested synergistic toxicity of paracetamol plus salicylates is the depletion by salicylate of glutathion in the renal medulla, but this effect is not well documented in animals. The alleged mechanism by which salicylates inhibit the pentose phosphate shunt has been documented only for high concentrations in vitro and has been cited in only a single published abstract (abstract; Goldberg et al, *J Clin Invest* 50:37a, 1971). Humans given paracetamol for two consecutive days showed no indication of a potentiating effect on the inhibition of prostaglandin synthesis by acetylsalicylic acid (ASA) [19]. It seems obvious that these sparse in vitro data do not constitute a basis to support the assumption of a special synergistic medullary toxicity of paracetamol plus acetylic acid.

The committee also evaluated the possibility of a special nephrotoxic effect by caffeine-containing mixed analgesics without phenacetin. Because the evidence from the only available epidemiological study [3] was not persuasive, the data were reviewed from a pharmacological perspective. Long-term toxicological studies [20], carcinogenicity studies [21, 22], and animal experiments trying to induce analgesic nephropathy [23] did not show an additional nephrotoxic effect when caffeine was added to combined analgesics. (The issue of caffeine habituation or dependence was deferred for a separate later review that is reported elsewhere [24].)

The committee concluded that the currently available evidence does not allow a special harmful toxicologic effect to be postulated for analgesics combined with caffeine. Furthermore, the limited amount of experimental pharmacologic data in humans and animals offers no convincing evidence that nonphenacetin combined analgesics are either as safe as or more nephrotoxic than single formulations.

CONCLUSIONS

The main conclusion of the committee was that there is insufficient evidence to claim that combined analgesics, in the absence of phenacetin, are causally associated with nephropathy. The committee also recommended that a new epidemiological study is needed to address this question and that the study be done, for completion in about three to four years, in the countries where regulatory authorities are most concerned about a potential risk of nonphenacetin combined analgesics. The design and manual of operations for such a study was discussed at a subsequent meeting of the review group in the spring of 2000.

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