EXHIBIT H

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TITLE: **Risk Of Kidney Failure Associated With The Use** Of Acetaminophen, Aspirin, And Nonsteroidal Antiinflammatory Drugs.

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ABSTRACT: Background. People who take analgesic drugs frequently may be at increased risk of end-stage renal disease (ESRD), but the extent of this risk remains unclear.

Methods. We studied 716 patients treated for ESRD and 361 control subjects of similar age from Maryland, Virginia, West Virginia, and Washington, D.C. The study participants were interviewed by telephone about their past use of medications containing acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs). For each analgesic drug, the average use (in pills per year) and the cumulative intake (in pills) were examined for any association with ESRD.

Results. Heavier acetaminophen use was associated with an increased risk of ESRD in a dose-dependent fashion. When persons who took an average of 0 to 104 pills per year were used for reference, the odds ratio of ESRD was 1.4 (95 percent confidence interval, 0.8 to 2.4) for those who took 105 to 365 pills per year and 2.1 (95 percent confidence interval, 1.1 to 3.7) for those who took 366 or more pills per year, after adjustment for race, sex, age, and intake of other

analgesic drugs. When persons who had taken fewer than 1000 pills containing acetaminophen in their lifetime were used for reference, the odds ratio was 2.0 (95 percent confidence interval, 1.3 to 3.2) for those who had taken 1000 to 4999 pills and 2.4 (95 percent confidence interval, 1.2 to 4.8) for those who had taken 5000 or more pills. Approximately 8 to 10 percent of the overall incidence of ESRD was attributable to acetaminophen use. A cumulative dose of 5000 or more pills containing NSAIDs was also associated with an increased odds of ESRD (odds ratio, 8.8), but the use of aspirin was not.

Conclusions. People who often take acetaminophen or NSAIDs have an increased risk of ESRD, but not those who often take aspirin. (N Engl J Med 1994;331:1675-9.)

TEXT:

Analgesic nephropathy was first described in the 1950s n1. Phenacetin was subsequently identified as the chief culprit and was withdrawn from the market. Evidence of the nephrotoxicity of other analgesic drugs -- acetaminophen, aspirin, and other nonsteroidal antiinflammatory drugs (NSAIDs) -- is scanty and inconsistent n2. In a prospective study of Swiss factory workers, subjects who took salicylates had no excess of kidney disease n3. Of four case-control studies, one n4 reported no association between the ingestion of analgesic drugs and end-stage renal disease (ESRD), but the others found associations between ESRD and salicylates, n5 pyrazolones, n5 aspirin, n6 acetaminophen, n6 n7 and NSAIDs n8.

None of these case-control studies were entirely population-based. In three, patients with ESRD were drawn from the general population but were compared with hospitalized control subjects, n4 n5 n6 and in the fourth study subjects from the general population were compared with hospitalized patients with chronic kidney failure n7 n8. Because hospitalized patients may differ from members of the general population in their analgesic-drug use regardless of the presence of kidney disease, the associations found in these studies between renal failure and the use of analgesic drugs may be spurious. We report here a case-control study of over-the-counter analgesic drugs as risk factors for ESRD in which both the case patients and the control subjects were drawn from the general population.

Methods

The study protocol was approved by the institutional review boards at Johns Hopkins University and the Health Care Financing Administration.

Study Participants

We studied residents of Maryland, Virginia, West Virginia, and Washington, D.C., who were 20 to 64 years old and had telephones in their homes. People who lived in institutions, were absent from their homes for more than two weeks, or were unable to complete the interview (because of deafness or a language

barrier) were excluded from the study.

The case patients had to have ESRD and had to have started long-term dialysis between January and July 1991. They were drawn from the Mid-Atlantic Renal Coalition, a population-based registry of patients with ESRD. Of 978 persons in the registry, 752 were eligible to participate. The others were excluded for the following reasons: 93 did not have a private telephone, 65 had died, 19 were institutionalized, 14 had moved out of the study area, 8 had recovered their renal function, 8 were too sick to be interviewed, 7 had hearing problems, 5 did not speak English, 5 were hospitalized for more than two weeks, and 2 were more than 64 years old. Of the 752 eligible persons, 716 (95 percent) were interviewed (of the others, 16 declined to be interviewed, 5 did not complete the interview, and 15 could not be reached). A median of five months elapsed between the start of therapy for ESRD and the time of the interview.

The control subjects lived in the same area as the patients n9 and were selected by random-digit dialing so that their age distribution matched that of the case patients. We sought to enroll half as many control subjects as case patients. Of 1311 residences reached by telephone, 1259 (96 percent) were screened for eligible residents, and 402 were found to contain one or more eligible residents. Of the remaining 857 households, 846 contained no members in the required age group, 7 contained no English-speaking respondents, 3 contained respondents who had difficulty hearing, and 1 contained a respondent who had ESRD. When several eligible control subjects lived in the same household, one was selected at random. Of the eligible control subjects, 361 (90 percent) completed the interview.

Data Collection

Trained interviewers contacted potential participants by telephone, explained the purpose of the study, provided a telephone number to call for additional information, obtained informed consent, and asked a set of standard questions. The interview lasted 24 minutes on average. People who initially declined to participate were contacted again after two weeks; about 40 percent agreed to participate when approached a second time.

Exposure Variables

The participants were asked separately about their lifetime exposure to the following five types of analgesic drugs, referred to by their common brand names: single drugs or mixtures containing acetaminophen, but not aspirin or phenacetin; single drugs or mixtures containing aspirin, but not acetaminophen or phenacetin; mixtures containing acetaminophen and aspirin, but not phenacetin; single drugs or mixtures that contained phenacetin before its withdrawal from the market; and common NSAIDs containing ibuprofen, naproxen, or indomethacin.

The list of NSAIDs was based on a review of over-the-counter medications sold in Baltimore pharmacies in 1990; indomethacin was included because it was one of the first NSAIDs on the market. The other lists of medications were based on an update of the information used by Sandler et al in their studies n7 n8. Phenacetin-based medications were identified in order to adjust the analysis for exposure to this substance known to be nephrotoxic.

For each type of analgesic drug, the study participants were asked whether they had taken one or more brands more than 10 times in their lives (before starting dialysis, in the case of the case patients). Those who said they had done so were asked about the average frequency of their analgesic-drug use (days per week, month, or year), the age at which they began to take the drugs regularly, and the average number of pills consumed per day when they took the drugs. Average intake (in pills per year) and cumulative intake (in pills, calculated as the average intake multiplied by the number of years since the first regular use) were computed. In the case of mixtures containing both acetaminophen and aspirin, the total consumption was considered to include equal amounts of each primary drug. Average intake was categorized as light (0 to 104 pills per year, or 0 to 2 pills per week), moderate (105 to 365 pills per year, or up to 1 pill per day), or heavy (366 or more pills per year, or more than 1 pill per day), and cumulative intake was categorized as low (0 to 999 pills), medium (1000 to 4999 pills), or high (5000 or more pills).

Statistical Analysis

The case patients and control subjects were compared by cross-tabulation and logistic-regression modeling n10. Odds ratios were used to estimate relative risks. Tests of linear trend were performed when appropriate.
Population-attributable risks were computed to estimate the potential effect of withdrawing a given analgesic drug on the incidence of ESRD n11. To examine the association of analgesic-drug use with different types of kidney disease, we used a five-level categorical outcome variable, with one level assigned to the control subjects and four levels assigned to the case patients according to the ascribed cause of ESRD: diabetes mellitus, hypertension, other specified causes, or no definite origin. The presumed cause of renal failure was based on each patient's recall of the diagnosis by his or her nephrologist. Polychotomous logistic-regression analysis n10 was used to analyze multilevel outcomes. All statistical tests were two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance. The analyses were conducted with Systat software n12.

Results

The case patients and the control subjects differed significantly with respect to sex and race. Of the 716 case patients, 304 (42 percent) were women; 310 (43 percent) were white, 384 (54 percent) were black, and 22 (3 percent) were of other races. Of the 361 control subjects, 235 (65 percent) were women; 303 (84 percent) were white, 51 (14 percent) were black, and 7 (2 percent) were

of other races. The age distributions were similar in the two groups (mean +/- SD , 47 +/- 12 years in both), indicating successful matching.

A majority of the study participants had taken analgesic drugs either sporadically or regularly. Of the case patients, 77 percent had taken acetaminophen, 77 percent had taken aspirin, and 31 percent had taken NSAIDs more than 10 times in their lives. Among the control subjects, the rates were 75 percent for acetaminophen, 86 percent for aspirin, and 46 percent for NSAIDs. Similar proportions of case patients (15 percent) and control subjects (17 percent) had taken analgesics that may have contained phenacetin.

Frequency of Use

In the univariate analysis, heavy users of acetaminophen (more than 365 pills per year) had an increased risk of ESRD, whereas moderate users (105 to 365 pills per year) did not (Table 1). No statistically significant associations were noted for aspirin and NSAIDs. Adjustment for age, sex, race, and the use of other analgesic drugs strengthened the odds ratios for acetaminophen use and revealed a significant dose-response relation (P for linear trend, 0.009). In contrast, this adjustment weakened the associations of ESRD with the use of aspirin and NSAIDs.

*Table 1. Average Annual Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD in Maryland, Virginia, West Virginia, and Washington, D.C., in 1991 *.

TABLE OMITTED

Cumulative Intake

The odds of ESRD increased with increasing cumulative intake of acetaminophen (Table 2), whereas persons who had taken 1000 to 4999 pills containing aspirin had a lower risk of ESRD than those with a lower cumulative intake. In contrast to heavy average intake, a high lifetime intake of NSAIDs was associated with a fourfold increase in the odds of ESRD. Although the confidence intervals were wide, the odds of ESRD were lowest with moderate intake of aspirin or NSAIDs. Adjustment for age, sex, race, and the intake of other analgesic drugs strengthened the associations between the cumulative intake of acetaminophen and ESRD (P for linear trend, <0.001) and between high doses of NSAIDs and ESRD.

*Table 2. Cumulative Lifetime Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD in Maryland, Virginia, West Virginia, and Washington, D.C., in 1991 *.

TABLE OMITTED

Effect of Race

Black subjects reported less use of analgesic drugs than white subjects, but the associations between the use of analgesic drugs and the risk of ESRD did not differ according to race (data not shown). In analyses of both average and cumulative intake, adjustment for race accounted for most of the difference between the unadjusted and the adjusted results; this was due to the large disparity between blacks and whites in the base-line risk of ESRD.

Risk Factors According to Cause of ESRD

The pattern of risk associated with a person's average intake of analgesic drugs differed little according to the causes of ESRD that we studied: diabetes mellitus, hypertension, any other specified cause, or no known cause (Table 3). Since there were only 20 patients with ESRD who had underlying diagnoses of interstitial nephritis, no separate analysis of that subgroup was performed. The patterns of risk associated with cumulative intake of analgesic drugs were also similar in the various subgroups (Table 4): a high intake of acetaminophen or NSAIDs was apparently harmful, whereas a medium intake of aspirin appeared to be protective.

*Table 3. Adjusted Odds Ratios and 95 Percent Confidence Intervals for the Average Annual Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD According to the Ascribed Cause of ESRD *.

TABLE OMITTED

*Table 4. Adjusted Odds Ratios and 95 Percent Confidence Intervals for the Cumulative Lifetime Intakes of Acetaminophen, Aspirin, and NSAIDs as Risk Factors for ESRD According to the Ascribed Cause of ESRD *.

TABLE OMITTED

Population-Attributable Risks

Estimation of the population-attributable risk of ESRD suggested that if each participant consumed fewer than 105 pills containing acetaminophen per year (fewer than 2 pills per week), the incidence of ESRD would decrease by 7.7 percent (Table 5). Changes in the average intake of aspirin and NSAIDs would have negligible effects on the incidence of ESRD. A reduction in lifetime acetaminophen use to fewer than 1000 pills could potentially lower the incidence of ESRD by 10.5 percent. Reducing the intake of aspirin would have the opposite effect, resulting in an increase in ESRD. These inferences assume that the observed associations (harmful in the case of acetaminophen and protective in the case of aspirin) are causal and correctly estimated.

*Table 5. Population-Attributable Risk of ESRD According to Average Intake and Cumulative Life-time Intake of Acetaminophen, Aspirin, and NSAIDs *.

TABLE OMITTED

Discussion

This study revealed several meaningful relations between analgesic-drug use and ESRD. The strength of these relations may have been underestimated, because drug use was measured rather imprecisely. These findings pertain only to adults 20 to 64 years of age who survived for about six months after the initiation of ESRD therapy.

Both heavy average intake (more than 1 pill per day) and medium-to-high cumulative intake (1000 or more pills in a lifetime) of acetaminophen appeared to double the odds of ESRD. These findings support those in two previous reports n6 n7. In our study, the estimated odds ratio of ESRD associated with daily use of acetaminophen was lower than that reported by Sandler et al n7; unlike them, we report a significant dose-response gradient. These discrepancies may be explained by differences in study methods: Sandler et al n7 measured analgesic use more precisely than we did, and they enrolled hospitalized case patients and control subjects drawn from the community, interviewed proxy respondents, and included patients at various stages of renal insufficiency.

Acetaminophen use apparently increased the odds of ESRD in patients with a variety of underlying renal diseases, including diabetic nephropathy. This may reflect the fact that tubulointerstitial changes (the typical analgesic-mediated injury) influence the progression of damage in a variety of renal diseases n13. Alternatively, acetaminophen can harm the kidney through several different pathogenic pathways n2. Because the diagnoses of underlying kidney disease were not validated in our study, misclassification may have obscured the differences between the effects of different diseases.

The potential effect of acetaminophen use on the overall incidence of ESRD is considerable. If our estimated odds ratios are valid and the association between acetaminophen use and ESRD is causal, reduced consumption of acetaminophen could decrease the overall incidence of ESRD by approximately 8 to 10 percent. This is 10 times more than would be inferred from the prevalence of analgesic nephropathy in patients with ESRD, as diagnosed by attending physicians (1 percent among patients 20 to 64 years of age in the United States from 1987 through 1990 n14). If our estimates could be extrapolated to the entire United States (which may not be possible, given the geographic variability in analgesic use n2) and to all age groups, such a reduction would represent a savings of $ 500 million to $ 700 million in costs for ESRD care each year. Because estimates of analgesic use based on recall by participants may be subject to misclassification, n15 the population-attributable risks provided by this study may underestimate the true potential benefits of reducing or stopping the consumption of acetaminophen.

Establishing the causality of the association between acetaminophen use and ESRD is critical. The association was dose-dependent, specific (i.e., unlike the

associations between other analgesics and ESRD), consistent with several previous reports, and biologically plausible, since acetaminophen is a metabolite of phenacetin. Thus, several criteria for causality were fulfilled. Nevertheless, the temporal precedence of the presumed cause still needs to be demonstrated, and experimental evidence for causality produced.

Unlike acetaminophen, aspirin did not increase the risk of ESRD. This confirms the results from some studies, n3 n7 but not others n5 n6. In our analysis, the risk of ESRD was slightly lower in persons taking an annual average of 105 to 365 pills and significantly lower in those who took 1000 to 4999 pills in their lifetime, as compared with persons who took aspirin less often. It is unlikely that aspirin has a true protective effect against renal failure. The J-shaped association, also observed for NSAIDs, may occur because persons with renal insufficiency (who are at high risk of ESRD) abstain from using aspirin. Heavy aspirin users may take analgesic drugs for serious indications, such as intense, protracted pain, and may be less concerned than moderate users about potential renal side effects. We cannot verify this hypothesis, because we did not investigate the reasons for analgesic use.

We detected no increase in the risk of renal failure among daily users of NSAIDs. An association of this type has been reported for men more than 65 years old, n8 but the age limits we used precluded verification of that finding. On the other hand, we found a steep increase in the odds of ESRD in persons who consumed 5000 or more pills containing NSAIDs during their lifetime. Although this finding is based on few observations (only 18 case patients and 2 control subjects reported taking NSAIDs in these quantities), it arouses concern about the safety of persons taking large quantities of NSAIDs. Our results may underestimate the toxicity of NSAIDs, because we did not thoroughly explore the use of preparations obtained by prescription and because patients with progressive kidney insufficiency may have been discouraged from using this class of drugs.

Previous research suggests that NSAIDs cause renal damage in persons with renal insufficiency by lowering the glomerular filtration rate through an anti-prostaglandin effect n16 n17. However, all NSAIDs may not have the same renal effects: ibuprofen may be more nephrotoxic than sulindac or other drugs n16 n17.

This study questions the safety of long-term acetaminophen use (more than 2 pills per day, or more than 1000 pills overall) and of consumption of large quantities of NSAIDs, but it suggests that aspirin use confers little or no excess risk of renal failure. Public health authorities should consider more careful oversight of the long-term use of acetaminophen in the general population. Possible options include using warning labels on packaging or requiring a prescription to purchase large amounts of acetaminophen. Any such decision must consider the substantial beneficial effects of this analgesic drug and the possible adverse effects of restricting access to it, such as a switch

by habitual acetaminophen users to other medicines, including NSAIDs, whose safety may also be questionable. Meanwhile, people requiring large quantities of analgesic medicines and those at high risk of renal failure may be best advised to use aspirin for pain control.

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