

Risk of Kidney Failure Associated with the Use of Acetaminophen, Aspirin, and Nonsteroidal Antiinflammatory Drugs

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FROM 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.

Persons who took an average of 0 to 104 pills per year were used for reference.

The odds ratio of ESRD was 1.4 for those who took 105 to 365 pills per year.

The odds ratio of ESRD was 2.1 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 for those who had taken 1000 to 4999 pills and 2.4 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.

THESE AUTHORS ALSO NOTE:

Analgesic nephropathy was first described in the 1950s, and the responsible drugs **[containing phenacetin]** were subsequently identified and withdrawn from the market.

[Acetaminophen {Tylenol} is a metabolite of phenacetin.]

In this study, the authors report 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.

STUDY PARTICIPANTS

The case patients were between 20 and 64 years of age, had ESRD, and had started long-term kidney dialysis.

The control subjects were of the same age, lived in the same area as the patients, and were selected at random.

The main over-the-counter drug assessed was acetaminophen [Tylenol].

The list of over-the-counter NSAIDs included ibuprofen, naproxen, or indomethacin.

Drug 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). **[AMAZING]**

RESULTS

“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.”

“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.”

CUMULATIVE INTAKE

“The odds of ESRD increased with increasing cumulative intake of acetaminophen.”

Also, “a high lifetime intake of NSAIDs was associated with a four-fold increase in the odds of ESRD.”

“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.”

“A reduction in lifetime acetaminophen use to fewer than 1000 pills could potentially lower the incidence of ESRD by 10.5 percent.”

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.”

[Pommer W, Bronder E, Greiser E, et al. Regular analgesic intake and the risk of end-stage renal failure. *Am J Nephrol* 1989;9:403-412.]

[Sandler DP, Smith JC, Weinberg CR, et al. Analgesic use and chronic renal disease. *N Engl J Med* 1989;320:1238-1243.]

“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."

"Acetaminophen can harm the kidney through several different pathogenic pathways."

"The potential effect of acetaminophen use on the overall incidence of ESRD is considerable."

"Reduced consumption of acetaminophen could decrease the overall incidence of ESRD by approximately 8 to 10 percent."

If these estimates were extrapolated to the entire United States "such a reduction would represent a savings of \$500 million to \$700 million in costs for ESRD care each year."

The "risks provided by this study may underestimate the true potential benefits of reducing or stopping the consumption of acetaminophen."

The dose-dependent association of ESRD and acetaminophen is consistent with several previous reports, and biologically plausible, since "acetaminophen is a metabolite of phenacetin."

In this study, but not others, aspirin did not increase the risk of ESRD.

The authors found no increase in the risk of renal failure among daily users of NSAIDs, but did find a "steep increase in the odds of ESRD in persons who consumed 5000 or more pills containing NSAIDs during their lifetime."

This finding "arouses concern about the safety of persons taking large quantities of NSAIDs."

"Our results may underestimate the toxicity of NSAIDs," because of research methods.

"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."

Those requiring large quantities of analgesic medicines and those at high risk of renal failure may be best advised to use aspirin for pain control.

EDITORIAL
Drug-Induced End-Stage Renal Disease

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“Chronic tubulointerstitial nephritis and nephritis of unknown origin account for 15 to 30 percent of the cases of end-stage renal disease (ESRD) in the United States and Europe.”

“A substantial but as yet undetermined proportion of these cases may be due to drug-induced nephrotoxicity.”

Phenacetin was shown to cause analgesic nephropathy in 1953 and was withdrawn from the market.

Acetaminophen is a metabolite of phenacetin. **[IMPORTANT]**

In the above study:

“Heavy average use of acetaminophen (more than 1 pill per day) and medium-to-high cumulative acetaminophen intake (more than 1000 pills in a lifetime) each doubled the odds of ESRD.”

“The results also suggested an association between ESRD and high lifetime intake (5000 or more pills) of NSAIDs other than aspirin.”

“Drugs can injure the kidney through dose-related toxic effects on the renal vasculature (leading to vasoconstriction and ischemia) or on tubular epithelial cells, or through non-dose-related immunologic mechanisms.”

“Because of the dose-dependent relation found between analgesic-drug use and the occurrence of renal disease in this and other studies, nonimmunologic mechanisms are probably important.”

[Sandler DP, Smith JC, Weinberg CR, et al. Analgesic use and chronic renal disease. *N Engl J Med* 1989;320:1238-1243.]

[Pommer W, Bronder E, Greiser E, et al. Regular analgesic intake and the risk of end-stage renal failure. *Am J Nephrol*, 1989;9:403-412.]

[Dubach UC, Rosner B, Sturmer T. An epidemiologic study of abuse of analgesic drugs -- effects of phenacetin and salicylate on mortality and cardiovascular morbidity (1968 to 1987). *N Engl J Med* 1991;324:155-160.]

This author notes:

- (1) A second question relates to the epidemiologic features and incidence of ESRD caused by drugs other than analgesics.
- (2) Many medications can induce acute renal failure, including antibiotics and diuretic agents.
- (3) Radiographic contrast agents were estimated to have caused 18 percent of cases of acute renal failure in North American and France. **[WOW!]**

"The advertisement and sale of analgesic drugs correlate better with the geographic distribution of analgesic-associated nephropathy than do any other factors, with high rates of both in Switzerland, Belgium, Austria, and the southeastern United States." **[WOW!]**

"The incidence of analgesic nephropathy has been dramatically reduced in Sweden and Australia, mainly because the over-the-counter sale of combination analgesics has been prohibited." **[WOW!]**

Reduced consumption of acetaminophen could lower the incidence of ESRD by 8 to 10 percent with a range of 2 to 20 percent.

KEY POINTS FROM DAN MURPHY

- (1) In the 1950s, analgesics containing phenacetin was shown to damage the kidney, and withdrawn from the market.
- (2) Acetaminophen (Tylenol) is a metabolite of phenacetin.
- (3) Light pain drug use was defined as 0 to 104 pills per year, or 0 to 2 pills per week.
- (4) Moderate pain drug use was defined 105 to 365 pills per year, or up to 1 pill per day.
- (5) Heavy pain drug use was defined 366 or more pills per year, or more than 1 pill per day.
- (6) Low cumulative pain drug intake was defined as 0 to 999 pills.
- (7) Medium cumulative pain drug intake was defined as 1000 to 4999 pills.
- (8) High cumulative pain drug intake was defined as 5000 or more pills.

- (9) Those taking 105 to 365 acetaminophen pills per year had increased ESRD by 1.4.
- (10) Those taking 366 or more acetaminophen pills per year had increased ESRD by 2.1.
- (11) Taking 1000 to 4999 acetaminophen pills in their lifetime increased ESRD by 2.0.
- (12) Taking 5000 or more acetaminophen pills in their lifetime increased ESRD by 2.4.
- (13) 8 to 10 percent of the overall incidence of ESRD is attributable to acetaminophen use.
- (14) A cumulative dose of 5000 or more pills containing NSAIDs [**like MOTRIN**] increased the odds of ESRD 8.8.
- (15) This study probably underestimated the risk because it is difficult to track over-the-counter drug use.
- (16) Renal failure is also caused by antibiotics, diuretic agents, radiographic contrast agents, and other drugs.
- (17) Countries, including the USA with the highest advertisement and sale of analgesic drugs have the highest incidence of analgesic-associated nephropathy.
- (18) The incidence of analgesic nephropathy is lowest where the sale of over-the-counter analgesics is prohibited.