Light to moderate drinking and therapeutic doses of acetaminophen: An assessment of risks for renal dysfunction

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Abstract

This study investigated the potential effect of therapeutic doses of acetaminophen (APAP) in combination with light-moderate amounts of alcohol on kidney functions controlling for factors such as hypertension, diabetes and obesity that may predispose the kidney to APAP and/or alcohol toxicity. Secondary analysis of the 2003–2004 National Health and Nutrition Examination Survey data was performed using SAS 9.4. Odds ratios (OR) and 95% confidence intervals (CI) comparing the likelihood that individuals who ingested therapeutic doses of APAP and light-moderate amount of alcohol, compared to those who did not, would have kidney dysfunction were generated from multiple logistics regression models by further controlling for potential predisposing factors namely hypertension, diabetes and obesity. Kidney dysfunction was defined based on self-reports and laboratory examination of serum creatinine (SCr), blood urea nitrogen (BUN), glomerular filtration rate (GFR) and albumin creatinine ratio (ABCR). Statistically significant increased odds of renal dysfunction were noted among respondents who reported use of therapeutic doses of APAP and light-moderate amount of alcohol (OR(95% CI) = 1.64(1.36–2.10) self-report, 2.18(1.81–2.63) SCr, 4.60(3.05–7.00) BUN, 3.14(2.42–4.07) GFR, and 1.71(1.36–2.14) ABCR) even after adjusting for hypertension, diabetes and obesity (Adjusted OR (95% CI) = 1.78 (1.22–2.58) self-report, 2.05 (1.07–3.92) GFR). The toxic effects of APAP and alcohol on the kidney were hypothesized. The threshold doses at which these effects begin to occur are unknown. The findings of this study suggest that even therapeutic doses of APAP and light-moderate amount of alcohol could be health problematic if consumed concomitantly.

1. Introduction

Pain is a common patient complaint and is frequently self-treated with over-the-counter (OTC) analgesics such as acetaminophen (APAP) (Kaufman et al., 2002). Alcohol consumption among adults is also very common. Currently, poisoning is the leading cause of injury-related mortality in the United States (US) with specific causation related to drug-related poisonings (National Institutes for Health, 2010). In particular, pain medications are among the most common, and an opiate epidemic is affecting major segments of rural America (Albert et al., 2015). Since OTC medications can be purchased without a prescription, consumers may not recognize the potential for toxicity of these medications. According to the National Institute of Diabetes and Digestive and Kidney Diseases arm of the National Institutes for Health, OTC pain relievers are not typically dangerous for people when used as recommended (Rudd et al., 2016). The dose for APAP should not exceed 4 g, per day (Claridge et al., 2010). The Food and Drug Administration (FDA) limit is at 325 mg per pill or tablet for all OTC products (Food and Drug Administration of the United States, n.d.-a) and warns against prescribing products that contain higher doses (Food and Drug Administration of the United States, 2004).
Administration of the United States, n.d.-b).

It is fairly well established that APAP ingestion at doses above the recommended levels causes end-stage renal disease (ESRD) and acute renal failure (Jeffery and Lafferty, 1981; Li and Martin, 2011; Nourjah et al., 2006; Perneger et al., 1994; Mazer and Perrone, 2008; Chen et al., 2015; Kelkar et al., 2012). A dose-response relation between the odds ratio for ESRD and APAP ingestion has been reported (Perneger et al., 1994) and higher median levels of serum alanine aminotransferase (ALT) was observed with reoccurring doses of APAP at 4 g, with or without combinations of pain relievers that also contain opiates (Watkins et al., 2006). Long-term daily use of APAP has been associated with a three-fold risk of chronic kidney disease after adjusting for phenacetin and aspirin use (Sandler et al., 1989). Mitic-Zlatkovic and Stefanovic (1999) showed that administration of 2 g of acetaminophen to patients with glomerular disease, tubular disease and to healthy members of nephropathic families resulted in a significant increase in excretion of β2-microglobulin and creatinine in all three groups, indicating that subjects with existing kidney disease are susceptible to acetaminophen toxicity. However, some have argued that many issues may be related to inadvertent overdoses suggesting that routine use at normal doses is extremely safe (Dart and Bailey, 2007).

When APAP is taken, the metabolic pathway involves catalase and cytochrome P450 2E1 (CYP2E1), which is a major enzyme produced when alcohol is metabolized (Tanaka et al., 2000; Heit et al., 2013). Since both act on this pathway, taking them together is believed to increase the specific risks for hepatotoxicity (Tanaka et al., 2000). Case-studies on hepatotoxicity from concurrent alcohol and APAP have been reported since 1977 (Kromhout et al., 1977). And studies have continued to discuss this pathogenesis over the past few decades, often debating acute vs chronic frequency of alcohol use in combination with the drug (Maddrey, 1987; Witcomb and Block, 1994; Zimmerman and Maddrey, 1995; Schädt et al., 1997; Schmidt et al., 2002; Lesser et al., 1986; Hirsch et al., 1994).

Renal toxicity due to alcohol has been heavily linked with acetaminophen as well as several factors and medically predisposing conditions. Lesser et al. reported on a man with alcoholism who died of hepatic necrosis following treatment with 650 mg acetaminophen at 12 noon and 650 mg at 11:00 p.m. on day one, and 650 mg at 1:30 a.m. and 650 mg at 8:00 p.m. on day 2 (Lesser et al., 1986). Hirsch et al. (1994) reported on patients who developed acute tubular necrosis with oliguric renal failure as a result of binge drinking. Renal biopsy showed acute tubular injury in all cases, including vacuolation and occasional cell death, epithelial cell desquamation from intact basement membrane, and loss of microvilli.

While chronic and heavy consumption of alcohol has been reported to be an independent risk factor to ESRD and acute renal failure (Kaartin et al., 2009), the consumption of light to moderate amount of alcohol seemed to prevent kidney function decline (Schaeffner et al., 2005).

Thus, the toxic effects of both APAP and alcohol at high doses, separately and concomitantly, on the kidney are fairly well established but not necessarily with therapeutic doses of APAP or light to moderate amounts of alcohol separately. No information seemed to be available on the effects of concomitant ingestion of therapeutic amounts of APAP and light-moderate amounts of alcohol. Consequently, the current study was designed to investigate the potential effect of ingesting therapeutic doses of APAP in combination with light-moderate amounts of alcohol on kidney functions among the US noninstitutionalized population. We further explored the potential impact of factors such as hypertension, diabetes, and obesity that may predispose the kidney to APAP and/or alcohol toxicity.

2. Data source and study design

The study was a secondary data analysis of the 2003–2004 National Health and Nutrition Examination Survey (NHANES) (NHANES, 2013).

NHANES is a series of cross-sectional, national noninstitutionalized representative surveys conducted by the National Center for Health Statistics to assess the health and nutritional status of adults and children in the US. It employs multistage probability design in a complex sample survey with US counties as Primary Sampling Units. The sample is constituted by persons selected from clusters of households selected from these counties. The survey is unique in that it combines interviews with physical and laboratory examinations. In 2003–2004, 12,761 persons were sampled among which, 10,122 were interviewed and 9643 examined/tested. Variables for this analysis were extracted from the questionnaire (interview), medical examination, and laboratory data (MEC) files, thus comprising 9643 participants.

2.1. Outcome measures

The outcome variable was kidney function defined separately based on self-reported survey responses and laboratory determined kidney function tests. Affirmative responses to survey questions that asked whether or not respondents were ever told they had “weak/failing kidneys,” “received dialysis in past 12 months,” “leaked urine during physical activities and frequency of occurrence,” “urinated before reaching the toilet and frequency of occurrence,” “leaked urine during nonphysical activities and frequency of occurrence” constituted abnormal kidney function (renal dysfunction) for “self-reports” as well as serum creatinine (SCr) > 1.0 mg/dL, blood urea nitrogen (BUN) > 23 mg/dL, Glomerular filtration rate (GFR) < 90 mL/min/1.73 m², and urinary albumin/creatinine ratio (ALB/CR) ≥ 17 mg/g, male; 25 mg/g, female) and normal otherwise.

GFR was estimated using the National Kidney Foundation (NKF)‘s prediction equation (National Kidney Foundation, 2002) as follows:

\[
\text{GFR} = 270 \times \left[\text{SCr}\right]^{-1.053} \times [\text{Age}]^{-0.203} \times [0.755 \text{ if patient is female}] \\
\times [1.178 \text{ if patient is black}] \times [\text{BUN}]^{-0.0159}.
\]

2.2. Acetaminophen exposure

In NHANES 2003–2004, participants were asked whether they had, “used pain relievers in the past 30 days,” followed by a list of pain-relievers including APAP/APAP-containing products. Respondents also reported the strength of the medication they were using as stated on the drug package. Exposure to therapeutic APAP was defined as “Yes” for taking up to but not > 6 pills or 4000 mg of APAP/APAP-containing product in a day on a regular basis and “No” if they reported not taking any.

2.3. Alcohol exposure

Survey questions queried respondents on how often they drank alcohol over past 12 months and the average number of alcoholic drinks they consumed per day. A drink was defined as 12 oz. of beer, a 4 oz. glass of wine, or an ounce of liquor. Consumption of up to 1 drink per day for women and up to 2 drinks per day for men constituted exposure to light-moderate amount of alcohol with no alcohol as the comparative group. Those who consumed more than these limits were considered heavy drinkers and were excluded from the main analysis.

2.4. Demographics and potential predisposing factors

Demographic variables considered for this analysis included age, race/ethnicity, sex, body mass index (BMI) and smoking status while predisposing factors included hypertension, obesity and diabetes.

During medical examination, three measurements of resting blood pressure (BP) were recorded for each participant. Hypertension was noted if the averages of last 2 readings of systolic BP was at least 130 mm Hg or diastolic BP was at least 80 mm Hg (Anon, 2018) or
whether a doctor had ever told the participant he/she has hypertension or they reported taking high blood pressure medication. Obesity was defined by BMI ≥ 30 kg/m² and diabetes by plasma glucose levels > 126 mg/dL.

2.5. Statistical analysis

Data analyses were performed using Statistical Analysis System, version 9.4 (SAS Institute, Cary, NC, USA) software. All analyses were designed-based, taken into consideration the complex multistage probability design structure such as the appropriate differential selection probabilities (MEC weight) and geographic clustering/stratification. This allows for generating unbiased parameter and variance estimates.

Odds ratios (OR) and corresponding 95% confidence intervals (CI) that assessed the likelihood that individuals exposed to therapeutic amounts of APAP and/or light-moderate amount of alcohol would have an abnormal kidney function (renal dysfunction) compared to the unexposed individuals were obtained using binary logistic regression models. Age, race, sex, smoking status and co-morbidities such as diabetes, hypertension, and obesity, that could predispose the kidney to APAP toxicity (Go et al., 2001; Ljungman, 1999) were controlled for, if necessary using multiple logistic regression models, generating adjusted odds ratio (AOR).

3. Results

3.1. Characteristics of study participants

The analysis was done on 9643 participants corresponding to a National Population Estimate (NPE) of 286,222,757. Among these, over 65% were aged 45 or less, 68.93% White, 13.23% Hispanic, and 12.23% Black. Females (51.17%) were marginally more represented than males (48.83%). Most of the participants (95.37%) were either non-smoker, 33.40% hypertensive, 25.48% obese and 35.31% diabetic or pre-diabetic (Table 1).

3.2. Exposures to acetaminophen and alcohol

APAP or combination pill use was reported by 1179 participants (NPE = 46,290,202, 16.21%), most (93.64%) of whom ingested therapeutic doses (n = 1104, NPE = 43,590,726) of regular strength. Alcohol consumption was reported by 87.80% (n = 8663, NPE = 251,297,123), most (73.27%) of whom were involved in light-moderate drinking (n = 7305, NPE = 184,118,201). Of particular interest were those who ingested therapeutic doses of APAP and light-moderate amount of alcohol and this was reported by 622 participants (NPE = 23,512,855, 8.23%); Table 2.

3.3. Prevalence of kidney dysfunction

Table 3 reports the prevalence of self-reported kidney dysfunction along with abnormal kidney function tests values of SCr, BUN, GFR and ALBSR. Kidney dysfunction was self-reported by 1647 participants (NPE = 65,223,770, 31.78%). Laboratory measurements indicated abnormal kidney function tests of SCr ≥ 1.0 mg/dL in 24.83%, BUN ≥ 23.0 mg/dL in 2.58%, GFR < 90.0 mL/min/1.73 m² in 23.76%, and ALBSR ≥ (17 mg/g, male; 25 mg/g, female) in 11.33% of the participants.

3.4. Association between kidney dysfunction and ingestion of therapeutic doses of acetaminophen and/or light-moderate amount of alcohol

Over 41.35% (n = 488, NPE = 17,821,984) of those ingesting therapeutic doses of APAP self-reported kidney disease, 39.42% (n = 480, NPE = 17,184,960) with SCr ≥ 1.0 mg/dL, 7.88% (n = 119, NPE = 3,434,104) with BUN ≥ 23.0 mg/dL, 41.97% (n = 491, NPE = 17,284,412) with GFR < 90.0 mL/min/1.73 m², and 17.47% (n = 258, NPE = 7,614,692) with ALBSR ≥ (17 mg/g, male; 25 mg/g, female). These reflected statistically significant increased odds of renal dysfunction among respondents compared to those who were not exposed to therapeutic doses of APAP [OR (95% CI) = 1.71 (1.40, 2.10)] self-reported, 2.28 (1.94, 2.68) SCr, 5.13 (3.79, 6.94) BUN, 2.96 (2.58, 3.38) GFR, and 1.86 (1.57, 2.21) ALBCR]. After adjusting for hypertension, obesity and diabetes (potential predisposing factor for Table 3

| Socio-demographic characteristics and potential predisposing factors of acetaminophen and/or alcohol toxicity to the kidney (NHANES 2003–2004; N = 9643; NPE = 286,222,757). |
|----------------------------------|-------|----------------|---------------|
| **Age (years)**                  | n     | NPE            | % (SE)        |
| ≤ 20                             | 4999  | 85,047,723     | 29.71 (0.58)  |
| 21–30                            | 857   | 38,437,832     | 13.43 (0.89)  |
| 31–45                            | 1170  | 63,549,300     | 22.20 (0.82)  |
| 46–65                            | 1335  | 66,611,226     | 23.27 (1.20)  |
| > 65                             | 1282  | 32,576,676     | 11.38 (0.54)  |
| **Race/ethnicity**               |       |                |               |
| Hispanic                         | 2761  | 37,859,928     | 13.23 (2.48)  |
| White                            | 3896  | 197,299,116    | 48.83 (0.89)  |
| Black                            | 2552  | 35,009,218     | 12.23 (1.94)  |
| Other                            | 434   | 16,054,495     | 5.61 (0.67)   |
| **Gender**                       |       |                |               |
| Male                             | 4731  | 139,762,652    | 48.83 (0.58)  |
| Female                           | 4912  | 146,460,105    | 51.17 (0.58)  |
| **Body mass index**              |       |                |               |
| Underweight                      | 1473  | 31,862,657     | 11.63 (0.47)  |
| Normal                           | 3213  | 95,713,884     | 34.93 (0.89)  |
| Overweight                       | 2112  | 76,583,394     | 27.95 (0.88)  |
| Obese                            | 1889  | 69,809,562     | 25.48 (0.97)  |
| **Cigarette smoking**            |       |                |               |
| Current smoker                   | 1134  | 55,563,519     | 50.90 (1.84)  |
| Former smoker                    | 1223  | 48,545,297     | 44.47 (1.83)  |
| Non-smoker                       | 101   | 5,046,863      | 4.62 (0.59)   |
| **Hypertension**                 |       |                |               |
| No                               | 7132  | 190,619,455    | 66.59 (1.10)  |
| Yes                              | 2511  | 95,603,302     | 33.40 (1.10)  |
| **Obesity**                      |       |                |               |
| No                               | 6798  | 204,159,934    | 74.51 (0.97)  |
| Yes                              | 1889  | 69,809,562     | 25.48 (0.97)  |
| **Diabetes: blood sugar level**  |       |                |               |
| Normal blood sugar               | 2131  | 68,722,131     | 64.68 (2.67)  |
| Pre-diabetes                     | 778   | 30,949,991     | 29.13 (2.57)  |
| Diabetes                         | 225   | 6,569,025      | 6.18 (0.63)   |
Renal dysfunction among those with concomitant consumption of therapeutic amount of APAP with light-moderate amount of alcohol was reported by 41.90% (n = 243, NPE = 9,062,965) self-reported, 40.18% (n = 249, NPE = 8,890,441) abnormal SCr, 8.86% (n = 64, NPE = 1,961,049) abnormal BUN, 46.21% (n = 265, NPE = 9,578,521) abnormal GFR and 17.15% (n = 131, NPE = 3,794,748) abnormal ALBCR.

Statistically significant increased odds of renal dysfunction among these respondents were noted compared to the unexposed individuals [OR (95% CI) = 1.64 (1.28, 2.10) self-reported, 2.18 (1.81, 2.63) SCr, 4.60 (3.03, 7.00) BUN, 3.14 (2.42, 4.07) GFR, and 1.71 (1.36, 2.14) ALBCR]. The directions of association and statistical significance were preserved after adjusted for hypertension, obesity and diabetes in self-report [AOR (95% CI) = 1.78 (1.22, 2.58)] and GFR [AOR (95% CI) = 2.05 (1.07, 3.92)], Table 4.

4. Discussion

The toxic effects of APAP and alcohol on the kidney at high doses are fairly well established. However, the threshold doses at which these effects begin to occur is unknown. It was important to investigate the effect of therapeutic doses of APAP alone, small (light-moderate) amounts of alcohol alone, and their combination on kidney dysfunction by analyzing data from the general US population.

In this analysis, less than a fifth of the study population reported the

use of therapeutic dose of APAP. Although alcohol use was high (mostly light-moderate drinking), the combined used of a therapeutic dose of APAP and light-moderate alcohol was only 8.23%. This seems low given the individual high prevalence of alcohol use. This sparks speculation on whether use may have been under-reported in the dataset.

About 41% of those exposed to therapeutic doses of APAP self-reported frank kidney disease which reflected a statistically significant increase in odds of renal dysfunction associated with therapeutic doses of APAP. This may suggest that even in therapeutic doses APAP may produce kidney toxicity. This is similar to the report by Mugdha and others (Mugdha et al., 2012) who indicated that taking > 4 g of APAP a day may put the kidney at increased risk of intoxication. However, findings should only spur further investigation since temporality cannot be ascertained. Also, some authors have suggested that the risk of renal disease with therapeutic APAP doses may be high among individuals with genetic alterations in acetylation processes, this may implicate not only genetic polymorphisms, but also ethnicity (Zhao and Pickering, 2011).

Light to moderate consumption of alcohol alone, may have a protective effect on kidney disease. This is also noted for hepatic risks as ethanol seems to block APAP’s primary toxic metabolites (Remack, 2004). For those who reported combined use of therapeutic doses of APAP and light-moderate alcohol, there were further increased odds at a level higher than what was seen among those who ingested therapeutic doses APAP alone. The presence of hypertension, obesity and diabetes which have been hypothesized to predispose the kidney to APAP and alcohol toxicity (Go et al., 2001; Ljungman, 1999) actually make the effect stronger as shown in this analysis. This may indicate that even small amounts of alcohol may augment the initial innocuous effect of therapeutic doses of APAP on the kidney. This mechanism of action may be similar to that previously proposed and demonstrated by Zhao and colleagues (Zhao et al., 2002), as both APAP and alcohol induce CYP2E1 and CYP3A4 production raising the possibility that APAP toxicity can be potentiated with alcohol ingestion through enhanced formation of NABQI. Generally, those who self-report daily drinking are more than twice as likely to also be regular users of APAP (Seifert and Anderson, 2007). Many may still be unaware of the risks that may be associated with combined use, even though some levels of regular alcohol use seem protective.

To the best of our knowledge, this study is the first to explore the combined effect of small amount of alcohol and therapeutic dose of acetaminophen on kidney function. Moreover, the analysis was conducted on a population-based sample using NHANES data, which generally is of high quality. Nonetheless, some limitations abound. As with any data set, NHANES data are subject to sampling and non-sampling errors, including measurement errors. Interview or questionnaire data are based on self-reports and are therefore subject to non-sampling errors such as recall bias, misunderstanding of question(s), and a variety of other factors. MEC (examination/laboratory) data are subject to measurement variation and possible examiner effects. However, the NHANES program maintains high standards to insure non-sampling and measurement errors are minimized. Further, with so many compounds containing APAP sold OTC, some respondents may not know they have recently taken a product that contains the ingredient. Therefore, underreporting of its use is possible in our study sample. Other continued research on the various physiologic mechanisms at work in possible APAP toxicity to the renal system is also needed. The conducted analysis may result in potential overestimation of the effect of APAP as NHANES 2003–2004 dataset captured APAP use even in combination pills such that this analysis was not able to delineate APAP use alone.

Regardless, this study highlights a very important public health concern as many adults are potentially exposed to both APAP and alcohol. The findings may have potential health policy implications. They should spur health care professionals to educate patients about the risk of consuming alcohol and acetaminophen concurrently and careful monitoring of the renal function of patients consuming alcohol and acetaminophen concomitantly should be in order.

5. Conclusion

The toxic effects of APAP on the kidney at high doses are fairly well established. The threshold doses at which these effects begin to occur is not known. The findings of this study suggest that even therapeutic doses could be problematic. From this study it seems evident that light to moderate amounts of alcohol alone may have a protective effect on renal risks. However, it may have a synergistic effect on the role of therapeutic amount of APAP in the detection of frank kidney disease when the reported values and thresholds of biomarkers applied here are used to assess risks, even more so in the presence of hypertension, obesity and diabetes. More research is needed to better define the actual risks of these readily available OTC medications and to determine if other labeling is warranted. Also, it would be of interest to explore the age, racial, gender and other disparities of these findings in further studies which the authors are interested to undertake.

Conflict of interest

No conflicts to declare.

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