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CLINICAL RESEARCH

Estimating the impact of adopting the revised United Kingdom acetaminophen treatment nomogram in the U.S. population

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ABSTRACT

Background: Acetaminophen toxicity is common in clinical practice. In recent years, several European countries have lowered the treatment threshold, which has resulted in increased number of patients being treated at a questionable clinical benefit.

Objective: The primary objective of this study is to estimate the cost and associated burden to the United States (U.S.) healthcare system, if such a change were adopted in the U.S.

Methods: This study is a retrospective review of all patients age 14 years or older who were admitted to one of eight different hospitals located throughout the U.S. with acetaminophen exposures during a five and a half year span, encompassing from 1 January 2008 to 30 June 2013. Those patients who would be treated with the revised nomogram, but not the current nomogram were included. The cost of such treatment was extrapolated to a national level.

Results: 139 subjects were identified who would be treated with the revised nomogram, but not the current nomogram. Extrapolating these numbers nationally, an additional 4507 (95%CI 3641–8751) Americans would be treated annually for acetaminophen toxicity. The cost of lowering the treatment threshold is estimated to be \$45 million (95%CI 36,400,000–87,500,000) annually.

Conclusions: Adopting the revised treatment threshold in the U.S. would result in a significant cost, yet provide an unclear clinical benefit.

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Introduction

Acetaminophen is one of the most commonly used analgesics and one of the most common xenobiotics encountered in overdose [1]. In 1971, Prescott and colleagues first examined acetaminophen toxicity. While the total number of subjects was small, they noted all subjects with a 4-hour acetaminophen concentration greater than 300 mcg/mL developed hepatic toxicity, while none developed hepatic toxicity at levels below 120 mcg/mL [2]. In 1975, Rumack and Matthew developed a nomogram recommending antidotal treatment with N-acetylcysteine when the acetaminophen concentration falls above a line connecting 200 mcg/mL at 4 hours and 50 mcg/mL at 12 hours [3]. While revised guidelines were created in which some high-risk individuals may be treated at lower levels [4], most patients in the United Kingdom (U.K.) were not treated if the 4-hour acetaminophen level was below 200 mcg/mL. Because of safety concerns, the United States (U.S.) Food and Drug Administration (FDA)

mandated a 25% reduction in the treatment line. Therefore, a revised nomogram was incorporated for use in the U.S., connecting a concentration of 150 mcg/mL at 4 hours to 37.5 mcg/mL at 12 hours. Despite treatment with N-acetylcysteine with the use of the 150 mcg/mL line within 8 hours of ingestion, some patients can still develop elevation of the hepatic transaminases [5]. Such an occurrence is rare and generally asymptomatic. Death in these cases is exceedingly rare, and when it occurs, is typically from incorrect histories or inappropriate application of the nomogram [6–8].

In September 2012, The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) lowered the treatment threshold by 50% [9]. Rather than beginning treatment with N-acetylcysteine for a 4 hour acetaminophen concentration exceeding 200 mcg/mL, the new recommendations are to treat all patients with a 4 hour acetaminophen concentration exceeding 100 mcg/mL (Figure 1). Following suit, other countries, including the Netherlands and the

Republic of Ireland, have also adopted these guidelines [10,11]. This change has resulted in a significant increase in the number of patients being treated with an unclear benefit [10–12].

Due to a growing concern regarding the widespread use of acetaminophen in the U.S., the impact of adopting the U.K. lowered treatment threshold is of increasing interest. The primary purpose of this study is to estimate the increased number of patients who would be treated annually if the U.S. was to adopt the U.K.’s treatment threshold. A secondary aim of this study is to approximate the cost, in U.S. dollars, associated with such a change.

Methods

This study includes a retrospective case series of all patients age 14 and older, who were evaluated in one of eight emergency departments throughout the U.S. following an acetaminophen ingestion. These eight emergency departments were located in seven different states, and included both urban and suburban emergency departments. Seven were in academic medical centers and one in a community hospital. At the time of the study, four of the eight hospitals had a clinical toxicology service. Approval from the IRB was achieved at each of the participating hospitals.

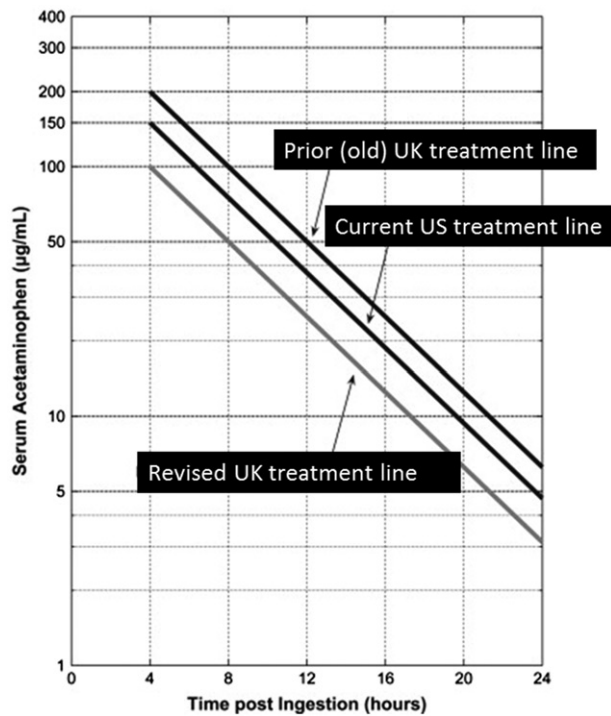


Figure 1. The various treatment thresholds for acute acetaminophen toxicity.

Patients

The records of all acetaminophen ingestions presenting between 1 January 2008 and 30 June 2013 were identified. Patients who were at least 14 years of age at the time of emergency department evaluation with an acetaminophen concentration above 10 mcg/mL and below 150 mcg/mL were screened. Those patients with multiple acute ingestions and those with chronic supratherapeutic use were excluded. In addition, cases in which the nomogram could not be utilized (e.g., unknown time of ingestion) were also excluded. The acetaminophen concentration was plotted on both the currently used U.S. nomogram as well as the revised U.K. nomogram. All subjects who would be treated on the U.S. nomogram and those who would not require treatment on either nomogram were excluded. Thus, the final study population consisted of those patients with a single acute acetaminophen ingestion requiring treatment per the revised U.K. nomogram, but not by the currently utilized U.S. nomogram (Table 1). Subjects were identified through a review of detectable acetaminophen levels, pharmacy records of N-acetylcysteine administration and/or ICD-9 diagnoses.

Data abstraction

Data abstracted from the medical records included demographic information (age and sex), laboratory data (acetaminophen level, aspartate transaminase (AST) and alanine transaminase (ALT)), time from ingestion to acetaminophen concentration obtained, reason for ingestion (deliberate self-harm, recreational misadventure, chronic supratherapeutic use), and disposition (e.g., admission or discharge).

The data were first collected onto a pre-designed data abstraction sheet and then entered into a spreadsheet (Excel 2000, version 9.0.2770. Microsoft; Redmond, WA). In order to verify internal consistency, a second investigator abstracted 10% of the charts previously abstracted from the various sites. The second investigator was blinded to the results of the first investigator. A kappa statistic was calculated to ensure high interrater reliability. Following data entry, the data were independently checked for accuracy by a second investigator.

Data analysis

The study analysis was conducted using Stata 14MP (Stata Corp, College Station, TX). Categorical variables’ associations were assessed with Fisher’s exact test. Kruskal–Wallis non-parametric testing was used to assess significance of non-categorical data. The skewness-kurtosis test was used to assess data normality. Significance was defined at the $p < .05$ level.

Table 1. Full review of inclusion and exclusion criteria.

Criteria	Inclusion	Exclusion
Age	≥14 years	≤13 years
Acetaminophen concentration	Levels falling between the 100 mcg/mL and 150 mcg/mL line	Levels above the 150 mcg/mL line Levels below 100 mcg/mL at 4 hours
Type of ingestion	Single, acute	Chronic supratherapeutic ingestion, multiple staggered ingestions, ingestion with unknown time

Table 2. Subjects by center based on proportion of ED visits.

Center	County	Cases	Total ED visits per study period	Proportion of ED visits
1	Los Angeles	3	99,000	0.0000303
2	Fresno	43	632,500	0.0000680
3	Maricopa	5	148,500	0.0000337
4	Tulsa	7	247,500	0.0000283
5	Suffolk	32	526,702	0.0000608
6	Monroe	20	550,000	0.0000364
7	Ramsey	20	440,000	0.0000455
8	Allegheny	9	294,250	0.0000306

ED: emergency department.

The binomial exact technique was used to calculate 95% confidence intervals (CIs) for proportions. For the main end-point (the number of antidote administrations that were not indicated by the U.S. cutoff but would have been required by the U.K. cutoff), the proportion and binomial CI are reported as cases per 100,000 ED census. Estimates of rates of unnecessary antidote administration (by U.S. cutoff) were calculated for each individual emergency department and were not pooled (since the case mix was different at each study center).

The study centers' results were used to generate coarse estimates for the one-year rate (and case *n*) of additional antidote treatment in the entire U.S. First, data from the Area Health Resources Files (AHRF) and the U.S. Department of Health and Human Services Administration (AHRF) were used to provide the total U.S. emergency department (ED) census annually [13]. Next, the study centers' rates (see Table 2) were applied to the U.S. census *n* [14]. The rate of additional antidote treatment from the study centers with the lowest and highest rates were applied to the national ED census. Finally, the median rate of additional antidote treatment was calculated and applied to the national ED census number.

The estimated incremental cost of treating additional patients was then calculated. Precise calculations were not possible given the lack of detailed clinical information (e.g., would the patient have been treated with intravenous or oral NAC) and the lack of charge and cost data. However, a rough and conservative estimate for additional costs per additional patient treated was hypothesized a priori to be \$10,000. This cost was determined based on literature estimates, and was applied to the patient *n* of additional antidote therapy, to calculate a rough estimate of the monetary impact of moving from the U.S. to the U.K. treatment guideline.

Results

During the study period, a total of 139 subjects were identified who would be treated on the revised U.K. nomogram, but not the current U.S. nomogram. The median (interquartile range) age was 24 (18–41) years. The majority of ingestions occurred in women (63%) and involved deliberate self-harm (86%). The median (IQR) first acetaminophen concentration which was able to be plotted on the nomogram was 110 (87–134) mcg/mL, with a median (IQR) time from ingestion to obtaining the acetaminophen concentration being 4 (4–6) hours. The median (IQR) initial AST and ALT were 23 (19–29) IU/L and 17.5 (13–26.5) IU/L, respectively. The median (IQR) initial prothrombin time was 13.9 (13.2–14.4) seconds.

If the U.S. were to adopt the revised U.K. nomogram, the median standard rate of additional treatments would be 3.5 additional cases (95%CI 2.83–6.80) per 100,000 emergency department visits. Extrapolated to a national (U.S.) level, an additional 4507 (95%CI 3641–8751) patients would be treated annually based on the revised U.K. nomogram. It is estimated these additional cases would cost ~\$45 million (95%CI 36,405,414–87,508,665) annually.

Discussion

This study extrapolates the clinical and financial impact if the U.S. were to adopt the revised U.K. treatment threshold for patients with acute acetaminophen exposure. Lowering the treatment threshold would undoubtedly result in additional emergency department patient referrals for evaluation of acetaminophen exposures. In addition, there would be increase burden on poison centers for referral and follow up. This study did not account for the increased referrals of patients that would likely fall below the treatment threshold. Nonetheless, such a practice would further increase national healthcare costs and further burden the healthcare system.

The purpose of lowering the treatment threshold to 100 mcg/mL rather than 150 mcg/mL at 4 hours is to eliminate the possibility of preventable hepatotoxicity. While this study was not designed to assess the efficacy of such a change, patients with an acetaminophen concentration less than 150 mcg/mL at 4 hours are generally considered to have such a safe level, hepatotoxicity would not be expected. Furthermore, the rare case of hepatotoxicity developing in this group may represent errors in patient's history, rather than failure of the Rumack–Matthew nomogram [6]. We are not aware of any published data showing improved clinical outcomes by changing the treatment threshold to 100 mcg/mL rather than 150 mcg/mL. In fact, because the rate of hepatic injury following acetaminophen overdose is so rare when the 4 hour acetaminophen level is less than 150 mcg/mL, we were unable to find any estimates to permit a cost-benefit analysis.

For the purpose of this analysis, we hypothesized each admission would cost \$10,000. A prior study at a pediatric hospital estimated the cost of admission for acetaminophen toxicity would be \$17,349 in 1992, which was reduced to \$7080 in 1995 (unadjusted costs) [15]. The reduction in cost between 1992 and 1995 was largely driven by reduced hospital lengths of stay [15]. An additional study in the mid-1990s estimated the cost of admission for an accidental acetaminophen overdose to be \$19,000 compared with \$8500 (unadjusted costs) for patients admitted with acetaminophen

toxicity following a suicide attempt [16]. More recently, Altyar et al. examined clinical characteristics and cost associated with acetaminophen toxicity in a cross-sectional retrospective study utilizing ED patients between 2006 and 2010. Using the National Emergency Department Sample (NEDS) from the Agency for Healthcare Research and Quality (AHRQ), the authors determined the average cost per patient evaluated for acetaminophen toxicity was \$12,766 ($\pm$ 28,414) [17]. Thus, we feel \$10,000 is a realistic, yet conservative estimate.

This study has several limitations. First, the study is retrospective in its design. Consequently, the conclusions are limited by the quality and completeness of the data. To minimize these effects, the data abstracted was primarily limited to continuous variables (e.g., AST level) or categorical valuable (e.g., sex) which are subject to little interpretation bias.

Second, this study did not measure any long-term outcome variables. Because we do not have long-term follow up on each patient who would not have been treated with the current U.S. nomogram, it is impossible to determine whether anyone would have developed hepatotoxicity. However, based on what is known from decades of research and clinical experience with acetaminophen toxicity, we feel this occurrence is most improbable.

This study opted to exclude children under 14 years. Young children tend to be somewhat protected from acetaminophen toxicity due to their disproportionately large liver and the increased sulfation compared with glucuronidation. Consequently, we opted to focus this paper on adults. While data from Scotland and England have shown the nomogram change proportionately affected children more than adults, the children continue to account for the minority of ingestions both before and after the nomogram change (7.7% and 8.9%, respectively) [18]. Therefore, we do not feel the exclusion of children should substantially impact our results. However, their inclusion would likely increase the burden slightly.

In this study, we selected a group of emergency departments throughout the United States. We tried to make this a heterogeneous sample (urban and suburban, teaching hospitals and community hospitals, etc.), it is possible the distribution is not representative. Nonetheless, because the proportion of visits at the given emergency department were compared with the total number in the county, we feel we have minimized any bias in the selection of these hospitals.

Conclusions

If the U.S. were to adopt the current U.K.'s nomogram and lower the treatment threshold of acute acetaminophen toxicity from 150 mcg/mL at 4 hours to 100 mcg/mL at 4 hours, more than 4500 additional patients would be treated annually. This would cost more than \$45 million nationally without any proven clinical benefit.

Disclosure statement

There are no financial, litigational, or other conflicts of interest to disclose.

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