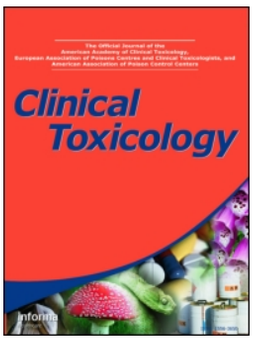

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CLINICAL RESEARCH

Changing nomogram risk zone classification with serial testing after acute acetaminophen overdose: a retrospective database analysis

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ABSTRACT

Context: The Rumack–Matthew nomogram stratifies patients into discrete risk zones following acetaminophen (APAP) overdose. Treatment decisions have traditionally been based on the initial risk zone. "Line-crossing" between zones occurs and is poorly understood. The study objective was to characterize line-crossing behavior in acute APAP overdose patients, especially moving from below to above the nomogram treatment threshold.

Methods and materials: The study was a secondary analysis of the Canadian Acetaminophen Overdose Study (CAOS) database, a large medical record review of patients hospitalized in eight large Canadian cities (1980–2005) following APAP poisoning. Population consisted of acute APAP overdose patients with at least two serum concentrations performed during hospitalization. Using ordinal logistic regression, we studied the effects of patient demographics, ingestion size/timing, APAP concentrations, time to *N*-acetylcysteine (NAC), and co-ingestants on a three-level dependent variable: patients whose risk increased two or more zones, those remaining in the same or adjacent zone, and those whose risk fell by two or more zones.

Results: Of the 3201 eligible hospitalizations with 7705 APAP concentrations, half (1679, 52.5%) crossed at least one zone (up or down) within 24 h of acute ingestion, including 190 (5.9%), who crossed at least two lines into a higher risk zone, and 516 (16.1%) at least two lines into a lower risk zone. Of the 1251 patients initially below the nomogram treatment line of 150 μg/mL, 131 (10.8%) patients crossed above this line. Being older, male, and co-ingesting opioids, antimuscarinics, or NSAIDs were independently associated with line-crossing.

Conclusions: Patients commonly crossed nomogram risk zones, including from below to above the current treatment threshold. These findings support recommendations for serial APAP testing until the individual risk of hepatic injury is clearly established.

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Introduction

Acetaminophen (APAP) poisoning remains a leading cause of morbidity and mortality in developed countries [1]. While APAP is one of the most commonly used analgesics in the world, overdose can result in hepatic injury and death when antidotal treatment is delayed [2]. For over 40 years, risk stratification decisions regarding antidotal treatment with *N*-acetylcysteine (NAC) have been guided by the Rumack–Matthew nomogram (the nomogram) [3]. Specifically, when an APAP concentration between 4 and 24 hours post-ingestion is below the nomogram treatment line, neither antidotal treatment nor additional measurement of APAP concentrations is recommended [4,5]. In the 1980s, distinct risk zone strata (e.g., ≥300 μg/mL at 4 h post-ingestion="high risk", or 150–200 μg/mL="possible hepatotoxicity") were added to the nomogram and patients continue to be classified into these zones to estimate risk of hepatotoxicity, if untreated based on an initial APAP concentration obtained at least 4 h after acute ingestion [6,7]. While a repeat concentration is often measured at the end of a 21-hour course of antidote, serial testing was previously discouraged [8–11], in part for frugality and in part to avoid a potential pitfall should a patient change risk zone and have NAC discontinued prematurely.

Despite the proven accuracy of the nomogram, "line-crossing" (moving from one risk zone to another on serial testing) does occur [12–17]. Possible etiologies include delayed gastric emptying from co-ingestants or combination products (opioids

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and antimuscarinics) [18], hepatic injury with delayed metabolism, pharmacobezoar formation [19], extended-release APAP formulation ingestions [20,21], and errors in patient history. While such isolated reports suggest that line-crossing is uncommon, understanding its frequency and predictors would provide a stronger evidence base for treatment recommendations (including initiating or modifying NAC therapy), and would inform the debate on the merits of measuring serial APAP concentrations and interpretation thereof [17,22].

The primary objective of this study was to use a large dataset of APAP overdose patients to characterize line-crossing behavior, especially moving either from below to above the treatment threshold or to a higher risk zone, after an acute overdose. Our secondary objective was to identify risk factors for line-crossing in an effort to better understand the underlying causes.

Methods

Design

This was a secondary analysis of the Canadian Acetaminophen Overdose Study (CAOS) database, a large retrospective medical record review of patients hospitalized following APAP poisoning from 34 hospitals in 8 large Canadian cities between 1980 and 2005. The Research Ethics Boards of each participating institution approved this study.

Participants and setting

The CAOS was a structured explicit medical record review of all patients admitted for APAP poisoning based on their primary or secondary discharge diagnosis classified using the International Classification of Diseases codes 965.4 (9th revision, poisoning by aromatic analgesic) and T39.1 (10th revision, poisoning by nonopioid analgesics, antipyretics, and antirheumatics (4-aminophenol derivatives)). A single investigator trained one to three medical record reviewers per city until a percentage agreement of 80% or greater and an inter-reviewer $\kappa > 0.8$ were established on a random subset of at least 50 records per reviewer. Medical record reviewers were blinded to the study hypothesis. The accuracy of data collection was assessed by an independent review of the first 100 charts for each data abstractor, followed by quarterly database assessment for the duration of data collection. Data were collected from paper medical records for the entire study period (July 1997–November 2005), which predated the widespread adoption of electronic medical records. Further details on the design, selection of participants, definitions, and data collection for CAOS have been described previously [14].

For the purpose of this study, we selected patients in whom at least two serum APAP concentrations could be plotted on the nomogram following an acute overdose.

Study definitions

We defined acute overdose to be either a single ingestion taken at a known time consistently reported in the medical record or when uncertainty in ingestion window from earliest to latest possible was no more than 4 hours. We considered only APAP concentrations obtained at least 4 hours but less than 24 hours after the end of the ingestion (termed *4+ h APAP concentration*) as per the usual clinical convention. Initial 4+ h APAP concentrations were plotted on the nomogram by converting to a *4-hour equivalent concentration* by calculating the vertical distance above the treatment line, as is customary in clinical risk stratification [23]. When the time of ingestion was not a single moment in time or not consistently reported, the time of ingestion was taken to be the start of the ingestion window, also as customary.

We defined seven nomogram risk zones using four traditional cutpoints, as well as two additional higher cutpoints chosen arbitrarily to provide more detail regarding larger ingestions: 100, 150, 200, 300, 400, and 500 μg/mL (to convert to molar units, divide by the molecular mass of 151 g/mol; i.e., 150 μg/mL ≃ 993 μmol/L) [6]. When subsequent APAP concentrations were at or below the local laboratory limit of quantification, these values were used only to demonstrate that a patient had either remained in the same or moved into a lower risk zone and never to classify a patient into a higher risk zone. To avoid overemphasizing very low concentrations, we excluded patients whose first 4+ h APAP concentration was below 15 μg/mL (99 μmol/L).

We categorized any reported co-ingestant into distinct, non-exclusive pharmacologic classes based on the drug itself or the most common formulation when a brand name was listed and did not attempt to corroborate the report with other information in the medical record (e.g., measured concentrations of salicylates or ethanol, urine immunoassay results, or clinical features). The classes used were: ethanol, antimuscarinics, opioids, and non-steroidal anti-inflammatories/salicylates.

When possible, we calculated the initial ψ parameter and APAP × AT multiplication product to provide additional measures of risk at presentation, as described elsewhere [23,24]. Hepatotoxicity was defined as a peak aminotransferase (either AST or ALT) of 1000 IU/L or greater [6].

Outcome measures

Beginning with initial 4+ h APAP concentration, we classified each subject into one or more nomogram risk zones based on every eligible APAP concentration to identify line-crossers. For each patient who changed risk zones, we recorded the *greatest increase* in nomogram risk zone observed relative to the initial zone (e.g., if the same patient increased by one zone then fell by three, the increase by one zone was selected; if a patient increased by one and then by another zone, an increase of two zones was used). We used this greatest increase parameter to create the primary outcome of *line-crossing* as a three-level ordinal variable: patients whose risk increased by two or more zones, those remaining in the same or adjacent zone, and those whose risk fell by two or more zones. In a prespecified sensitivity analysis, we compared subjects who increased two or more risk zones to the others by dichotomizing the three-level primary outcome into two levels.

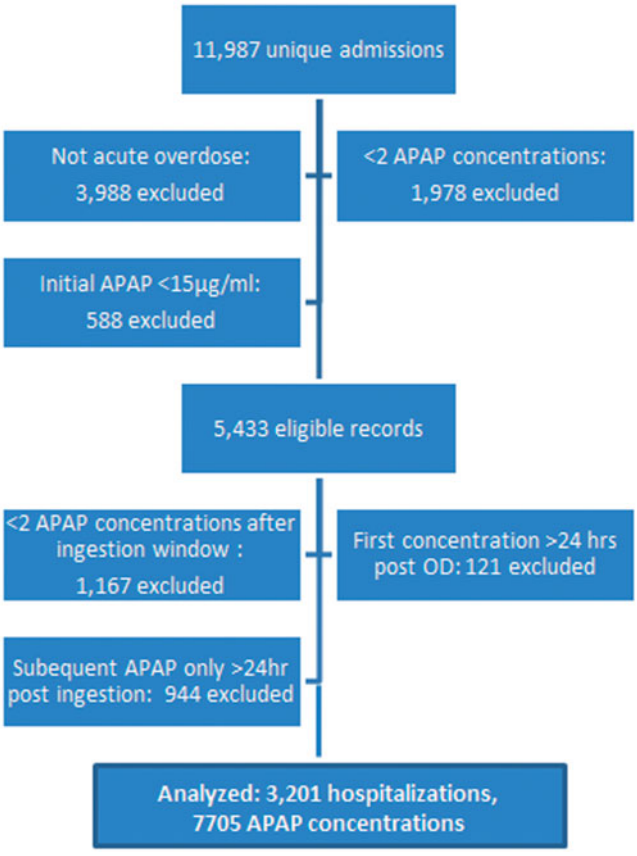

Figure 1 Selection of participants.

The average APAP elimination half-life was also estimated for patients grouped by their initial nomogram risk zone. For this pharmacokinetic analysis, we retained only APAP concentrations greater than 15 µg/mL and obtained within 24 hours of the first 4+ hour APAP concentration, in order to limit the influence of outliers and of very low concentrations.

Data analysis

In the primary analysis, line-crossing was modeled using ordered logistic regression (addition threshold 0.1, removal 0.05) using the following pre-specified factors of greatest interest: age, sex, dose reportedly ingested, first four-hour equivalent APAP concentration, alcoholism, co-ingestants, and hepatotoxicity. In separate secondary exploratory analyses, we removed subjects not treated with NAC, deleted the subjective measure of ingested dose, restricted the analysis to subjects with an initial four-hour equivalent concentration between 150 and 400 µg/mL and tested whether introducing the logarithmically transformed ψ or APAP × AT parameters reduced the influence of other predictors while using the same basic model construction. The average elimination half-life stratified by initial risk zone was estimated by plotting the logarithm of the ratio between each valid measured APAP concentration and the 4+ hour APAP concentration versus time and calculating the slope of the least squares regression line constrained to pass through the origin. Analyses were performed using SAS version 9.4 (64-bit, SAS Institute, Cary, NC).

Results

Of the 11,987 unique hospital admissions in the parent study database, 8786 were excluded for pre-selected criteria, giving a study cohort of 3201 hospitalizations and 7705 APAP concentrations (~2.4 APAP concentrations/hospitalization) for analysis (Figure 1). Most were young women who reported an acute ingestion of 10–30 g, had frequently co-ingested ethanol or other substances and were treated with intravenous NAC. Most (2384, 74.5%) reported a single and consistent time of ingestion and all but 140 (4.4%) reported an ingestion window of 2 hours or less. In those patients who were below the 150 µg/mL nomogram line and remained below the line on serial testing, 624/1084 (57.6%) were given NAC; in the subset of those who were between 100 and 150 µg/mL either initially or on serial testing, 380/500 (76%) were given NAC. Of the 3201 hospitalizations, a total of 124 (3.9%) patients developed hepatotoxicity and 10 (0.3%) died or underwent a liver transplant.

When compared to the initial 4+ h APAP concentration, subsequent concentrations often crossed into different nomogram risk zones (Table 1). The more common pattern was to cross into a lower risk zone, especially in patients whose initial risk zone was lower. Altogether, 2699 (84.3%) remained consistently within the same or lower risk zone (Table 2). However, some patients crossed into higher risk zones including a few who were initially deemed to be at very low risk based on the first measured APAP concentration. Notably, 190 (5.9%) crossed at least two lines into a higher risk zone. Of the 1215 patients initially below the standard treatment line of 150 µg/mL at 4 hours, 131 (10.8%) crossed over this line at some later time, including 65 (5.3%) who also crossed the 200 µg/mL line. Of these, 131 who crossed over the treatment line, two (1.5%) developed hepatotoxicity and 10 others had a measured peak aminotransferase between 100 and 1000 IU/L.

Table 3 displays the univariate analysis of factors associated with line-crossing. Being older, male and co-ingesting NSAIDS, opioids, or antimuscarinics were associated with line-crossing. On multivariate modeling, the strongest association was the presence of hepatotoxicity (adjusted odds ratio 3.18 [95%CI 2.00, 5.05]; Figure 2).

The above findings were robust across the planned sensitivity and exploratory secondary analyses. When restricting the analysis to patients treated with NAC (i.e., those for whom time-to-NAC was available to calculate ψ), an increase in the time-weighted pre-treatment exposure to supratherapeutic APAP as measured by the ψ parameter was also independently associated with line-crossing (adjusted odds ratio 1.09 [1.03, 1.16] for every 10-fold increase). Patients with higher initial four-hour equivalent APAP concentrations were less likely to migrate into a higher risk zone, presumably reflecting the impossibility of patients in the highest risk zones moving up further and *vice versa*. When the model was run on the middle three risk zones only, the association was reversed (adjusted odds ratio 1.38 [1.17, 1.62] for every 100 µg/mL increase). Finally, the elimination half-life grouped by initial risk zone was longest in the patients in the two highest risk zones, averaging 5.2 hours as compared to values ranging from 4.1 to 4.5 hours in the lower risk zones.

Table 1. The Rumack–Matthew nomogram zone of the first eligible (i.e., obtained at least 4 h post the end of the reported ingestion window and >15 μg/mL) and every subsequent valid serum acetaminophen concentration (APAP) measurements obtained within 24 hours of ingestion.

Initial 4 + h (APAP) nomogram zone (μg/mL)	Subsequent (APAP) by nomogram zone (μg/mL)							
	<100	100–150	150–200	200–300	300–400	400–500	≥500	Total
<100	704	35	27	21	6	5	4	802
100–150	409	277	77	28	17	5	3	816
150–200	327	221	242	99	27	4	10	930
200–300	178	186	196	289	100	27	19	995
300–400	36	48	43	105	92	49	57	430
400–500	7	7	23	31	38	48	75	229
≥500	4	2	7	17	22	30	220	302
Total	1665	776	615	590	302	168	388	4504

The main diagonal (shaded) indicates a pair of (APAP), which remain in the same nomogram risk zone, while pairs above the diagonal demonstrate "line-crossing" into a higher risk zone. When subsequent (APAP) were below the local assay level of quantification (LOQ), the (APAP) was assigned the zone based on this local LOQ, or the same zone as the initial (APAP), whichever was lower.

Table 2. The highest Rumack–Matthew nomogram zone achieved within 24 hours of ingestion is shown along with the initial zone.

Initial nomogram zone (μg/mL)	Highest subsequent nomogram zone (μg/mL)							
	<100	100–150	150–200	200–300	300–400	400–500	≥500	Total
<100	584	24	13	11	4	4	3	643
100–150	251	225	53	24	12	4	3	572
150–200	179	149	200	72	24	5	8	637
200–300	81	117	139	232	76	21	15	681
300–400	18	26	29	76	75	34	39	297
400–500	1	2	11	19	28	34	53	148
≥500	3	0	5	11	14	18	172	223
Total	1117	543	450	445	233	120	293	3201

The primary outcome of *line-crossing* is illustrated by the shading intensity: the heaviest shading shows patients who crossed at least two lines into a higher risk zone, the light shading those who remained within one zone and unshaded those who decreased by at least two risk zones. No (APAP) below the local assay level of quantification (LOQ) was used to move a patient into a higher risk zone.

Table 3. Univariate analysis of risk factors for line-crossing.

Patient characteristics	Greatest change in nomogram risk zone			*p* Value
	≥2 zone increase ($N = 190$)	±1 zone ($N = 2495$)	≥2 zone decrease ($N = 516$)	
Age, in years	25.6 [18.2, 35.9]	20.9 [16.6, 32.0]	20.9 [16.3, 30.8]	<.001
Sex, female	113 (59.5%)	1814 (72.7%)	404 (78.3%)	<.001
Dose reportedly ingested, in g	20 [10, 33]	15 [7.5, 25]	20 [10, 33]	<.001
First 4+ hour (APAP), in μg/mL	133 [75.8, 220]	115 [60.3, 178]	161 [97.3, 199]	<.001
Time of first 4+ hour (APAP), in hours from start of ingestion	5.2 [4.3, 6.9]	5.3 [4.3, 7.9]	6.4 [4.7, 8.9]	<.001
4-Hour equivalent (APAP), in μg/mL	171 [121, 287]	162 [101, 264]	224 [187, 306]	<.001
Time to NAC, in hours from start of ingestion	7.5 [6.0, 10.5]	7.3 [5.8, 9.8]	6.9 [5.5, 9.4]	.03
ψ, in mM·hours	1.52 [0, 3.13]	0.038 [0, 0.987]	0.405 [0, 1.52]	<.001
First (AT), in IU/L	23 [17, 32]	23 [17, 33]	22 [16, 31]	.2
APAP × AT, in mM·IU/L	15.8 [6.60, 33.8]	16.0 [6.10, 31.4]	18.2 [7.10, 33.0]	.42
Peak INR	1.2 [1.1, 1.3]	1.2 [1.1, 1.3]	1.1 [1.1, 1.3]	.02
Peak AT, IU/L	27 [18, 59]	26 [18, 42]	25 [19, 40]	.4
Hepatotoxicity, yes	9 (4.7%)	112 (4.5%)	3 (0.6%)	<.001
Death or liver transplant	0 (0%)	8 (0.3%)	2 (0.4%)	.7
NAC administered, yes	175 (92.1%)	2000 (80.2%)	508 (98.5%)	<.001
Alcoholic, yes vs. no/not mentioned	43 (22.6%)	367 (14.7%)	85 (16.5%)	.011
Co-ingested ethanol, yes	52 (27.4%)	606 (24.3%)	119 (23.1%)	.5
Co-ingested opioid, yes	48 (25.3%)	499 (20.0%)	77 (14.9%)	.003
Co-ingested antimuscarinic, yes	36 (18.9)	417 (16.7%)	46 (8.9%)	<.001
Co-ingested NSAID/ASA, yes	38 (20.0%)	337 (13.5%)	52 (10.1%)	.002

g: grams; IQR: interquartile range; INR: international normalized ratio; NSAID: non-steroidal anti-inflammatory drug; ASA: acetylsalicylic acid.
The columns show the subjects classified by the greatest change in the Rumack–Matthew nomogram risk zone compared to their initial risk zone. Continuous characteristics are summarized by the median (IQR); binary characteristics by count (% of total). Shaded items were used to model the primary outcome using ordered logistic regression, using the non-parametric Kruskal–Wallis test by ranks for continuous characteristics and the χ^2 test for nominal characteristics.

Discussion

In this large, national cohort of APAP overdose patients, one in two crossed from one nomogram risk zone into another on serial testing, with two-thirds of these moving exclusively to a lower risk zone. Such a pattern is clearly reassuring and not a trivial finding and may eventually inform decisions regarding the duration of antidotal therapy [25]. We also found, however, that approximately one in six patients cross at least one line into a *higher* risk zone, including one in 16, who cross at least two lines. Of particular clinical concern, 1 in 10 move from below the treatment threshold of

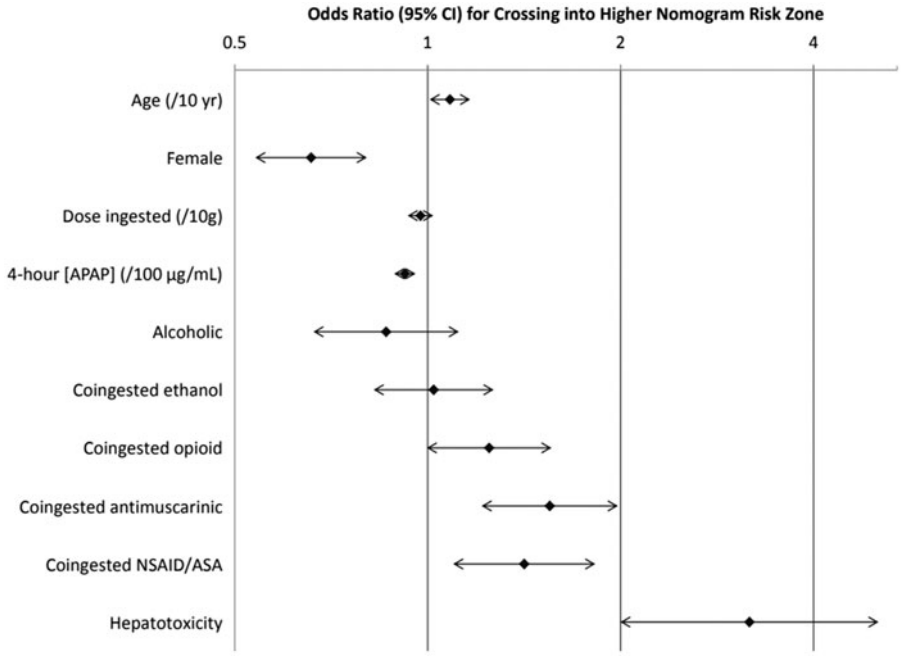

Figure 2. Odds ratios of selected risk factors associated with two or more Rumack Matthew nomogram risk zone increases after acute acetaminophen overdose.

150 µg/mL at 4 hours to above, and half of these move above 200 µg/mL within 24 hours of acute overdose. During the development of the nomogram, the original 200 µg/mL threshold had been intentionally lowered to 150 µg/mL at the request of the U.S. Food and Drug Administration precisely to minimize the risk of such events [3,6,7].

We found that being older, male, and co-ingesting opioids, antimuscarinics, or NSAIDs/ASA were each independently associated with line-crossing. A larger and longer exposure to supratherapeutic APAP prior to initiation of antidotal therapy and subsequent hepatotoxicity were also strongly associated with moving into higher risk zones. While it is not possible to separate ongoing absorption from delayed elimination due to hepatic injury as the cause of line crossing upwards, our findings make a compelling argument in favor of serial APAP testing in order to establish both that absorption is nearly complete and that hepatic elimination is working well. In effect, the interpretation of serial APAP concentrations remains a key risk predictor and is the earliest available measure of hepatic function and adequacy of treatment [3,24,26].

While the Rumack–Matthew nomogram has remained an excellent risk stratification tool for generations, over the years, there have been occasional reports of hepatotoxicity and even death in patients with initial APAP concentration below the treatment line [16,18,27–29]. The nomogram incorporates somewhat idealized elimination phase kinetics for APAP beginning 4 hours after the acute overdose. Indeed, it appears difficult to reconcile the scarcity of clinically serious outcomes in the medical literature with our findings, despite decades of withholding NAC based on the nomogram. Part of the explanation must include the high rate of antidotal treatment of patients below the treatment threshold. Given the low risk of NAC, many clinicians presumably err on the side of caution and empirically administer NAC, despite poison centre recommendations to the contrary [30]. Another partial explanation may be that our study cohort was selected from patients admitted to hospital and who had serial APAP testing, and therefore, the very low risk and clinically well the patient is underrepresented in the denominator of the risk estimates. Conversely, waning enthusiasm for any form of gastrointestinal decontamination including activated charcoal may explain some of the recent cases with delayed peaks and slower falls in APAP concentrations. Regardless, line crossing is not rare.

Our incidence of patients crossing from below to above the standard treatment line of 150 µg/mL at 4 hours is similar to that reported in previous studies. Kirschner et al. prospectively studied 76 APAP overdose patients, who had co-ingested opioids or antihistamines and had an initial 4 hour APAP concentration below the treatment line. They recommended repeating APAP concentration between 7 and 8 hours post-ingestion and determined the incidence of patients crossing from below to above the line. In their cohort, five (6.6%) crossed the treatment line, four of whom were treated with NAC. None of these five patients developed hepatotoxicity [17]. Graudins demonstrated line-crossing in 4/27 (15%) patients in a retrospective analysis of acute and staggered modified-release APAP ingestions. In this study, line-crossers tended to have an initial serum (APAP) at 4 h above 75 µg/mL (500 µmol/L) and a reported dose more than 10 g, suggesting that in this group, there should be a high suspicion for a subsequent "toxic" concentration [20].

Delayed absorption due to prolonged gastric emptying, extended-release formulations, massive ingestion, or errors in time of ingestion presumably account for some early line crossing into a higher risk zone. We did find that several co-ingestants were predictive of line-crossing to a higher risk zone, consistent with other studies, although the odds ratios were modest [15–18,31]. While opioids and antimuscarinics are

expected to decrease gastric motility, the effect of anti-inflammatories may be due to the induction of pylorospasm [32]. During the study years in question, only a very small fraction of APAP sold in Canada was formulated as extended-release.

Prolonged elimination due to acute hepatic injury will also cause line crossing into a higher risk zone over time. The subsequent development of hepatotoxicity, based on peak aminotransferases often days after presentation, was strongly associated with line-crossing. While the slope of the nomogram corresponds to an elimination half-life of 4 hours and APAP elimination is normally slightly faster, it is well-known that hepatotoxic patients eliminate APAP more slowly regardless of treatment with NAC [24,26]. Thus, on serial testing, the trajectory of APAP concentrations on the nomogram diverges upwards and away from the treatment line, contributing to the nomogram's excellent sensitivity even many hours after APAP concentrations peak. As such, line crossing from the high risk to higher risk zones is not surprising and consistent with prior science. More concerning is the crossing from below to above the current treatment line, representing unexpected risk changes. While many have been recently explicitly recommending that acetylcysteine only be discontinued when the serum APAP is below the limit of quantification, clinicians have little information with which to estimate when this event is likely to happen. While the nomogram effectively incorporated a 4-hour elimination half-life into the slope of the treatment threshold, our findings can be used to estimate the variability in the expected elimination rate for patients being treated with acetylcysteine.

It is worth noting that even in the original studies of nomogram efficacy, patients with APAP concentrations below the treatment line of 150 μg/mL at 4 hours had a non-zero risk of hepatotoxicity if left untreated, similar to the low rate of 1.5% in our study [3,6]. The deliberate lowering of the original discriminatory line from 200 μg/mL at 4 hours to 150 μg/mL and subsequently to 100 μg/mL in some countries, represents a trade-off between safety and overtreatment [3,22,29,33]. Serial testing contributes new information to risk stratification [24], but current guidelines do not call for repeat APAP testing after an initial value below the treatment line [4,5]. Guidelines which discouraged serial testing based on long turnaround times or potential for premature discontinuation of NAC, appear to us to be out of step with widespread availability of testing and with ongoing efforts to individualize and shorten antidotal therapy. We favor serial testing of APAP every 12 hours in all patients being treated with NAC until NAC is no longer indicated. For patients whose initial four-hour APAP concentration is near yet below the 150 μg/mL nomogram treatment threshold, we believe our findings provide additional evidence supporting repeat APAP testing in this group.

Limitations

Our study has several limitations. We were unable to study the effect of the formulation of APAP ingested (immediate, modified, or extended release) or the use of gastrointestinal decontamination (activated charcoal, gastric lavage) as these data were not abstracted into the study dataset. Our dataset was created using hospitalized patients and did not include patients tested and discharged from the emergency department with or without a brief course of treatment. Nevertheless, most patients, given NAC were admitted to hospital in Canada during the study years. The study of patients in whom multiple APAP concentrations were obtained may reflect some inherent clinical bias, such as alterations in consciousness, perceived higher risk, or other concerns. Despite our database spanning February 1980 to November 2005, there have not been substantive secular changes in the measurement of APAP concentrations in Canada since 2005 and we believe our results remain applicable to current practice.

Conclusions

Following acute APAP overdose, one-half of the patients cross nomogram risk zones, including about 1 in 10 from below to above the current treatment threshold of 150 μg/mL at 4 hours post-ingestion. Older age, male sex, co-ingestants, and eventual hepatic injury are independently associated with a patient moving into higher risk zones. These findings support recommendations calling for serial APAP concentrations until the individual risk of hepatic injury is clearly established and the need for practical decision instruments to interpret such serial testing.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Mowry JB, Spyker DA, Brooks DE, et al. 2015 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd annual report. Clin Toxicol. 2016;54:924–1109.

[2] Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. Crit Care Clin. 2012;28:499–516.

[3] Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. J Toxicol Clin Toxicol. 2002;40:3–20.

[4] Chiew AL, Fountain JS, Graudins A, et al. Summary statement: new guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust. 2015;203:215–218.

[5] Hoffman RS, Howland MA, Lewin NA, et al. Goldfrank's toxicologic emergencies 2014. 10th ed. New York: McGraw-Hill Medical; 1904.

[6] Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral *N*-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976–1985). N Engl J Med. 1988;319:1557–1562.

[7] Rumack BH, Peterson RC, Koch GG, et al. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. Arch Intern Med. 1981;141:380–385.

[8] Smilkstein M. Acetaminophen. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Weisman RS, editors. Goldfrank's toxicologic emergencies. 6th ed. Stamford (CT): Appleton & Lange; 1998.

[9] Hendrickson RG, MN. Acetaminophen. In: Marx JA, Hockberger RS, Walls RM, editors. Rosen's emergency medicine. 8th ed. Philadelphia (PA): Elsevier Saunders; 2014.

[10] Salhanik SD, SM. Acetaminophen. In: SM, et al., editor. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, (PA): Saunders Elsevier; 2006.

[11] Wallace CI, Dargan PI, Jones AL. Paracetamol overdose: an evidence based flowchart to guide management. Emerg Med J. 2002;19:202–205.
[12] Tighe TV, Walter FG. Delayed toxic acetaminophen level after initial four hour nontoxic level. J Toxicol Clin Toxicol. 1994;32:431–434.
[13] Bizovi K, Aks S, Paloucek F, et al. Late increase in acetaminophen concentration after overdose of Tylenol extended relief. Ann Emerg Med. 1996;28:549–551.
[14] Ho SY, Arellano M, Zolkowski-Wynne J. Delayed increase in acetaminophen concentration after Tylenol PM overdose. Am J Emerg Med. 1999;17:315–317.
[15] Hendrickson RG, McKeown NJ, West PL, et al. Bactrian ("double hump") acetaminophen pharmacokinetics: a case series and review of the literature. J Med Toxicol. 2010;6:337–344.
[16] Dougherty PP, Klein-Schwartz W. Unexpected late rise in plasma acetaminophen concentrations with change in risk stratification in acute acetaminophen overdoses. J Emerg Med. 2012;43:58–63.
[17] Kirschner RI, Rozier CM, Smith LM, et al. Nomogram line crossing after acetaminophen combination product overdose. Clin Toxicol. 2016;54:40–46.
[18] Schwartz EA, Hayes BD, Sarmiento KF. Development of hepatic failure despite use of intravenous acetylcysteine after a massive ingestion of acetaminophen and diphenhydramine. Ann Emerg Med. 2009;54:421–423.
[19] Spiller HA. Persistently elevated acetaminophen concentrations for two days after an initial four-hour non-toxic concentration. Vet Hum Toxicol. 2001;43:218–219.
[20] Graudins A. Overdose with modified-release paracetamol (Panadol Osteo(R)) presenting to a metropolitan emergency medicine network: a case series. Emerg Med Aust. 2014;26:398–402.
[21] Roberts DM, Buckley NA. Prolonged absorption and delayed peak paracetamol concentration following poisoning with extended-release formulation. Med J Aust. 2008;188:310–311.
[22] Rumack BH, Bateman DN. Acetaminophen and acetylcysteine dose and duration: past, present and future. Clin Toxicol. 2012;50:91–98.
[23] Sivilotti MLA, Yarema MC, Juurlink DN, et al. A risk quantification instrument for acute acetaminophen overdose patients treated with N-acetylcysteine. Ann Emerg Med. 2005;46:263–271.
[24] Sivilotti MLA, Green TJ, Langmann C, et al. Multiplying the serum aminotransferase by the acetaminophen concentration to predict toxicity following overdose. Clin Toxicol. 2010;48:793–799.
[25] Wong A, McNulty R, Taylor DM, et al. The NACSTOP trial: a multicentre, cluster-controlled trial of early cessation of acetylcysteine in acetaminophen overdose. Hepatology. 2018. doi:doi:10.1002/hep.30224 (In press).
[26] Prescott LF, Roscoe P, Wright N, et al. Plasma-paracetamol half-life and hepatic necrosis in patients with paracetamol overdosage. Lancet. 1971;1:519–522.
[27] Beer C, Pakravan N, Hudson M, et al. Liver unit admission following paracetamol overdose with concentrations below current UK treatment thresholds. QJM. 2006;100:93–96.
[28] MHRA. Benefit risk profile of acetylcysteine in the management of paracetamol overdose; 2012; [cited 2012 May 20]. Available from: http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con184709.pdf
[29] Bateman DN, Carroll R, Pettie J, et al. Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. Br J Clin Pharmacol. 2014;78:610–618.
[30] Yarema MC, Green JP, Sivilotti MLA, et al. Can a serum acetaminophen concentration obtained less than 4 hours post-ingestion determine which patients do not require treatment with acetylcysteine? Clin Toxicol. 2017;55:102–108.
[31] Halcomb SE, Sivilotti MLA, Goklaney A, et al. Pharmacokinetic effects of diphenhydramine or oxycodone in simulated acetaminophen overdose. Acad Emerg Med. 2005;12:169–172.
[32] Hasler WL, Soudah HC, Dulai G, et al. Mediation of hyperglycemia-evoked gastric slow-wave dysrhythmias by endogenous prostaglandins. Gastroenterology. 1995;108:727–736.
[33] Levine M, Stellpflug S, Pizon AF, et al. Estimating the impact of adopting the revised United Kingdom acetaminophen treatment nomogram in the U.S. population. Clin Toxicol. 2017;55:569–572.