A descriptive analysis of aspartate and alanine aminotransferase rise and fall following acetaminophen overdose

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.Context: Risk prediction following acetaminophen (paracetamol, APAP) overdose is based on serum APAP, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels. One recently proposed risk stratification tool, the APAPxAT multiplication product, uses either AST or ALT, whichever is higher, yet their interrelation is not well known following APAP-induced hepatic injury. Objective: To describe the kinetics of AST and ALT release into and disappearance from the circulation following APAP overdose. Materials and Methods: An observational case series of adult patients with peak AST or ALT > 100 IU/L attributable to APAP toxicity. Cases were identified by electronic search of hospital laboratory database and by discharge diagnosis corroborated by structured explicit medical record review. Results: Of 68 cases identified (mean age (SD): 39 (18) years, 63% female, and 21% ethanol co-ingested), 28 (41%) developed hepatotoxicity (peak AST or ALT > 1000 IU/L), 28 (41%) coagulopathy (international normalized ratio or INR > 2), and 21 (31%) both. Three patients (4%) were transferred for liver transplantation and ultimately six (8.8%) died. Serum AST and ALT activity rose in a closely aligned 1:1 AST:ALT ratio, but fell at distinctly different rates: AST activity fell with a half-life (interquartile range [IQR]) of 15.1 (12.2, 19.4) hours, and ALT 39.6 (32.9, 47.6) hours. Using an aminotransferase falling to below 50% of peak as the basis for discontinuing acetylcysteine would have resulted in antidotal treatment being stopped 24 (IQR: 9.6, 40) hours earlier (and in no cases later) using AST rather than ALT. Only six patients had an AST:ALT ratio greater than 2:1 at the time of acetylcysteine administration; of these six, four died and one survivor developed coagulopathy. Discussion: AST and ALT release into the circulation appears tightly linked and numerically similar, except in the sickest patients. Once the aminotransferases peak, AST returns to baseline more quickly. Conclusion: Either AST or ALT can be used for early risk stratification tools when only one is known. Any criterion for N-AC discontinuation should be based on the decline of AST rather than ALT, with a potential benefit measured in days.

Keywords Paracetamol; Liver; aspartate aminotransferase; alanine aminotransferase; N-acetylcysteine

Introduction

Acetaminophen (paracetamol, APAP) is the most common over-the-counter medication used for pain and fever. In the developed world, it is also the most common pharmaceutical taken in overdose, and a leading cause of fulminant hepatic failure and death. The treatment of APAP toxicity is based largely on the timely administration of the antidote, acetylcysteine (N-AC). However, the dosing and duration of N-AC administration remains largely empirical. Many toxicologists currently favor a patient-tailored approach to treatment, yet how best to individualize treatment is uncertain. Of particular interest, the identification of early prognostic indicators following overdose is fundamental to such an approach. Thus, risk stratification lies at the center of optimal treatment.

Our group has focused on characterizing the readily available liver function tests, including serial measurements of APAP and the aminotransferases (ATs; i.e., aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) in serum, to identify at-risk patients earlier in the disease process, shortly after hospital presentation. Of note, the serum AT activity* is now recognized to rise much sooner after overdose than previously thought. Specifically, the ATs are often abnormal at hospital presentation in the most severely ill patients. To couple the falling serum APAP concentration (an early measure of hepatic function) with a rising AT activity (due to hepatocyte injury), our group has proposed using the multiplication product of AT and APAP as an attractive, clinically available, and early prognostic marker. This product is somewhat independent of the reported time of ingestion, and can also be used following multiple or chronic APAP ingestions. This product has recently been independently validated in a Thai population, and the specificity improved when more than 8 hours had elapsed from acute ingestion. In our previous work, we have used either AST or ALT, whichever was greater, to calculate the product as not all hospitals measure both. Much of the literature surrounding APAP toxicity has focused exclusively

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*because aminotransferase measurements are expressed as IU/L, the term “activity” is preferred to “concentration”; moreover, the disappearance from the serum represents “inactivation” rather than necessarily “clearance”.

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on ALT, and increasingly hospital laboratories have discontinued measuring AST.\textsuperscript{13} While the AST and ALT ratio has been characterized for alcoholic, viral, and other causes of hepatic injury,\textsuperscript{13} there is little information regarding this ratio following APAP overdose.\textsuperscript{14} We therefore wondered if the choice of AT would bias the APAPxAT product.

Describing the post-peak phase of AT disappearance was also of interest to us. It has long been recognized that the absolute magnitude of the peak AT is, of itself, somewhat unhelpful as a single, stand-alone measure of prognosis. In fact, patients with the highest peak AST or ALT values (at times over 10 000 IU/L) often survive and recover completely, whereas fatalities exhibit more modest peak AT values. Acidemia, encephalopathy, and coagulopathy are more specific measures of liver failure and are used for identifying patients at risk of death.\textsuperscript{15,16} Moreover, the large majority of patients who develop elevated serum measurements of AT after APAP overdose recover. Such patients typically remain hospitalized for several days and antidotal treatment with N-AC continues until the ATs have clearly peaked and are falling or even near normal, even if the patient’s mentation and acid–base status is normal. While precise stopping criteria for N-AC are variable, waiting for the AT to fall below 50% of peak is often the only remaining criterion preventing discharge or transfer.

We set out to characterize the rise and fall of both AST and ALT, individually and with relation to each other, in APAP overdose patients. We were interested in their individual time course, as well as their ratio. By doing so, we hoped to add to the growing understanding of early prognostication in APAP overdose treated with antidote.

**Methods**

**Design**

An explicit structured medical record review of all patients treated in two tertiary care hospitals for APAP toxicity. Research ethics board approval was granted for this study.

**Study Population**

We attempted to identify every patient with elevated AT potentially related to APAP from 1987 to 2014. This search strategy was implemented in two distinct time cohorts: for 1987–2002 we screened an existing study database of patients hospitalized at our center for APAP overdose\textsuperscript{17} for any AT value > 100 IU/L; for 2002–2014, we electronically searched the hospital laboratory database for all patients with any AST or ALT value > 100 IU/L and a serum APAP > 100 μmol/L (15 μg/mL) within 24 hours of each other and during the same hospital visit. We used these somewhat arbitrary thresholds in an effort to identify as many potential cases as possible. We then manually reviewed the medical record to identify whether the AT elevation was attributable to a cause other than APAP overdose (e.g., ischemic hepatitis, viral hepatitis, and alcoholic liver disease). We also excluded uncertain cases in which the measured serum APAP concentration was never above the therapeutic range (< 134 μmol/L or 20 μg/mL), and N-AC was not administered. Patients under the age of 16 years were also excluded.

**Measurements/Outcomes**

All available measurements of serum APAP, ALT, AST, prothrombin time, international normalized ratio (INR), and creatinine were extracted from the medical record, with the reported time of testing. For each parameter, ‘peak’ was the highest value observed. For the few cases in which the time of peak AST and ALT differed, we used the earlier time as “time to peak AT.” The time of APAP ingestion was determined based on manual review of the ambulance record, emergency physician and nursing notes, consultations, and the admission record. If the estimated time of ingestion varied between these sources, the earliest time was used. When subjects ingested APAP in multiple stages, but all within period of 8 hours (still defined as an “acute ingestion”), the midpoint of the earliest and latest time was used for analysis. All other cases in which the reported times of ingestion exceeded 8 hours were defined as “non-acute.” Cases with no available ingestion times were defined as “unknown.”

The time, dose, and route of N-AC administration were obtained from the medication administration record as recorded by the nurse. In-hospital outcomes (encephalopathy, transfer for liver transplant, death, and survival to discharge) were ascertained from the progress notes and discharge record. “Hepatotoxicity” was defined to be a peak AT > 1000 IU/L, and “coagulopathy” as a peak INR > 2 or PT:control ratio > 2. As this study is descriptive in nature, there is no a priori statistical null hypothesis to be tested. Summary statistics and in particular, analysis of the kinetics of serum AT release and inactivation was employed, as with prior work by our group.\textsuperscript{9}

**Results**

A total of 82 potentially eligible cases were identified, of whom 14 were deemed to have AT elevations secondary to causes other than APAP overdose. Of these excluded subjects, none were suspected of APAP overdose; five were deemed secondary to ischemic hepatitis, three alcoholic hepatitis, one hepatocellular carcinoma, one pancreatitis, one congestive heart failure, one laboratory error, and two unclear. Only one had a peak AT greater than 1000 IU/L and had received N-AC empirically. The remaining 68 admissions represent the study cohort, and involved 67 patients (Table 1), of whom five died in our center. Three of these five deaths were known to chronically abuse ethanol. One additional death was identified among the three subjects transferred to another city for possible hepatic transplant. Table 2 contains further information regarding these six deaths. A total of 13 patients did not receive N-AC: one presented with hepatotoxicity approximately 48 hours after last APAP ingestion, and the rest had peak AT below 1000 IU/L.

The timed serum APAP concentrations of the 33 acute overdose patients with known time of ingestions are displayed in Supplementary Figure 1 (online appendix to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1077968). Most of these acute overdose patients

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had an APAP elimination half-life of 4 or more hours, but none died. Of the 10 patients who had a normal serum ALT measurement (<50 IU/L) at presentation to hospital and start of antidotal treatment, only one developed coagulopathy, and none developed hepatotoxicity.

The time course of every measured serum AST and ALT relative to start of N-AC for all patients treated is displayed in Supplementary Figure 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1077968. The highest initial serum AT activities were in the six patients who died, all of whom had markedly abnormal AT on presentation and peak AT within 24 hours of antidote initiation. The rising (pre-peak) and falling (post-peak) phases of AST versus ALT are plotted separately in Fig. 1.

The serum AST and ALT activities closely rose in a 1:1 ratio, and only rarely exceeded a 2:1 (AST:ALT) ratio. Notably, of the five patients who exceeded the 2:1 ratio at presentation and whose initial AST was greater than 1000 IU/L, all were coagulopathic and three died. None appeared to have AST release due to rhabdomyolysis, as serum creatinine kinase activity never exceeded 5000 IU/L.

The median (interquartile range [IQR]) AST/ALT ratio around the time of N-AC initiation (Fig. 2) was 1.12 (0.74, 1.28) in patients who recovered without coagulopathy, and exceeded 2 in only one patient. On the other hand, this ratio was substantially higher in the six subjects who died and usually above 2.

After peaking, serum AST and ALT activity almost always fell to below 100 IU/L with a relatively uniform pattern, consistent with first-order inactivation, as shown by a similar slope on the graph. However, two subjects, both of whom died, had a markedly different slope because the rate of AST inactivation was as slow as, or slower, than ALT inactivation. Patient A was a 49-year-old female with a history of chronic ethanol abuse who presented with acidemia, encephalopathy, and coagulopathy. Only one APAP concentration (278 μmol/L) was obtained on admission, and the patient died at 10 hours post admission. She was classified as an “unknown” type of ingestion. Patient B was a 44-year-old female who presented acidemic, comatose, and coagulopathic following APAP overdose and self-inflicted stab wounds to the epigastrium. She underwent emergency laparotomy and subsequently died 13 hours after presentation.

The AST/ALT ratio plotted against time before and after peak AT is shown in Fig. 3. Again, during the rising phase, the AST/ALT ratio was very close to 1 until peak, and then declined with a uniform slope again reflecting predominantly first-order kinetics. The declining phase from peak to 100 IU/L (Supplementary Figure 3 to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1077968) was used to calculate the median (IQR) inactivation half-life of 15.1 hours (12.2, 19.4) for AST, and 39.6 hours (32.9, 47.6) for ALT. The ratio of these inactivation rates can be shown to correspond to the time-independent solution to the two declining exponential functions describing the fall in AST and ALT activity. Specifically, if

\[
\text{post-peak AST} = \text{AST}_{\text{peak}} \exp(-k_{\text{AST}} \cdot t),
\]

and

\[
\text{post-peak ALT} = \text{ALT}_{\text{peak}} \exp(-k_{\text{ALT}} \cdot t).
\]

Table 1. Characteristics of acetaminophen overdose patients who developed serum AT rise above 100 IU/L.

| Characteristic                        | n = 68 |
|---------------------------------------|--------|
| Mean age in Years (SD)                | 39.1 (18) |
| Female Sex, %                         | 43 (63) |
| Ethanol Coingested, %                 | 14 (21) |
| Type of Overdose, %                   |        |
| Acute                                 | 33 (49) |
| Non-acute                             | 13 (19) |
| Unknown                               | 22 (32) |
| Duration of Antidote Therapy, %       |        |
| No NAC                                | 13 (19) |
| <24 Hours of NAC                      | 20 (29) |
| >24 Hours of NAC                      | 35 (51) |
| Clinical Progression, %               |        |
| Coagulopathy                          | 28 (41) |
| Hepatotoxicity                        | 28 (41) |
| Both                                  | 21 (31) |
| Encephalopathy                        | 10 (15) |
| Outcome, %                            |        |
| Discharged                            | 60 (88) |
| Transfer for hepatic transplant       | 3 (4.4) |
| Death                                 | 6 (8.8) |

Table 2. Detailed variables of subjects who died.

| Characteristic            | Death A | Death B | Death C | Death D | Death E | Death F |
|---------------------------|---------|---------|---------|---------|---------|---------|
| Age in Years              | 49      | 44      | 71      | 30      | 51      | 53      |
| Sex                       | F       | F       | M       | F       | F       | F       |
| Type of Overdose          | unknown | unknown | unknown | unknown | unknown | non-acute |
| Initial Lab Values        |         |         |         |         |         |         |
| APAP (μmol/L)             | 278     | 1375    | 159     | 76      | 1547.4  | 185     |
| INR                       | 5.6     | >10     | >10     | >10     | 2.5     | 3       |
| pH (arterial)             | 7.11    | 6.99    | 6.93    | 7.25    | 7.28 (venous) | 7.09 |
| Lactate (mmol/L)          | 23.2    | 27.4    | 19.9    | 5.1     | 12.6    | >20.0   |
| Peak CK (U/L)             | 976     | 670     | 3723    | 61      | n/a     | 239     |
| Encephalopathy            | Yes     | Yes     | Yes     | Yes     | Yes     | Yes     |
| Chronic EtOH Abuser       | Yes     | unknown | Yes     | No      | No      | Yes     |
| Time from admission to death (hours) | 10      | 13      | 6       | 100*    | 74      | 310     |

Abbreviations: CK-creatinine kinase; EtOH-ethanol; M-male; F-female.

*Death approximately 48 hours after transfer to transplant facility.
and both peak at similar times, then solving for $t$ yields a straight line when plotting $\text{AST}$ versus $\text{ALT}$ on a logarithmic scale of the form $y = mx + b$:

$$\log_{10} \text{AST} = k' \cdot \log_{10} \text{ALT} + \log_{10} \left( \frac{\text{AST}_{\text{peak}}}{\text{ALT}_{\text{peak}}} \right)^{-k},$$

with slope $k' = k_{\text{AST}} / k_{\text{ALT}}$, or equivalently the ratio of the half-lives. This relationship can be verified by inspection of the bottom panel of Fig. 1, in which the best-fit slope of the dashed line has a median (IQR) of 2.56 (2.15, 2.81). The $y$-intercept term simplifies to $\log_{10} \left( \frac{\text{AST}_{\text{peak}}}{\text{ALT}_{\text{peak}}} \right)^{-k}$ when $\text{ALT}_{\text{peak}} = \text{AST}_{\text{peak}}$.

Moreover, by dividing equations 1 and 2, one can see that the post-peak ratio of $\text{AST/ALT}$ over time is also a first-order exponential equation whose rate constant is the arithmetic difference between $k_{\text{AST}}$ and $k_{\text{ALT}}$:

$$\text{AST/ALT} = \text{AST}_{\text{peak}} / \text{ALT}_{\text{peak}} \exp(-k_{\text{ratio}} \cdot t),$$

in which $k_{\text{ratio}} = k_{\text{AST}} - k_{\text{ALT}}$, and the intercept simplifies to 1 when $\text{AST}_{\text{peak}} = \text{ALT}_{\text{peak}}$. The time required for the ratio to fall by half is simply $\ln(2)/k_{\text{ratio}}$, or approximately 24.7 hours as demonstrated in Fig. 3.

The time needed from N-AC initiation for each AT to fall by at least 50% is shown in Fig. 4. Patients reached this criterion at a median (IQR) of 24 (9.6, 40) hours earlier based on $\text{AST}$ rather than $\text{ALT}$, and no patient reached it earlier based on $\text{ALT}$. Fig. 5 represents the fall of each AT normalized by its peak activity. The serum $\text{AST}$ activity had generally fallen to below 20% of its peak (range 8%–25%) by the time the $\text{ALT}$ reached 50% of its peak.

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**Fig. 1.** Simultaneously measured serum AST and ALT concentrations of subjects during the rising (top panel) and declining phase (bottom panel). 2:1 and 10:1 ratios are expressed as dashed and dotted lines, respectively, in the rising phase. Subjects who died are expressed in open large circles. The transplant patient who survived is shown in unfilled triangles. The dashed line (bottom panel) corresponds to the median slope from peak to 100 IU/L using the ratio of the elimination rates (see Results).

**Fig. 2.** AST/ALT ratio closest to acetylcysteine initiation, grouped by outcome. The median (bar), with interquartile range (whiskers) is displayed. Student’s t-test of unequal variance comparing death and non-death patients demonstrated a significant ($p = 0.04$) difference. The median time between N-AC delivery and first available measurement of AT ratio was 1.6 hours (IQR 1.1-2.5) in non-coagulopathic patients, 2.0 hours (IQR 1.0-3.3) in coagulopathic patients and 2.7 hours (IQR 1.0-5.0) in patients who died.

**Fig. 3.** Aminotransferase ratios of subjects in relation to their peak. Only values $>100$ IU/L are plotted, representing the rise and subsequent fall of serum aminotransferases. Subjects who died are expressed in open large circles. The transplant patient who survived is shown in unfilled triangles.
Toxicologists are often called upon to interpret liver function test abnormalities in the context of potential APAP exposure and a serum APAP concentration. Understanding the patterns of laboratory abnormalities over time is therefore essential. Our group has previously shown that the initial ATs demonstrate value in risk stratification, specifically with regards to presenting value, rate of rise, and time to cross the hepatotoxic threshold of 1000 IU/L, an observation corroborated by Al-Hourani et al.\textsuperscript{10} In the present study, initial AT activities were the highest in the sickest patients and none of the patients with a normal ALT at presentation developed hepatotoxicity, in keeping with previous investigations.\textsuperscript{10}

We have proposed using the multiplication product of a rising AT and falling APAP as an early risk stratification tool, especially for the non-acute or time-unknown overdose.\textsuperscript{11} Yet, increasingly, hospital laboratories have discontinued or restrict testing for AT, especially if the ALT is normal. As a result, the multiplication product has incorporated a practical decision from the outset, namely to use either AST or ALT, whichever is greater, when both are measured. The present study was motivated by the desire to test whether this assumption would affect the value of the product. We observed a tightly linked release of AST and ALT during their rising phase, very close to a 1:1 ratio from presentation to peak. Our findings thus confirm minimal bias whether one uses AST or ALT to calculate the APAPxAT product, assuming one is not already in the phase when the ATs are declining.

We also observed a small number of patients, including some of the few deaths in this cohort, with a unique pattern—notably an AST:ALT ratio $> 2$ at time of presentation. Chronic ethanol abuse, a known risk factor for APAP toxicity and for higher serum AST,\textsuperscript{13,18,19} was recognized in the medical record of some of these cases. We searched for and excluded rhabdomyolysis and myocardial infarction as the source of AST, since skeletal and cardiac muscle are known to contain substantially more AST than ALT,\textsuperscript{13,20,21} and have contributed to the reputation of AST as being too non-specific in the judgment of some.

Interestingly, it has long been known that both cytosolic and mitochondrial isoenzyme forms of AST exist, allowing the malate-aspartate shuttle to carry electrons into the mitochondrion for respiration\textsuperscript{22,23} while ALT is exclusively found in the cytosol. In fact, 80% of AST activity in the human liver is localized to the mitochondrion. As such, rather than invoking different tissues such as skeletal or cardiac muscle, it is also possible that the mitochondrion may be the source of the additional AST. The ability of APAP to disrupt mitochondrial function, as manifested by early lactic acidosis, hypothermia, and coma at very high doses, is just now being recognized in humans\textsuperscript{24,25} nearly 40 years after being described in rodents.\textsuperscript{26,27} Linking these two threads, it is tempting to speculate that an early and dramatic AT elevation with an AST:ALT ratio $> 2$ may reflect mitochondrial disruption in more severely poisoned patients, and herald a worse prognosis especially in the absence of an increased creatine kinase to suggest rhabdomyolysis. Chronic ethanol abuse may well potentiate this toxicity. Since the AST...
of mitochondrial origin is inactivated in the serum much more slowly than cytosolic AST or ALT (half-life averaging 87 hours), the much slower fall in AST and in the AST:ALT ratio that we observed in the sickest patients lends indirect support to this hypothesis of mitochondrial disruption. Characterizing the specific origin of the AST activity seen in the serum of patients with hepatic failure would add considerable insight into the pathophysiology of APAP toxicity.

This study also provides a detailed description of the disappearance of AST and ALT activity from the serum following APAP overdose. Criteria to extend, intensify, and discontinue N-AC therapy in the setting of abnormal liver function tests are not well established. In practice, the low risk of N-AC results in prolonged infusions over many days in patients with any AT abnormality, even in the absence of more serious hepatic failure (i.e., coagulopathy, acidemia, and encephalopathy). Treating physicians may even be reluctant to discontinue N-AC because the ALT is slow to fall, even though the AST is nearly normal, prolonging hospitalization and uncertainty for the patient by days. Historical sources quote a half-life of 17 ± 5 hours for total AST and 47 ± 10 hours for ALT in the circulation, which correspond closely to our findings in patients recovering from APAP overdose. Recently, McGovern et al. have reported that an AST:ALT ratio < 0.4 is rarely seen unless the aminotransferases have peaked and are falling, based on a cohort of 37 patients with a peak AST or ALT > 1000 IU/L but not meeting King’s College Criteria or undergoing transplant. Taken together, these findings demonstrate conclusively that any criterion for N-AC discontinuation should be based on the decline of AST rather than ALT (again in the absence of rhabdomyolysis), with a potential benefit measured in days.

Limitations

The retrospective nature of this study limits our data to those available within the medical records, which span approximately 25 years. During this time, assay variability, changes in practice patterns, and variability of documentation are inevitable. The distinction between cytosolic versus mitochondrial origin of AST is not routinely available, yet may be inferred from a substantially slower fall in total serum AST and a post-peak AST:ALT ratio remaining above unity. The limited number of deaths in our study population precludes a detailed comparison of AST and ALT release and inactivation in patients who succumb to APAP toxicity. Nonetheless, using only clinically available and easily calculated measures such as the AST:ALT ratio, we hope to provide clinicians with prognostic tools to tailor the treatment of APAP overdose. We recommend testing of both AST and ALT approximately every 12 hours at first when either is abnormal, or when N-AC is being administered.

Conclusions

Following acetaminophen overdose, the appearance and disappearance of AST and ALT activity in the serum is highly consistent. The aminotransferases typically rise in a 1:1 ratio, except for the sickest patients in whom the AST:ALT ratio often exceeds 2. Because of the tightly linked rise between AST and ALT, either may be used to calculate the APAPxAT product when only one is available. After peaking, serum AST activity returns to baseline faster than ALT (except in the sickest patients), allowing antidotal therapy to be discontinued about one day earlier when based on a fall in AST rather than ALT to below half of the peak. Ultimately, this work supports the utility of serial testing in patients being treated for acetaminophen toxicity.

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Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Appendix to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2015.1077968.

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