The administration of N-acetylcysteine causes a decrease in prothrombin time in patients with paracetamol overdose but without evidence of liver impairment

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Objective To explore the effect of intravenous N-acetylcysteine (NAC) on the prothrombin time (PT) in patients with paracetamol overdose and a persistent normal liver profile.

Materials and methods This retrospective case series study examined all admissions with a diagnosis of paracetamol poisoning in a tertiary hospital between 1989 and 2002. Patients were included if they had received NAC infusion, had no biochemical evidence of liver damage, and had more than two measurements of PT. Patients who had also ingested other drugs were excluded.

Results Of 65 admissions with paracetamol poisoning, 18 patients (10 men) met the inclusion criteria. The median age was 29 years, and the median quantity of paracetamol ingested was 186 mg/kg. The mean number of PT measurements per patient was 4.8. The baseline PT (as a percentage) 8.6 h after paracetamol ingestion was 89.6%. During NAC infusion the PT fell in all patients (range, 4.8–53.4% relative to baseline; \( P < 0.0001 \)) at 14 h. The PT was less than 60% in 28% of the patients. Eight hours after the initiation of NAC there was a 16% fall in PT (range, 4.3–34%; \( P < 0.0001 \)). At the end of NAC infusion all PTs returned to values close to baseline. Nine patients were hospitalized.

Conclusions In patients with paracetamol overdose without evidence of liver damage a marked decrease in PT often occurs, which seems to be due to the overload of NAC infused at the beginning of treatment. This particular feature should be noted in clinical practice guidelines as a potentially misleading indicator of the development of severe liver dysfunction. Eur J Gastroenterol Hepatol 17:59–63 2005 Lippincott Williams & Wilkins

Keywords: paracetamol overdose, N-acetylcysteine infusion, prothrombin time

Introduction Paracetamol-induced hepatotoxicity is currently the main cause of acute liver failure in the USA and the UK, accounting for almost 39% of the cases [1]. N-Acetylcysteine (NAC) is an effective therapy for paracetamol poisoning since it is a source of hepatic glutathione depleted by the electrophilic reactive metabolite (NAPQ1) formed by oxidation of the drug in cytochrome P450 2E1 [2].

In patients with suspected paracetamol overdose, NAC should be administered as soon as possible, whatever the initial paracetamol blood level, and careful scrutiny for signs of impending liver failure is warranted. This includes monitoring of liver enzymes, prothrombin time and blood pH [3]. The prothrombin time, which is a sensitive prognostic indicator of acute liver failure, is impaired as an isolated finding in patients with paracetamol poisoning without other evidence of liver damage. Although this has recently been attributed to NAC therapy [4], the issue remains controversial [5,6].

We assessed the effect of NAC on prothrombin time in a cohort of patients hospitalized for paracetamol overdose who had a normal liver profile.

Patients and methods A retrospective case series study was undertaken to examine all admissions with a diagnosis of paracetamol poisoning in a tertiary care center (serving a population of 303,106 inhabitants) in southern Spain between May 1989 and December 2002. The patients’ medical records were identified, retrieved and reviewed for consistency of the diagnosis. Patients were included if they had received an NAC infusion, had no biochemical evidence of liver damage [aspartate aminotransferase (AST) < 30 U/l or alanine aminotransferase (ALT) < 40 U/l] in any of the determinations throughout the
observation period, and had more than two serial measurements of prothrombin time. Patients who had also ingested other drugs were excluded. The NAC regimen followed in the hospital was 150 mg/kg in 200 ml of 5% dextrose over 15 min, followed by 50 mg/kg in 500 ml of 5% dextrose over 4 h and 100 mg/kg in 1 l of 5% dextrose over 16 h.

A structured protocol was used to analyze the clinical, biochemical, and epidemiologic data. We recorded demographic data, the amount of paracetamol ingested, the reason for ingestion, the time elapsed between ingestion and arrival at the hospital, the time to the start of antidote therapy with NAC, the unit of hospitalization where patients were referred, and alcohol intake. Laboratory data included paracetamol levels on admission, values for AST and ALT, and all prothrombin time values.

An analysis of the subset of patients who did not receive antidote therapy and had more than one measurement of prothrombin time (four patients) was made. The amount of paracetamol ingested in this population was less than 150 mg/kg in all patients.

Prothrombin times were measured using coagulometric analyses (Sysmex CA 6000; Dade Behring, Deerfield, Illinois, USA). The coefficient of variation for prothrombin time measurements was < 5%.

We used the prothrombin time (expressed as a percentage) instead of the International Normalized Ratio values because the latter were not in use at our hospital during the first years of the study period. A decrease in prothrombin time is equivalent to an increase in the International Normalized Ratio.

The periods chosen to measure prothrombin time were as follows: baseline (first monitoring after admission), first prothrombin time after the initiation of NAC infusion, minimum prothrombin time during NAC infusion, and the last prothrombin time recorded before discharge.

The study protocol was approved by the Local Ethics Committee at the Virgen de la Victoria University Hospital in Málaga. This is a retrospective case series study and therefore patient consent was deemed unnecessary since the data collected were later anonymized.

Data management and statistical analysis
Data were analyzed with the Statistical Package for Social Sciences (version 10.0 for Windows, SPSS Inc., Chicago, Illinois, USA). Variables were recorded as descriptive frequencies. Bivariate associations were measured with t tests for continuous variables. Differences were reported as statistically significant if the P value was less than 0.05. Data are expressed as means, standard deviations and 95% confidence intervals (CIs).

Curve-fitting was carried out with GraphPad Prism version 3.0 for Windows (GraphPad software; San Diego, California, USA).

Results
In all, 65 patients were admitted to our hospital with a diagnosis of paracetamol poisoning between May 1989 and December 2002. We excluded nine patients because they presented with overt liver damage. Other reasons for exclusion were concomitant ingestion of other drugs (non-steroid anti-inflammatory drugs, antidepressants, codeine) that could modify prothrombin time (12 patients), moderate and transitory increases in AST or ALT values (six patients), and inconclusive data because the medical record could not be retrieved (five patients). About one-half of the patients (33 patients, 51%) had a diagnosis of paracetamol intoxication and a normal liver profile, and had not taken other drugs. Five of these patients did not receive NAC infusion and 10 patients had fewer than three determinations of prothrombin time, and were not considered further. A total of 18 patients (10 men) were eligible for analysis. The mean age was 29 years (range, 15–69 years), the median quantity of paracetamol ingested was 186 mg/kg (range, 67–357 mg/kg), and one patient had an extrapolated 4-h paracetamol concentration greater than 150 mg/l. Eleven patients had consumed paracetamol in excess of 150 mg/kg. Five patients also had acute alcohol ingestion. All patients had ingested paracetamol because of attempted suicide. Nine patients were hospitalized in specialized units: four in the intensive care unit, three in internal medicine and two in the digestive diseases unit for follow-up because of a marked decrease in prothrombin time as the only laboratory finding of note. The mean number of measurements of prothrombin time per patient was 4.8 (range, 3–8).

The mean baseline prothrombin time was 89.6% (95% CI, 83.3–95.9%), measured at a mean time since paracetamol ingestion of 8.6 h (range, 2–30 h) (Table 1).

After intravenous NAC was started, the prothrombin time decreased in all patients and reached a minimum mean of 68.5% (95% CI, 61.1–75.9%), which represented a decrease of 21% (range, 4.8–53.4%) relative to baseline (P < 0.0001). This decrease in prothrombin time was achieved within a median time of 14 h (range, 2–46 h) after NAC treatment was started. Overall, five of the 18 patients (28%) had a prothrombin time less than 60% (Fig. 1a).
Table 1. Changes in prothrombin time (PT) values in individual patients with paracetamol overdose and normal hepatic function before, during and after the end of N-acetylcysteine (NAC) treatment

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Baseline PT (%)</th>
<th>Time after paracetamol (h)</th>
<th>First PT measurement</th>
<th>Time (h)</th>
<th>Minimum PT</th>
<th>Time (h)</th>
<th>PT (%)</th>
<th>Time (h)</th>
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<tr>
<td>Mean ± standard deviation</td>
<td>89.8 ± 12.8</td>
<td>8.6 ± 6.8</td>
<td>73.5 ± 12.4*</td>
<td>8.3 ± 10.2</td>
<td>68.5 ± 14.8*</td>
<td>13.8 ± 10.2</td>
<td>87.2 ± 9.2</td>
<td>50.9 ± 38.5</td>
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</table>

* P < 0.001 different from baseline and after NAC was ended.

Fig. 1

(a) Time course of prothrombin time values in five patients with paracetamol overdose and a normal liver profile. We selected patients who achieved the greatest decrease in prothrombin time values after N-acetylcysteine (NAC) infusion. The black arrow indicates the end of NAC infusion. (b) Time course of prothrombin time values in four patients with paracetamol overdose and normal liver profile who did not receive NAC therapy.
Analyses of the first measurement of prothrombin time after NAC infusion showed that 8 h (range, 2–46 h) after the initiation of NAC, the mean prothrombin time was 73.5% (95% CI, 67.2–79.6%). The fall in prothrombin time relative to baseline was 16% (range, 4.3–34%; $P < 0.0001$), which represents a 77% decrease referred to the maximum decrease achieved (21%). At the end of NAC infusion all prothrombin time values had approached baseline values, with a mean of 87.2% (95% CI, 82.7–91.8%) after a mean time of 51 h post-ingestion (range, 17–160 h). The final prothrombin time values did not differ from those obtained at baseline.

Patients co-intoxicated with alcohol (patients 1, 6, 13, 15, and 16) did not differ from those with pure paracetamol intoxication in the prothrombin time outcome. Alcohol abuse did not affect the minimum prothrombin time reached during NAC infusion (77.4%).

The subset of patients who did not receive antidote therapy and had more than one measurement of prothrombin time showed a mean ± standard deviation baseline prothrombin time of 84.8 ± 17%, at 4 ± 1.3 h after paracetamol ingestion, that decreased to 77.95 ± 10% at 10 ± 4 h, which represented a mean decrease of 6.6 ± 10.4% relative to baseline (Fig. 1b).

**Discussion**

This study was specifically undertaken to evaluate the influence of NAC infusion on prothrombin time in patients with paracetamol overdose and a normal liver profile. A single altered result for prothrombin time without any other evidence of hepatocellular injury was seen in one-half of the patients admitted to our hospital for paracetamol intoxication, a figure that is similar to that reported in another large series [6]. Conversely, hepatotoxicity due to suicidal overdoses of paracetamol is an uncommon diagnosis in our area, although in other countries such as the UK, the USA and Scandinavian countries, it remains the most common cause of acute liver failure requiring transplantation [7]. This may reflect cultural differences in attitudes toward suicide, prescription practices and the legal status of paracetamol.

This study supports the previously described influence of NAC treatment on prothrombin time in patients presenting at various times after paracetamol overdose, and seems to confirm that paracetamol itself plays a minor role in the impairment of coagulation factors in this population. In fact, the maximum decrease in prothrombin time achieved during NAC infusion was 21% after 14 h, with a 16% decrease evident as soon as 8 h after treatment was begun. The largest decrease in prothrombin time was seen during the initial phase of NAC infusion, when 67% of the total dose of NAC to be given over 20 h and 15 min had been administered, and plasma concentrations of NAC were consequently expected to be very high. An additional finding that further supports the role of NAC in impairing prothrombin time is the consistent fall in this parameter seen at any time during NAC treatment in comparison with the values at baseline and after treatment was stopped.

Our findings are in agreement with those of Schmidt and colleagues [4]. In their retrospective analysis in 87 patients with paracetamol poisoning without signs of hepatocellular injury, they found that the initial decrease in prothrombin index was strongly associated with the start of NAC therapy. Furthermore, an in vivo experimental study of increasing concentrations of NAC (100–600 μmol/l, concentrations likely to be found during treatment) found a dose-dependent decrease in prothrombin time [8].

The documented anticoagulant effect of NAC infusion has also been reported in healthy persons with a demonstrated decrease in the activity of factor II, factor VII and factor X in the absence of any change in activated partial thromboplastin time [8], and in patients with adult respiratory distress syndrome [9]. The mechanism underlying the interaction between NAC and coagulation time is not clear, but may be related with the capacity of this sulfhydryl compound to reduce the disulfide bridges that bind glycoproteins to other proteins [10]. The sulfhydryl groups and disulfide bonds are essential to maintain the structure and catalytic role of clotting factors.

Perhaps more important from a practical standpoint was the unnecessary allocation of patients with the largest decrease in prothrombin time to various medical wards, including the intensive care unit. This policy may reflect the concern of the specialist in charge to recognize impending liver failure as early as possible, and the rooted belief that any impairment in prothrombin time, even without other accompanying features, heralds this complication and is as a major prognostic factor. It is noteworthy that current recommendations for the management of paracetamol poisoning do not mention this particular parameter in patients who are given NAC [11,12]. Questions still remain about the possible effects of NAC on the concentration of factor V, claimed to be the most sensitive and specific prognostic indicator of outcome in severe paracetamol-induced hepatotoxicity [3].

In summary, in patients with paracetamol overdose and a normal liver profile the decrease in prothrombin time seems to be due mostly to the overload of NAC infused at the beginning of therapy. In this scenario, physicians should not consider an isolated abnormal prothrombin time value as an indicator of severe liver dysfunction.
Awareness of the potential effect of acetylcysteine therapy on coagulation is crucial for the management and monitoring of patients with paracetamol intoxication, and the effects of this therapy should be taken into account in clinical practice guidelines.

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Conflicts of interest
None declared.

Authors’ contributions
M. Isabel Lucena conceived and designed the study, took part in the case review process, performed the main analysis of the data and wrote the paper. Enrique López-Torres and Carmen Verge coordinated the case review process, helped in the analysis, drew the figure and table, and contributed to the interpretation of the data. M. José Puche and Julia Seoane helped in the case review process and performed the literature search. Raúl J. Andrade contributed significantly to the study design, analysis and interpretation of the data and wrote the first version of the paper. Felipe Sánchez de la Cuesta contributed to the writing of the final version of the manuscript.

References