LIVER

Effect of intravenous N-acetylcysteine infusion on haemostatic parameters in healthy subjects

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Background and aim: N-acetylcysteine is used to treat paracetamol overdose but depresses the activity of plasma coagulation factors II, VII, and X, which are often used to assess liver injury. The aim of this study was to investigate the effect of N-acetylcysteine on haemostasis in normal volunteers.

Methods: Haemostatic parameters in 10 healthy subjects were analysed before and following intravenous infusion of therapeutic doses of N-acetylcysteine, as well as *in vitro*.

Results: N-acetylcysteine induced significant decreases in plasma levels of vitamin K dependent haemostatic proteins *in vivo*, being maximal at one hour following the start of infusion, with maximal decreases from 1.00 to 0.73 (0.67–0.79) (mean (95% confidence interval)), 0.66 (0.58–0.73), 0.81 (0.73–0.90), 0.64 (0.57–0.70), 0.74 (0.65–0.82), and 0.61 (0.54–0.67) for factor II, VII, IX, and X activities, protein C activity, and free protein S reactivity, respectively. These data suggest that N-acetylcysteine induces protein modifications affecting activity. Five subjects developed an adverse reaction to infusion of N-acetylcysteine and these were associated with a rapid increase in levels of factor VIII and its carrier protein von Willebrand factor (vWf) from 1.0 to 1.85 (1.08–2.62) and 1.77 (0.83–2.71), respectively, which suggests that the allergic reaction induced release of vWf from endothelial cells. N-acetylcysteine did not affect factor VIII or vWf in subjects without adverse reactions, and nor did it affect factor V or antithrombin in any of the subjects.

Conclusion: Therapeutic doses of N-acetylcysteine cause abnormal haemostatic activity, and this should be taken into account when using haemostatic function tests as an indicator of hepatic injury.

N-acetylcysteine (NAC) is the treatment of choice to prevent hepatotoxicity after paracetamol intoxication^{1–3} which is the most common cause of acute liver failure in Denmark, the UK, and the USA.^{4–6} It has also been used to treat other critically ill patients such as those with non-paracetamol induced acute liver failure, sepsis, or acute respiratory distress syndrome, but the therapeutic effect of NAC in these illnesses are equivocal.^{7–9} The rationale of using NAC in critically ill patients is its antioxidant function and its modulating effect on the proinflammatory cytokine response. It has a direct antioxidant effect and it stimulates synthesis of glutathione, an important endogenous intracellular antioxidant.^{10–11}

Acute liver failure is associated with severe derangement of haemostatic function as the liver is the main site of synthesis of coagulation factors and anticoagulant proteins.^{12–13} Plasma levels of the vitamin K dependent coagulation factors II, VII, and X decrease at an early stage of hepatocellular damage. Therefore, it is widely accepted that the reduction in coagulation factor II+VII+X is a prognostic marker for the severity of liver damage.^{14–16}

Intravenous infusion of therapeutic doses of NAC to healthy subjects was reported to depress the plasma activity of coagulation factor II+VII+X as well as the activities of the single factors II, VII, and X.¹⁷ NAC also decreased the plasma activity of factor II+VII+X *in vitro*. This effect of NAC may be misinterpreted as a sign of liver failure and complicate the management of patients with paracetamol poisoning.¹⁸ The aim of the present study was to investigate in more detail the effect of NAC on haemostatic plasma parameters after intravenous infusion in healthy subjects. The *in vivo* data were in all instances compared with those obtained *in vitro* in order to address the mechanism of action of NAC. Our study expands previously cited work¹⁷ by including data on the effect of NAC on factors V, VIII, and IX, von Willebrand factor

(vWf), and the anticoagulant proteins antithrombin, protein C, and free protein S. Approximately 30% of protein S in human plasma is free while the remainder is bound to the complement regulatory protein C4 binding protein.¹⁹ Only free protein S has anticoagulant function.

METHODS

Subjects

Ten healthy subjects (six males and four females) participated in the study. Their age and weight (median (range)) were 29 (21–32) years and 68 (52–93) kg. Before the start of the study, all subjects were judged as healthy by interview, physical examination, and routine laboratory investigations. Three additional normal subjects donated blood for the *in vivo* study (males aged 25–30 years). Written consent was obtained from each subject participating in the study and the study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the regional ethics committee (protocol No KF 01-177/00) and the Danish Medicines Agency.

Analytical techniques

Blood for determination of haemostatic parameters was stabilised by 0.1 vol 0.129 mmol/l trisodium citrate. Plasma was separated and stored at –80°C (for assay of factor V and VIII) or –20°C (for assay of the other parameters) until analysed. If not otherwise stated, haemostatic parameters were analysed on ACL Futura or ACL 3000 (both Instrumentation Laboratories, Milan, Italy). Activated partial thromboplastin time (APTT) was analysed by Platelin Plus (Organon Teknika, Durham, North Carolina, USA). The activity of coagulation factor II+VII+X was analysed by

Abbreviations: NAC, N-acetylcysteine; CRP, C reactive protein; vWf, von Willebrand factor; APTT, activated partial thromboplastin time

Nycotest PT (Nycomed, Oslo, Norway) and expressed as a fraction of normal coagulation activity (arbitrary U/l), which was derived from prothrombin time measurements according to the manufacturer's instruction. The activities of coagulation factors II, V, VII, and X were analysed by the one stage clotting assay using Dade Thromboplastin-IS and Dade Coagulation Factor Deficient Plasma II, V, VII, and X (Dade Behring, Marburg, Germany). The activities of coagulation factors VIII and IX were analysed by the one stage clotting assay using Automated APTT (Organon Teknika) and Dade Coagulation Factor VIII and IX Deficient Plasma (Dade Behring). The activities of antithrombin and protein C, and the reactivity of free protein S, were analysed by Coamatic Antithrombin, Coamatic Protein C (both Chromogenix-Instrumentation Laboratory, Milan, Italy) and IL Test Free Protein S (Instrumentation Laboratories), respectively.

The antigen concentration of vWf was measured by an enzyme linked immunosorbent assay using rabbit immunoglobulin against human vWf as the catching antibody and peroxidase conjugated rabbit immunoglobulin against human vWf as the detecting antibody (code No. P 0082 and P 0226; Dako, Glostrup, Denmark). The interassay coefficient of variations at normal levels of the haemostatic parameters were 3.2% (APTT), 5.1% (factor II+VII+X activity), 4.7% (factor II activity), 6.0% (factor V activity), 7.3% (factor VII activity), 6.6% (factor VIII activity), 4.0% (factor IX activity), 7.3% (factor X activity), 4.9% (antithrombin activity), 2.9% (protein C activity), 6.3% (free protein S reactivity), and 6.3% (vWf antigen).

Haemoglobin and platelet count in EDTA stabilised blood were analysed on an Advia 120 Hematology System (Bayer Diagnostics, Tarrytown, New York, USA). Alanine aminotransferase, alkaline phosphatase, creatinine, and lactate dehydrogenase in serum were analysed on a Vitros 950 Chemistry Analyzer (Ortho-Clinical Diagnostics, Rochester, New York, USA). Albumin and C reactive protein (CRP) in trisodium citrate stabilised plasma were analysed by Alb/BCP (bromocresol purple) and Tina-quant a CRP, respectively, using Modular Analytics-P (Roche Diagnostics, Mannheim, Germany). NAC up to 10 mmol/l did not influence assay of albumin or CRP when examined as described below in the in vitro protocol for haemostatic parameters.

In vivo protocol

Subjects were given NAC 400 mg/kg bodyweight (N-acetylcysteine 200 mg/ml; SAD, Copenhagen, Denmark) intravenously over 36 hours, distributed as a 150 mg/kg bolus over 15 min, 50 mg/kg over four hours, and 200 mg/kg over 32 hours. This corresponds to the regimen recommended by the Danish Association for the Study of the Liver and the

Danish National Board of Health for the treatment of paracetamol poisoning. Blood samples were collected by separate vein punctures before and at 1, 3, 6, 8, 12, 16, 24, 32, 38, 48, 72, and 120 hours after start of the NAC infusion.

In vitro protocol

The influence of NAC on haemostatic parameters was examined after incubation of 0.8 vol trisodium citrate stabilised plasma for one hour at 37°C with 0.2 vol NAC in citrate-Tris buffer (1 vol trisodium citrate 129 mmol/l+9 vol Tris HCl 100 mmol/l, NaCl 50 mmol/l, pH 7.40 (37°C), adjusted with NaOH), yielding final concentrations of the drug ranging from 0.02 to 10 mmol/l.

Data treatment and statistical analysis

Haemostatic parameters were normalised to the same scale and presented as fractions of baseline values obtained before the start of the NAC infusion (in vivo study) or values obtained without NAC (in vitro study). Statistical analysis was performed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, California, USA; www.graphpad.com). A p value of <0.05 was considered significant. Two groups were analysed by the Student's *t* test and three or more groups were analysed by one way or two way ANOVA of data before normalisation to their baseline values. Descriptive normalised data are given as mean (95% confidence interval (CI)) and in the in vivo study *n* = 10 at each time point, if not otherwise indicated. In the case of factor VII, one subject was excluded due to preanalytical or analytical mistakes in the samples obtained at baseline and at other time points.

RESULTS

In vivo study

Basic laboratory investigation and clinical course

Haemoglobin and platelet count were measured at baseline and at 120 hours after the start of the NAC infusion, while albumin, creatinine, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase were measured at one and three hours (albumin) and at 12, 32, and 120 hours (all components) after the start of infusion of the drug. All values were within the normal range (not shown). Normalised mean albumin concentration ranged between 0.92 and 1.06 of baseline values at 1, 3, 12, 32, and 120 hours. These deviations from baseline may reflect plasma volume changes. Correction for albumin concentrations did not alter the pattern of changes observed with the haemostatic parameters during NAC infusion. For this reason only uncorrected data for haemostatic parameters are presented. The haemostatic parameters at baseline are shown in table 1. They did not deviate significantly from the 95% reference interval of our laboratory.

Five of the 10 subjects developed moderate adverse reactions characterised by both cutaneous and systemic manifestations in relation to the initial bolus infusion (table 2). Three of these subjects received antihistamines. None of the subjects had any signs of adverse reactions after the first hour and all received NAC as planned.

Effect of NAC on global coagulation tests

Infusion of NAC depressed factor II+VII+X activity to 0.73 (0.69–0.76) of baseline values three hours after start of the infusion, and activity remained at this level until 38 hours (two hours after cessation of the infusion) (fig 1). Activity gradually reached baseline levels. NAC infusion had no overall significant effect on APTT (*p* = 0.93).

Table 1 Median (range) baseline values for the haemostatic plasma parameters in the 10 healthy individuals given an infusion N-acetylcysteine

APTT (s)	31 (28–35)
Factor II+VII+X activity (arbitrary U/l)	0.91 (0.84–1.27)
Factor II activity (kIU/l)	0.81 (0.66–1.02)
Factor V activity (arbitrary U/l)	0.83 (0.64–1.31)
Factor VII activity (kIU/l)	1.00 (0.80–1.38)*
Factor VIII activity (kIU/l)	0.99 (0.62–1.30)
Factor IX activity (kIU/l)	0.88 (0.63–1.04)
Factor X activity (kIU/l)	1.07 (0.77–1.55)
Antithrombin activity (kIU/l)	1.07 (0.74–1.20)
Protein C activity (kIU/l)	1.13 (0.74–1.67)
Free protein S reactivity (kIU/l)	0.97 (0.83–1.12)
Von Willebrand factor antigen (kIU/l)	0.91 (0.46–1.26)

APTT, activated partial thromboplastin time.

**n* = 9 (see methods).

Table 2 Clinical course and plasma levels of factor VIII activity and von Willebrand factor (vWf) antigen one hour after the start of the N-acetylcysteine (NAC) infusion in subjects with moderate adverse reactions

Sex; age (y)	Adverse reactions	Antihistamine	Plasma level at 1 hour	
			Factor VIII activity	vWf antigen
Female 21	Nausea, vomiting, flushing	No	1.83	1.26
Female 29	Nausea, flushing, dizziness, bronchospasm	Yes	2.63	2.78
Male 29	Nausea, vomiting, dizziness	Yes	1.48	1.52
Male 32	Nausea, abdominal pain	No	2.25	2.32
Female 21	Nausea, skin rash, dizziness	Yes	1.06	0.97

Plasma factor VIII activity and vWf antigen at one hour are expressed as fractions of baseline values obtained before the start of the NAC infusion. Four subjects responded with a marked increase in levels of the two factors while one subject did not respond.

Effect of NAC on vitamin K dependent single coagulation factors II, VII, IX, and X

The activities of the single factors II, VII, IX, and X decreased abruptly at one hour after the start of the NAC infusion to 0.73 (0.67–0.79), 0.66 (0.58–0.73), 0.81 (0.73–0.90), and 0.64 (0.57–0.70) of their baseline values, respectively (figs 1, 2). In all instances this was followed by an increase in their activity level. Factor II and IX activities returned to baseline by six hours after the start of the NAC infusion while factor VII activity gradually returned to baseline at 38 hours. Factor X activity increased from one to six hours. Thereafter, the mean level was sustained at 0.7–0.8 of baseline values until 72 hours after the start of the infusion before it reached baseline at 120 hours.

Effect of NAC on anticoagulant proteins

NAC also depressed levels of the vitamin K dependent factors protein C and protein S (fig 2). Protein C activity and free protein S reactivity decreased abruptly at one hour to 0.74 (0.65–0.82) and 0.61 (0.54–0.67) of baseline values, respec-

tively. Thereafter, protein C activity gradually increased until it reached baseline values at 38–48 hours after the start of the NAC infusion. The reactivity of free protein S increased to 0.88 (0.85–0.92) of baseline values at six hours, and this concentration was sustained (range of means 0.76–0.91) until the end of the observation period.

The overall effect of NAC on antithrombin activity was not significant when analysed at 1, 3, 12, and 32 hours (n = 10) and at 120 hours (n = 8) after the start of the infusion (p = 0.22) (data not shown).

Effect of NAC on coagulation factor V and VIII, and on vWf

NAC infusion induced concordant changes in levels of factor VIII activity and vWf antigen. The groups with and without moderate adverse reactions (n = 5 in each group) responded differently to NAC. Four of the subjects in the group with moderate adverse reactions showed a marked change in levels of factor VIII activity and vWf antigen within one hour, leading to an increase in the levels of the two parameters in

Figure 1 Effect of N-acetylcysteine (NAC) infusion on the activity of coagulation factor II+VII+X and the activities of the single factors II, VII, and X in plasma. Values on the X axis are times after drug infusion. In each subject concentrations were normalised to baseline values obtained before the start of the NAC infusion and results are presented as fractions of this value. Each group of data is presented as the mean and upper limit of the 95% confidence interval. Empty bars indicate n = 10; values n < 10 are shown inside the bars.

Figure 2 Effect of N-acetylcysteine (NAC) infusion on the activities of coagulation factor IX and protein C, and the reactivity of free protein S in plasma from the same subjects as in fig 1. Data are normalised and presented as in fig 1.

this group to 1.85 (1.08–2.62) and 1.77 (0.83–2.71) of baseline values, respectively (tables 2, 3). Thereafter, levels slowly decreased towards baseline values (table 3). The

Figure 3 In vitro effect of N-acetylcysteine (NAC) on factor II+VII+X activity, factor II, VII, IX, and X activities, protein C activity, and free protein S reactivity in plasma from three healthy subjects. In each subject concentrations of haemostatic proteins were normalised and expressed as fraction of baseline values obtained without NAC. Each group of data is presented as mean (SEM).

overall effect of NAC on levels of factor VIII activity and vWf antigen in the group without adverse reactions was insignificant ($p = 0.35$ and 0.83 , respectively).

The sensitive marker of the acute phase reaction, CRP, was measured before, and eight and 16 hours after the start of the NAC infusion in four subjects with a rapid marked response of factor VIII activity and vWf antigen to NAC. In all instances levels of CRP were ≤ 3 mg/l (reference interval <10 mg/l).

The overall effect of NAC infusion on the level of factor V activity was not significant ($p = 0.78$) when analysed in all subjects at the same time points as in table 3 (not shown).

Table 3 Effect of N-acetylcysteine (NAC) infusion on factor VIII activity and von Willebrand factor (vWf) antigen				
Time (h)	Subjects with moderate adverse reactions (n = 5)		Subjects without adverse reactions (n = 5)	
	vWf antigen	Factor VIII activity	vWf antigen	Factor VIII activity
0	1 [0.72, 0.63–1.24]	1 [0.95, 0.81–1.30]	1 [1.06, 0.46–1.26]	1 [1.01, 0.62–1.12]
1	1.77 (0.83–2.71)	1.85 (1.08–2.62)	0.97 (0.87–1.08)	1.00 (0.91–1.09)
3	1.65 (0.70–2.59)	1.76 (0.97–2.54)	0.97 (0.94–1.00)	1.06 (0.97–1.16)
6	1.55 (0.77–2.33)	1.71 (1.13–2.29)	1.06 (0.95–1.18)	1.24 (1.13–1.34)
12	1.55 (0.87–2.23)	1.63 (1.16–2.09)	1.12 (0.97–1.27)	1.23 (1.11–1.35)
24	1.43 (0.95–1.90)	1.44 (1.18–1.70)	1.15 (0.97–1.33)	1.21 (1.01–1.40)
32	1.49 (1.00–1.98)	1.47 (1.28–1.67)	1.13 (0.85–1.42)	1.21 (0.97–1.44)
48	1.66 (1.18–2.14)	1.35 (1.22–1.49)	1.34 (1.11–1.57)	1.22 (1.14–1.31)
120	1.40 (1.14–1.66)	1.35 (1.10–1.59)	1.22 (0.97–1.28)	1.18 (1.06–1.30)

Results are mean (95% confidence interval). In each subject, data were normalised to baseline values obtained before the start of the NAC infusion. $p < 0.0001$ and $p = 0.0011$ for adverse versus non-adverse reactions, and $p = 0.025$ and 0.46 for time with factor VIII and vWf, respectively (two way ANOVA). Values in parentheses at 0 hours are baseline values [median, range] in kIU/l for factor VIII activity and vWf antigen. These values did not differ in subjects with and without adverse reactions ($p = 0.68$ for factor VIII and $p = 0.73$ for vWf; two tailed unpaired t test).

In vitro study

Incubation of plasma for one hour at 37°C in vitro with increasing concentrations of NAC resulted in a progressive decrease in levels of the vitamin K dependent proteins (fig 3). Concentrations of NAC that reduced levels of the respective proteins to 0.70 of their baseline values (comparable with the decreases in vivo) were approximately 3.5 (factor II+VII+X activity), 10 (factor II activity), 3.5 (factor VII activity), 5 (factor IX activity), 0.9 (factor X activity), 1.5 (protein C activity), and 0.3 mmol/l (free protein S reactivity). NAC from 0.5 to 10 mmol/l resulted in a progressive small decrease in coagulation factor V activity (mean (SEM)) to 0.81 (0.018) but it had no effect on factor VIII activity, vWf antigen, or antithrombin activity (not shown).

DISCUSSION

Apart from decreasing the activity levels of factors II, VII, and X,¹⁷ the present study shows that intravenous infusion of NAC to healthy subjects also depresses plasma levels of other vitamin K dependent proteins participating in the coagulation cascade (factor IX activity, protein C activity, and free protein S reactivity). The maximal effect of NAC on vitamin K dependent proteins occurred within one hour in our study and after several hours in a previously reported study,¹⁷ probably because we used a threefold higher bolus dose of NAC. Data on the effect of NAC on vitamin K dependent proteins in healthy subjects can most likely be extended to include patients treated with NAC, as a comparable decrease in factor II+VII+X activity as observed in the present study after initiation of NAC infusion was seen in patients with paracetamol poisoning but without any sign of hepatocellular damage.¹⁸

In agreement with the just cited study,¹⁷ we found that NAC infusion did not affect APTT, which is in agreement with the notion that APTT is rather insensitive to changes in activities of coagulation factors, contributing to the outcome of the test.²⁰

Depressed levels of vitamin K dependent proteins are most likely caused by modification of their structure/function by NAC. This is supported by the following evidence. (A) Concentrations of NAC affecting levels of the respective proteins in vivo and in vitro were comparable. The dose regimen of NAC used in the present study has been reported to give rise to a total plasma mean concentration of the drug of 3.4 mmol/l after the initial loading dose.²¹ Then, the mean concentration fell to a steady state level of 0.21 mmol/l after approximately 12 hours. After discontinuation of NAC it disappeared from plasma with a half life of approximately six hours. In vitro, we observed that NAC in the range 0.2–10 mmol/l induced a progressive decrease in levels of vitamin K dependent proteins. (B) In all instances the maximal fall in vitamin K dependent protein levels occurred within one hour after the initial loading dose of NAC, irrespective of their plasma half lives, which range from about six hours (factor VII) to approximately 70 hours (factor II).^{22–24} (C) Factor II and IX activities reached their baseline values by six hours after the start of the NAC infusion, despite the fact that their half lives are approximately 24 and 70 hours, respectively. As these two factors are among the least sensitive to the effect of NAC in vitro, the relatively rapid normalisation of activity levels could be explained by a decline in the concentration of NAC after the initial loading dose, leading to dissociation of NAC from the two proteins and restoration of their normal function. (D) Depression of factor X activity and free protein S reactivity was sustained several hours after cessation of the NAC infusion. This sustained effect is in agreement with the observation that the activities of these two proteins are the most sensitive to the effect of NAC in vitro and therefore are also affected by the drug at the low concentrations achieved

after the initial loading dose. The sustained effect of NAC on factor X activity is most likely responsible for the sustained effect of the drug on factor II+VII+X activity.

The fall in free protein S reactivity in response to NAC could be due to a modifying effect of the drug, leading to a decrease in the affinity of one or both of the targets for the protein S detecting reagents in the assay. The targets are the sex hormone binding globulin-like domain and the N terminal Gla domain, which are recognised by C4 binding protein and monoclonal antibody coated latex particles, respectively.²⁵

Vitamin K dependent proteins are homologous multi-domain proteins that share a unique Gla domain of pivotal significance for their function,²⁶ indicating that NAC affects the structure/function of these proteins by a common mechanism. One mechanism could be reduction of exposed sensitive intramolecular disulphide bonds required for maintenance of their structure/function. By using thiol reactive agents, evidence has been provided that NAC can reversibly reduce disulphide bonds in the insulin receptor, matrix proteins, and intracellular signal transducers at concentrations similar to those impairing the vitamin K dependent proteins in the present study.^{27–29} Another mechanism of impairment could be that the vitamin K dependent proteins analogous to other plasma proteins (primarily albumin) are nitrosylated,³⁰ that this nitrosylation enhances their activity, and that NAC induces denitrosylation resulting in a decrease in activity. This mechanism seems less likely as preliminary experiments in vitro showed that the nitrosylating agent DETA NONOate at 1–10 mmol/l had no effect on factor II or X activity or on free protein S reactivity in plasma incubated for one or two hours at 37°C (unpublished).

VWf serves as a stabilising carrier of factor VIII and any change in the plasma level of vWf is associated with a concordant change in the level of factor VIII.^{31–32} In the present work, four of five subjects with moderate adverse reactions in response to NAC showed concordant and rapid marked increases in factor VIII activity and vWf antigen followed by progressive slow decreases in their levels. This is compatible with the immediate release of vWf from storage sites (Weibel-Palade bodies) in endothelial cells and the subsequent elimination of the factor VIII-vWf complex from plasma with the reported half life of approximately 14 hours.^{23–32} Histamine may be the responsible agonist for the release of vWf as NAC liberates histamine in cell cultures^{33–34} and histamine liberates vWf from its storage pools in vivo.³⁵ The proposed mechanism agrees with the observation that a controlled insect sting challenge resulted in a rapid and marked parallel increase in plasma levels of histamine and vWf in subjects who developed anaphylactic reactions and hypotension.³⁶ Interestingly, the one subject with systemic adverse reactions, but without an increase in levels of factor VIII activity and vWf antigen, was among the three subjects who received antihistamines. Both factor VIII and vWf are acute phase reactants.³⁷ It is unlikely that the NAC induced increases in the levels of these two factors in the four subjects with systemic adverse reactions were mediated by an acute phase reaction, as the level of the sensitive acute phase reactant CRP was unaffected. It is also unlikely that a gain in function mechanism was involved, as NAC did not affect plasma levels of factor VIII activity and vWf antigen in subjects without adverse reactions or in vitro.

The frequency of systemic adverse reactions in response to intravenous NAC infusion in patients with paracetamol intoxication varies from 3% to 48%.^{38–40} This great variation in frequency could be caused by underestimation of adverse reactions in some studies as paracetamol can produce nausea and vomiting, making it difficult to distinguish these symptoms from those caused by NAC itself. Another

explanation could be that adverse reactions may be under-reported. In the present study, the frequency of systemic adverse reactions was 50%. The nature of these reactions and their early manifestation in relation to bolus infusion of NAC are in agreement with results obtained by others.^{38–40} In a similar study to ours in healthy subjects, no systemic reactions occurred.¹⁷ This may be explained by the three times lower bolus dose used in this study.

There is no general consensus on when to stop NAC administration in patients being treated for paracetamol intoxication but the activity of coagulation factor II+VII+X remains essential in the monitoring of these patients.^{15 41–46} It remains to be determined whether derangements of the haemostatic system observed here will be of future clinical relevance for decision making in the treatment of paracetamol intoxication. It is notable that NAC infusion has little effect on factor V activity and may increase factor VIII activity, as levels of both of these factors have been reported to be of prognostic value in fulminant hepatic failure.^{47 48}

The bioavailability of NAC after oral administration is much lower (approximately 9%) than after intravenous administration.⁴⁹ This means that the conclusions of the present study cannot be directly transferred to patients receiving NAC orally.

In conclusion, we have demonstrated that NAC infusion in doses used to treat paracetamol intoxication causes small to moderate derangements of the coagulation system, which affect both vitamin K dependent coagulant and anticoagulant proteins, some of which are used as early predictors of hepatic damage. We also found that adverse reactions can be associated with increases in the levels of factor VIII and its carrier protein vWf. Further studies are needed to elucidate the biochemical and pharmacokinetic bases for the observed changes in haemostatic parameters.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 460

The histological findings are characteristic of enterocolic lymphocytic phlebitis. This is a rare condition of unclear aetiology, exclusively involving the veins of the colonic wall and pericolic soft tissue. In this patient the cause of systemic vasculitis, including cryoglobulinaemia, was not found. Although intestinal vasculitis may occur in the context of systemic diseases such as systemic lupus erythematosus, polyarteritis nodosa, Churg-Strauss syndrome, Henoch-Schönlein purpura, and/or rheumatoid arthritis, isolated intestinal vasculitis is a rare event. It may appear in diseases such as Crohn's disease where it primarily involves the arteries but not the veins. The isolated intestinal venulitis, better known as enterocolic lymphocytic phlebitis, is an uncommon cause of intestinal ischaemia recently described by Saraga and Costa.¹ The disease is characterised by intestinal necrosis caused by a vasculitis restricted to the veins of the intestinal tract without involvement of arteries.^{1–2} On histological examination a wide variety of venous lesions are found but lymphocytic phlebitis is the most frequent lesion seen. In fig 1C, involvement of the vein with numerous lymphocytes is seen (arrowhead) whereas the artery (arrow) is uninvolved. Thrombotic obstruction may occur as a complication of the venous inflammation causing ischaemia and necrosis of the bowel.³ The aetiology and pathogenesis of this entity are unknown. None the less it has been speculated that lymphocyte mediated vascular damage linked to a hypersensitivity reaction may cause this type of vasculitis.³ In all reported series, patients had a favourable outcome without recurrence of intestinal ischaemia. To our knowledge this entity has not been reported in association with hepatitis C cirrhosis. Our patient recovered well and was discharged home one week after surgery.

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