

Recommendations for the paracetamol treatment nomogram and side effects of N-acetylcysteine

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ABSTRACT

Treatment of paracetamol intoxication consists of administration of N-acetylcysteine, preferably shortly after paracetamol ingestion. In most countries, the decision to treat patients with N-acetylcysteine depends on the paracetamol plasma concentration. In the literature, different arguments are given regarding when to treat paracetamol overdose. Some authors do not recommend treatment with N-acetylcysteine at low paracetamol plasma concentrations since unnecessary adverse effects may be induced. But no treatment with N-acetylcysteine at higher paracetamol plasma concentrations may lead to unnecessary severe morbidity and mortality. In this review, we provide an overview on the severity and prevalence of adverse side effects after N-acetylcysteine administration and the consequences these side effects may have for the treatment of paracetamol intoxication. The final conclusion is to continue using the guidelines of the Dutch National Poisons Information Centre for N-acetylcysteine administration in paracetamol intoxication.

KEYWORDS

Paracetamol, acetylcysteine, adverse effects, nomogram

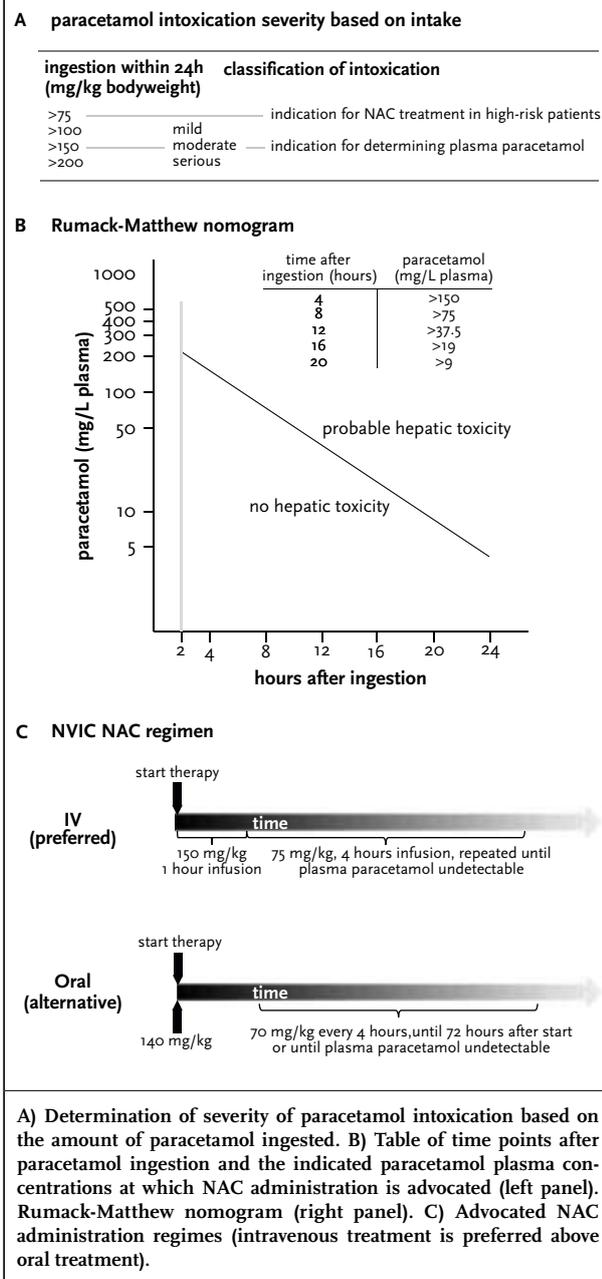
INTRODUCTION

In the Netherlands, overdose with paracetamol forms the largest group of medicine overdoses reported to the Dutch Poisons Information Centre (NVIC).¹ Worldwide and especially in adults, the analgesic paracetamol is often intentionally taken in overdose, potentially resulting in severe morbidity and mortality.² The main clinical risk of high doses of paracetamol is liver failure, due to the hepatotoxic effects of the paracetamol metabolite

N-acetyl-para-benzoquinone imine (NAPQI).³ In the US, 39-49% of all cases with acute liver failure in the period 1998-2003 were attributed to paracetamol overdose.⁴ The most efficacious way to prevent paracetamol-induced hepatotoxicity is the timely administration of the antidote N-acetylcysteine (NAC). The toxic paracetamol metabolite NAPQI can normally be inactivated in the liver by conjugation with glutathione. When high amounts of paracetamol are ingested, the normal glutathione amount in liver cells is not adequate to inactivate all formed NAPQI, resulting in hepatotoxicity. NAC, an acetylated cysteine residue, is a precursor of glutathione, and NAC administration results in increased hepatic glutathione concentrations.⁵ Already in the 1970s, experiments and trials with NAC showed the superiority of NAC above other cysteine derivatives, mainly in terms of less side effects. In the UK, NAC treatment started as intravenous (IV) administration, while in the US oral administration was preferred.⁶ Even today studies are being performed to determine the advantages of the various administration routes in terms of drug efficacy and cost efficiency,⁷ although oral administration is usually more frequently accompanied by nausea and vomiting.⁸

Treatment decision-making for acute paracetamol overdose is usually based on the Rumack-Matthew nomogram (with its subsequent adaptations). Plasma paracetamol levels above the indicated treatment line in the nomogram indicate the need for NAC treatment (*figure 1*).⁹ In the US and the Netherlands this so-called treatment line in order to decide whether patients should be treated with NAC starts at a plasma paracetamol concentration of 150 mg/l at 4 hours post-ingestion. In the UK the guidelines concerning NAC administration after single acute ingestion of paracetamol have recently been adapted. The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK now recommends NAC

Figure 1. Regimen of NAC administration recommended by the Dutch National Poisoning Information Center (NVIC)^{4,6}



treatment at plasma paracetamol concentrations of 100 mg/l at 4 hours post-ingestion.¹⁰ From 1995 till 2012 two treatment lines of 100 mg/l or 200 mg/l were used with the choice of line depending on the clinical condition of the patient.^{10,11} The main reasons for this change were concerns over a small number of patients who developed hepatotoxicity despite plasma paracetamol concentrations below the Rumack-Matthew treatment line and the simplification of treatment decisions and, as a consequence, risk minimisation.^{10,12} Although similar

cases of failure of the existing nomogram were already described in 1998,¹³ the UK nomogram was only adapted in 2012. The main drawback of the new UK guideline for NAC administration in paracetamol overdose is that more patients will be treated with NAC, potentially resulting in an increased risk of adverse effects of NAC. Also, there will be a considerable increase in hospitalisation with an additional increase in health care costs.¹⁴

The adaptation of the Rumack-Matthew nomogram in the UK leads to the question whether Dutch clinicians should also change their treatment guidelines. In this review, we will provide an overview on the risks and benefits of NAC administration based on prospective and retrospective studies published in the last ten years. We will discuss the considerations to alter treatment guidelines in line with the new UK guidelines. Finally we will end with a recommendation of treatment guidelines for the Dutch emergency departments.

ADVERSE DRUG REACTIONS OF N-ACETYLCYSTEINE

Between 2001 and 2013 several studies were performed in order to systematically obtain an overview of the adverse drug reactions (ADRs) of NAC infusion (table 1). The studies used for this review all concern human exposures and the studies were performed either in a case-controlled prospective manner, or in a more observational retrospective way. In nine of these ten studies NAC was administered intravenously after ingestion of high doses of paracetamol. In one study all patients who were given NAC, irrespective of paracetamol ingestion, were analysed.¹⁵ The studies were performed in the UK, Denmark, Malaysia and Australia. NAC infusion rates were equal in nine studies (150 mg/kg for 15 minutes, 50 mg/kg for 4 hours, 100 mg/kg for 16 hours), while in the study by Whyte *et al.*¹⁵ the infusion rate was 300 mg/kg for 20-21 hours, with no further specification. Several symptoms appeared uniformly in these studies, including anaphylactoid symptoms such as rash, flushing and pruritus, gastrointestinal symptoms such as nausea and vomiting, and pulmonary symptoms such as shortness of breath and bronchospasm, chest pain, angioedema and hypotension (table 1). Strikingly, the incidence of ADRs differed highly among the studies, ranging from 9% of the NAC-treated patients¹⁵ to 77%.¹⁶ The variation in the relative number of each specific adverse effect was also considerable between the different studies. For instance, nausea and vomiting ranged from 3-70%, while flushing, pruritus and rash differed in range from 2-31%. An important factor in this variation is probably the difference in classification of ADRs. In the work by Pakravan *et al.*¹⁶ a distinction is made between minimal, moderate and

Table 1. Overview of studies on adverse reactions of NAC

Study	Country	Type of study	n	% ADR	Symptoms reported
Yamamoto, 201328	UK	Prospective	660	12	Flushing (2%), pruritus (2%), urticaria (2%), angio-oedema (1%), breathlessness (2%), chest pain (1%), bronchospasm (1%), tachycardia (1%), nausea (3%) and vomiting (3%)
Schmidt, 201332	Denmark	Retrospective	1218	19	Flushing, pruritus and rash (31%), bronchospasm, hypotension and angio-oedema (13%), nausea and vomiting (4%)
Carroll, 201341	UK	Prospective	71	68	Rash (11%), severe anaphylactoid reaction (23%), shortness of breath (3%), nausea and vomiting (52%)
Zyoud, 201043	Malaysia	Retrospective	139	68	Flushing, rash and pruritus (16%), headache, dizziness and convulsion (34%), chest pain, bronchospasm and coughing (17%), cardiovascular reactions (7%), nausea and vomiting (39%)
Zyoud, 201044	Malaysia	Retrospective	125	68	Flushing (7%), rash (6%), headache (15%), dizziness (11%), chest pain (6%), nausea (15%) and vomiting (12%)
Pakravan, 200816	UK	Prospective	169	77	Flushing (25%), pruritus (20%), rash and urticaria (4%), wheezing and bronchospasm (7%), dyspnoea (14%), chest pain (7%), dizziness (8%), fever (5%), nausea (70%) and vomiting (60%)
Waring, 200845	UK	Prospective	362	41	Anaphylactoid reactions (15%), localised skin reactions at the infusion site (1%) and gastrointestinal reactions (25%)
Whyte, 200715	Australia	Retrospective	399	9	Anaphylactoid reactions (2%), most of the adverse drug reactions in the other patients (8%) consisted of nausea and vomiting.
Lynch, 200417	UK	Prospective	64	48	Flushing (22%), pruritus (6%), rash (30%), bronchospasm (6%), nausea and vomiting (22%)
Schmidt, 200140	Denmark	Retrospective	529	10	Flushing, rash and pruritus (8%), bronchospasm, angioedema and nausea (3%)

In this table the studies performed between 2001-2013 are listed (column 1), country where the study was performed (column 2), type of study (prospective or retrospective, column 3), number of included cases (n, column 4), percentage of cases presenting with adverse reactions (% ADR, column 5) and percentage of specific adverse reactions (column 6).

severe symptoms. Minimal symptoms represent either no reaction or mild gastrointestinal symptoms. About 60% of the patients have minimal symptoms, while 70% of the patients present with nausea, suggesting that nausea was often considered a mild symptom. It is plausible to assume that in other studies these patients were considered to be asymptomatic. It is relevant to realise that gastrointestinal symptoms such as nausea and vomiting are frequently observed in paracetamol intoxication, making a causal relation between NAC administration and gastrointestinal symptoms difficult.

ANAPHYLACTOID REACTIONS

Despite the variation in incidence of the ADRs in the different studies, it is obvious that NAC infusion may cause anaphylactoid reactions such as flushing, rash, pruritus and bronchospasms, symptoms which are usually not associated with paracetamol ingestion (table 1). These symptoms usually appear within 1-2 hours after starting NAC infusion. In the study by Lynch *et al.*¹⁷ 71% of the patients show ADRs within the first 15 minutes after infusion. Lynch *et al.* used a high infusion rate suggesting that a high infusion rate, and hence a high NAC

concentration, is associated with anaphylactoid reactions. It is thought that NAC induces histamine secretion by both mononucleocytes and mast cells, as has been shown by *in vitro* experiments and studies in humans.^{16,18} In addition, prophylactic antihistamine treatment can abolish NAC-induced anaphylactoid reactions.¹⁹ Interestingly, in six of the ten studies, an association has been shown between ADR severity and plasma paracetamol concentrations. Adverse effects to NAC were less frequent at higher plasma paracetamol concentrations, suggesting that plasma paracetamol protects against NAC-induced ADRs. Treatment of ADRs induced by NAC consists of temporary or permanent discontinuation of NAC infusion and/or by administration of antiemetics, antihistamines, corticosteroids or selective β_2 -adrenoreceptoragonists (table 2). Management guidelines for discontinuation of NAC treatment after development of NAC side effects are not objective, although it has been suggested that respiratory symptoms, angio-oedema or hypotension are indications to (temporarily) discontinue NAC infusion.²⁰ All clinical studies discussed in this paper mention that treatment of NAC-induced ADRs is well achievable and that no patients developed serious side effects requiring intensive care. These studies indicate that there is no absolute contraindication for NAC treatment.

SEVERE AND FATAL CASES FOLLOWING THERAPEUTIC NAC DOSES AND OVERDOSES

In the literature two patients with asthma and paracetamol overdose are described with severe adverse reactions following therapeutic administration of NAC.^{21,22} Both developed a respiratory arrest after NAC infusion. Treatment of these patients consisted of administration of salbutamol and corticosteroids, and respiratory support. One patient finally died due to severe hypoxic brain injury.

At supratherapeutic doses of NAC severe or fatal adverse effects may occur. Administration errors of NAC occur in the treatment of paracetamol intoxication, and might lead to supratherapeutic NAC concentrations. In the literature

only a few cases are reported of patients receiving high doses of NAC and showing severe clinical symptoms, despite the treatment of millions of patients with NAC. Furthermore, in these cases direct causality between high NAC levels and the observed clinical symptoms was not obvious, as was also discussed by the presenting authors. In some cases the observed symptoms could also be attributed to the paracetamol intoxication. Clinical symptoms which were observed included severe hypotension, coagulation disorder, cardiac arrest,^{23,24} seizures progressing to cerebral oedema, uncal herniation and severe brain injury.^{25,26} In one specific case, initial high levels of NAC were related to an atypical haemolytic-uraemic syndrome although the time course of haemolysis was not in accordance with the NAC concentration when the NAC elimination half-life is taken in account.²⁷

Table 2. Overview of therapy provided after adverse reactions of NAC

Study	Corr. with [paracetamol]p	Time of onset of ADRs (min.)	Infusion regime	NAC administration criterion	Therapy
Yamamoto, 2013 ²⁸	n.a.	0 to 122 (median 32.5)	IV 150-50-100	Unknown	(Temporarily) stop NAC infusion (5%), antiemetics (5%), antihistamines (4%), corticosteroids (2%), inhaled B2 agonists (1%), adrenaline (1%)
Schmidt, 2013 ³²	Yes	n.a.	IV 150-50-100	To all patients with paracetamol intoxication	Temporarily stop NAC infusion (12%), antihistamines (17%), corticosteroids (15%), switch from NAC to oral L-methionine (1%), no treatment (1%)
Carroll, 2013 ⁴¹	Yes	n.a.	n.a.	Rumack-Matthew	Unknown
Zyoud, 2010 ⁴³	Yes	<60 minutes	IV 150-50-100	n.a.	(Temporarily) stop NAC infusion (22%), IV corticosteroids (16%), IV chlorpheniramine following skin reactions (9%), oxygen nebuliser (7%, only with bronchospasm), antiemetics (39%)
Zyoud, 2010 ⁴⁴	No	15 to 60	IV 150-50-100	n.a.	(Temporarily) stop NAC infusion (21%), IV corticosteroids (14%), IV chlorpheniramine (8%, only with skin reactions), oxygen nebuliser (6%, only with bronchospasm), antiemetics (51%)
Pakravan, 2008 ⁴⁶	Yes	n.a.	IV 150-50-100	n.a.	(Temporarily) stop NAC infusion (11%)
Waring, 2008 ⁴⁵	Yes	50 to 112 (median 75)	IV 150-50-100	Rumack-Matthew	Temporarily stop NAC infusion and antiemetics (20%), temporarily stop NAC infusion (38%), antihistamines (14%), corticosteroids (1%), inhaled albuterol (1%)
Whyte, 2007 ¹⁵	n.a.	n.a.	IV 300	Based on dose/symptoms	Unknown
Lynch, 2004 ¹⁷	n.a.	<60, 71% of patients <15	IV 150-50-100	n.a.	Temporarily stop NAC infusion (34%), IV chlorpheniramine (44%), corticosteroids (42%), nebulised salbutamol (6%, only with bronchospasm)
Schmidt, 2001 ⁴⁰	Yes	n.a.	IV 150-50-100	To all patients with paracetamol intoxication	

In this table the same studies as in table 1 are listed (column 1). The association between adverse NAC reactions and the paracetamol plasma level is indicated (column 2), time of onset of adverse NAC reaction in minutes (column 3), NAC infusion regime provided (IV 150-50-100 = intravenous infusion, 150 mg/kg during 15 minutes, 50 mg/kg during 4 hours and 100 mg/kg during 16 hours, IV 300 = intravenous infusion, 300 mg/kg during 20 hours; column 4), criteria to infuse NAC (column 5) and percentage of cases given a specific therapy (column 5). N.a. = not available.

RATE OF INFUSION

Since most NAC ADRs appear within one hour after the start of NAC infusion, it is suggested that ADRs can be induced by high NAC infusion rates. This suggestion is underpinned by the observation that ADRs often diminish after discontinuation of NAC infusion (*table 2*) and by the fact that reducing infusion speed is used to reduce ADRs.²⁸ Few studies with the focus on infusion rate and adverse NAC reactions have been performed. Kerr *et al.*²⁹ performed a randomised prospective trial to compare the primary infusion rate of 150 mg/kg IV NAC in 15 minutes versus 60 minutes, followed by 50 mg/kg for 4 hours and 100 mg/kg for 16 hours. Although a statistically significant reduction in ADRs was not observed, there was a trend toward decreased anaphylactoid reactions in the slower infusion group. There was no difference between the two groups in terms of efficacy of paracetamol intoxication treatment. Bateman *et al.*³⁰ compared a NAC infusion regime of 150 mg/kg for 15 minutes, 50 mg/kg for 4 hours and 100 mg/kg for 16 hours with a regime consisting of 2 hours of 100 mg/kg and 10 hours of 200 mg/kg. Their results convincingly show that lower initial NAC levels reduce the frequency of vomiting and anaphylactoid reactions. Although these results are promising in order to reduce side effects, further studies have to be performed to evaluate whether, in paracetamol intoxication, NAC administration in a slower infusion rate is as efficacious as in the standard infusion rate.

PROPHYLACTIC TREATMENT OF NAC ADVERSE DRUG EFFECTS

Although preventing ADRs by prophylactic administration of antiemetics and/or antihistamines seems reasonable, only a few data are available regarding this treatment. In a study by Wright *et al.*³¹ it was shown that only high doses of the antiemetic metoclopramide (20-50 mg IV) prevented emesis after orally administered NAC, while lower doses of metoclopramide (5-15 mg intravenously) had no effect. However, the patients treated with the high dose of metoclopramide had adverse side effects of metoclopramide, thus high-dose treatment with metoclopramide is not really a good option. In a study of Schmidt *et al.*³² prophylactic treatment (with antihistamines with or without steroids) administered to patients with previous ADRs to NAC resulted in lower incidence of NAC-related ADRs compared with untreated patients (15% vs. 42%). Nevertheless, further studies on prophylactic treatment to prevent or attenuate ADRs are required to evaluate the efficacy of this treatment.

DISCUSSION

In order to decide how to treat patients with paracetamol overdose, the following issues should be weighed. First, the efficacy of paracetamol intoxication treatment is the most important factor. In a meta-analysis, Green *et al.* studied the efficacy of NAC treatment in paracetamol intoxication.³³ Patients treated with either IV or oral NAC before 8-10 hours after paracetamol ingestion developed hepatotoxicity in 5.7% of the cases, and hepatotoxicity in these cases was not severe. When NAC was administered late (>8 hours) after paracetamol ingestion, hepatotoxicity was more frequent and more severe. Kerr *et al.*²⁹ showed that NAC treatment started before eight hours after paracetamol ingestion does not result in hepatotoxicity at all. One should bear in mind that the paracetamol plasma level at a certain time after paracetamol intake is an important parameter for starting NAC treatment. The time of paracetamol ingestion is indicated by the patient or by an accompanying person and thus has some level of uncertainty in it. This may lead to an underestimation of the severity of the paracetamol intoxication based on plasma paracetamol levels at a certain time point, with an associated risk of under-treatment of the patient. Most publications on NAC administration for paracetamol intoxication do not comment on the reliability of the estimation of the time of ingestion. Medical professionals, however, should be aware of this uncertainty when treating patients with paracetamol intoxication. Bateman *et al.* state that they and others have previously reported that most episodes of hepatotoxicity occur as a result of late presentation to hospital, and this should be a target for public health intervention.^{15,17,34-36} We underpin this statement. Interestingly, recent studies suggest that new biomarkers, which indicate hepatotoxicity, may become good predictors for the indication of NAC treatment in patients with a late presentation.³⁷

Secondly, the prevalence and severity of adverse effects of the treatment are important for the choice of therapy. For instance, methionine can also be effective as paracetamol antidote, but it has been reported that it may be less reliable in the treatment of a paracetamol intoxication than NAC.³⁸ There are doubts concerning the safety of late treatment with methionine, since methionine may aggravate hepatic encephalopathy. In addition, methionine may also induce nausea and vomiting.³⁹ Altogether, NAC is a safer treatment of paracetamol intoxication than methionine; this is also the case for patients with a known allergy for NAC. Also the choice when to start NAC therapy affects the total number of patients with NAC ADRs. In Denmark all patients with suspected paracetamol intoxication are treated with NAC, irrespective of the paracetamol plasma concentration. This may lead to unnecessary NAC exposure and accompanying ADRs. However, in this review two studies from Denmark are included, which do not seem to show higher numbers of ADRs compared with studies in countries which strictly

follow the paracetamol plasma level for NAC treatment (*table 1*). Surprisingly, the highest rates of ADRs were observed in studies performed in the UK. This may be attributed to differences in valuing clinical symptoms or in differences in ethnic composition of patient populations. Schmidt *et al.*³² show that in their cohort there is a difference in the rate of ADRs between people of Danish and non-Danish origin.

In order to reduce side effects of NAC administration, it is possible to adapt the NAC administration regimen for patients with increased risk for NAC ADRs. Side effects may occur more frequently in patients who are asthmatic, although only two of the ten studies mentioned in *table 1* show a significant correlation between asthma and rate of ADRs. In the study by Schmidt and Dalhoff⁴⁰ it was shown that asthmatic patients are 2.9 times more likely to develop ADRs, although there is no difference in severity of ADRs between asthmatic and non-asthmatic patients. Carroll *et al.*⁴¹ showed an increased prevalence of anaphylactoid reactions (flushing, urticarial, angioedema or shortness of breath) in asthmatic patients. Six of the studies mentioned in *table 1* showed an inverse correlation between paracetamol plasma levels and severity of NAC ADRs. Thus, paracetamol plasma level seems to be a factor for developing NAC ADRs. The precise mechanism behind the protective capacity of high paracetamol plasma levels against NAC ADRs is not fully understood, although studies suggest that paracetamol inhibits NAC-induced histamine secretion by mast cells.^{16,18} The adaptation of NAC administration regimen mainly consists of lowering the initial NAC dose, as was shown by Bateman *et al.*³⁰

Thirdly, minimisation of costs is an important factor in the choice of treatment. Costs of treatment are determined by factors such as the kind of therapy provided, ADRs induced by the treatment, length of hospitalisation, and treatment efficacy. Martello *et al.*⁷ compared the costs of oral versus IV NAC treatment, and came to the conclusion that patients who received IV NAC treatment had decreased health costs compared with oral treatment due to reduced length of hospital stay, while there was no difference between the efficacy of both treatments.

In the Netherlands, if we were to follow the new UK guidelines for NAC treatment (at a plasma paracetamol concentration of 100 mg/l instead of 150 mg/l at 4 hours after ingestion), this would imply an increase in the number of patients treated with NAC, and hence an increase in health costs. Furthermore, it is highly uncertain whether the number of patients with liver toxicity would decrease when the nomogram line is lowered from 150 mg/l to 100 mg/l at 4 hours post-ingestion, since the 150 mg/l line is already a safety line based on the original Rumack-Matthews 200 mg/l nomogram.⁴² Recently, a study was performed in the UK where patient admission and estimated costs were compared before and after the introduction of the new UK

NAC administration regime. An increase of 13.2% of NAC use in admitted patients was observed during the period of study, with an estimated annual cost increase of £ 8.3 M (€ 10 M). A life would be saved every 2.1 years, resulting in a cost-per-life saved of £ 17.4 M (€ 21 M) and this might even be higher because not all the information is available to perform a more precise calculation.³⁴ Unfortunately, for the Dutch situation no suitable data are available to perform an adequate cost-benefit analysis. The reason is that in Dutch hospitals the information needed for such analyses is not properly archived.

CONCLUSIONS

In view of the fact that NAC treatment has been and still is given to millions of people with a paracetamol intoxication, and the fact that adverse effects of NAC treatment are generally mild, there is no reason to avoid NAC administration in paracetamol intoxication. The seriousness of paracetamol intoxication, with life-threatening hepatotoxicity, outweighs the possibility to develop severe adverse effects from NAC administration. It is important to realise that severe adverse effects of NAC are seldom observed. Patients with increased risk for NAC ADRs are primarily severe asthmatic patients, although NAC administration is not considered a contraindication in these patients, and patients with a known allergy for NAC. In these patients, severe NAC ADRs can be minimised by prophylactic treatment with antihistamines or corticosteroids, or adjustment of the NAC infusion rate. On the other hand, over-treatment with NAC, for instance by lowering the current nomogram treatment line, is not recommended, since the 150 mg/l nomogram sufficiently discriminates between patients at risk for hepatotoxicity and patients who are not at risk. Furthermore, in the Netherlands the paracetamol concentration of 150 mg/l at 4 hours post-ingestion nomogram has already been operational for more than 30 years and has proved to be very safe. We therefore recommend the continuation of the 150 mg/l at 4 hours post-ingestion nomogram, which is in use in Dutch hospitals. When the time point of ingestion is uncertain, it is important that treatment with NAC is started until more information is gathered on the severity of the paracetamol intoxication, for example, by drawing another blood sample to evaluate whether the paracetamol concentration is increasing or that the paracetamol metabolism is already hampered by paracetamol-induced liver injury.

In *figure 1A* and *1B* the indication for NAC administration following paracetamol ingestion is provided. Patients who have taken an acute oral paracetamol dose of >150 mg/kg (or >75 mg/kg in high-risk groups) should be treated with NAC.¹¹ The recommended NAC administration regimen is given in *figure 1C*.

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