Predicting the Need for Continuation of N-acetylcysteine Treatment among Acute Paracetamol Overdose Patients with Psi Parameter

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ABSTRACT

Objective: AcetaCalc was used to evaluate Psi's accuracy in predicting cases that required prolonged N-acetylcysteine (NAC) therapy, as well as Psi's optimal cut-off.

Materials and Methods: This is a retrospective study of patients with acute paracetamol overdose who were treated with NAC at Siriraj Hospital between 2007 and 2016. The Psi parameter was calculated using the Acetacalc after entering paracetamol concentrations, blood sampling times, and NAC onset times. Indications for NAC continuation is in accordance with the guidelines, which recommended that NAC treatment be continued if the follow-up aminotransferase reached 50 U/L or higher.

Results: We enrolled 403 patients, the proportion of NAC prolongation was 50.4 %. Psi was shown to be a significant predictor of NAC prolongation ($p < 0.001$) with area under the receiver operational characteristics curve 0.766 (95% confidence interval (CI) 0.719-0.813). The Psi cutoff with highest Youden index was 1.757 mM-hour. The sensitivities and specificities of the cutoff were 0.517 (95% CI 0.449-0.585) and 0.940 (95% CI 0.898-0.965), respectively.

Conclusion: Psi parameter calculated through AcetaCalc is a useful tool for the prediction of cases where extension of NAC therapy beyond the standard regimen is indicated.

Keywords: Paracetamol; acute liver injury; N-acetylcysteine; prognosis; psi (Siriraj Med J 2022; 74: 658-665)

INTRODUCTION

Hepatotoxicity from paracetamol overdose remains a significant healthcare burden in Thailand and worldwide.[1] The most definitive treatment for the overdose is the timely and sufficient use of N-acetylcysteine (NAC), administered as a 300 mg/kg intravenous infusion over 21 hours.[1] When NAC therapy is started early, usually within 8 hours after the overdose, hepatotoxicity can effectively be minimized. Factors that can contribute to the development of hepatotoxicity secondary to paracetamol overdose are a high initial serum paracetamol concentration and a delay in the initiation of NAC treatment. Studies have shown that the risks of hepatotoxicity (defined by aminotransferase concentration ≥ 1,000 U/L) when NAC is initiated before 8 hours after ingestion can range from 3.5-7.7%. That risk increases progressively to 10.3-22.2 % when NAC is given at 10-16 hours post ingestion. Subsequently, it can be as high as 12.9-45.1% when NAC is given later than 16 hours after ingestion.[1,2]

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In addition, even in instances where paracetamol-induced hepatitis has already occurred, NAC therapy beyond the initial 21-hour period has been shown to reduce the severity of hepatotoxicity, as well as the rate of complications and mortality.[3,4] The indication for prolonging NAC therapy is an aminotransferase concentration of 50 U/L or higher.[5] It is recommended that the infusion be maintained until aspartate aminotransferase concentration has decreased to half of the peak level or lower.[6] On the other hand, the assessment of hepatotoxicity risks has many interacting clinical parameters such as the time of ingestion, the dose of ingestion, the time to treatment initiation with NAC, and the initial paracetamol level.[1,2] These parameters make up a risk profile which, with the right tool namely the Psi parameter, can be individualized and extended to predict the need for prolonged NAC treatment in specific patients.[1,7] The Psi (Greek letter Ψ) parameter is a composite calculation that accounts for both timed serum paracetamol concentration and the time after ingestion until N-acetylcysteine therapy is initiated. It was developed based on a toxicokinetic model as a quasi-trapezoidal area-under–the-curve of paracetamol concentration and the duration of hepatic glutathione deficiency.[8,9] (Fig 1) Its purpose is to individualize each patient's hepatotoxicity risk which can help clinicians determine the disease prognosis with reasonable accuracy. Overall, the Psi parameter reflects exposure to N-acetyl-p-benzoquinone imine (NAPQI), paracetamol's hepatotoxic metabolite, prior to starting NAC. Higher paracetamol concentration and longer delay in NAC treatment results in a higher calculated Psi parameter.[10,11] The details about mathematical derivation of Psi can be found in previously published works.[8,9] Consequently, the utility and accuracy of the Psi parameter in predicting individual risk of hepatotoxicity have been substantiated in various publications.[9-12] In the Thai population, high Psi (≥ 5.0 mM-hour) predicts hepatotoxicity with sensitivity of 96.9% (95% confidence interval (CI) 84.3-99.4) and specificity of 91.5% (95% CI 87.1-94.5).[10] However, despite such excellent clinical data, its complex calculations severely limit its usefulness in busy clinical settings.[9] In 2021, AcetaCalc, a web-based application developed jointly by the Faculty of Medicine Siriraj Hospital, Mahidol University and Mahidol University International College, has made this task much simpler. Users can simply input paracetamol concentration, time after ingestion when paracetamol level was obtained, and the time to NAC initiation and the application can calculate Psi parameter, as well as other predictors of hepatotoxicity. This application can be accessed at https://sunsern.github.io/aceta-calc/#/tabs/info. In the present study, we evaluate the use of Psi parameter, which is derived with AcetaCalc, as a predictor of the need for prolonging NAC treatment among patients with acute paracetamol overdose.

MATERIALS AND METHODS

This was a retrospective review of patients who presented at Siriraj Hospital, Bangkok, Thailand from January 1, 2007 to December 31, 2016 with paracetamol overdose. Inclusion criteria included age 12 years or older and treatment with N-acetylcysteine. Patients were excluded if they fit one of the following criteria: mixed ingestion, staggered ingestion (overdose process longer than 1 hour) and abnormal initial aminotransferase concentrations. A standard case record form was used to extract the information from the medical records, including age, gender, type and dose of the overdose, initial paracetamol concentration, blood chemistry results, treatment, follow-up blood chemistry results and clinical outcomes. The study protocol was approved by the Siriraj Human Research Protection Unit (MU-MOU CoA 472/2021).

The Psi parameter was calculated using the AcetaCalc Application. Input data for Psi calculation included time of blood sampling (hours after overdose), measured paracetamol

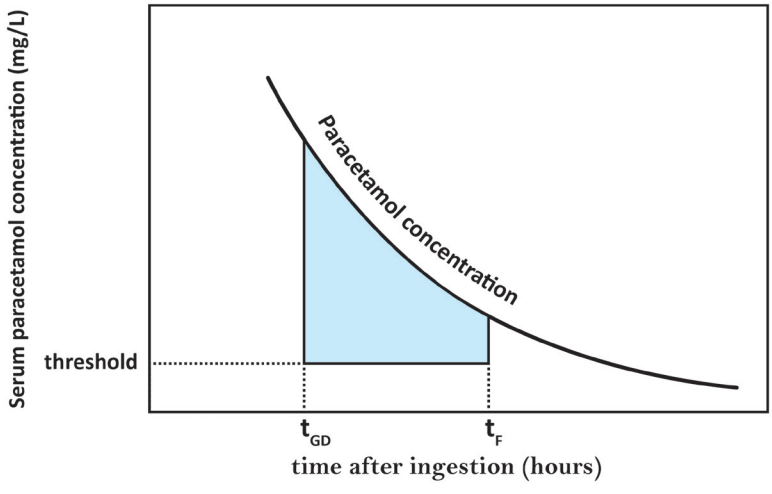

Fig 1. Calculation of Psi parameter
Shaded area represents Psi parameter, tGD = time of glutathione depletion (6 hours is used as a default), tF = time of N-acetylcysteine initiation, threshold = threshold paracetamol concentration (45 mg/L is used)

concentration (mg/L) and lag time from overdose to NAC initiation (hours). Patients fulfilled the primary outcome of the study if the follow-up aminotransferase concentration was 50 U/L or higher, indicating the need for prolonged NAC therapy. Hepatotoxicity was defined as an aminotransferase concentration of 1,000 U/L or above. For the purpose of comparison, extrapolated paracetamol concentration at 4 hours post ingestion ($[APAP]_{4hour}$) was calculated using the formula $[APAP]_{4hour} = C_t/2e^{>-(0.693/4)t}$ where C_t represents measured paracetamol concentrations and t indicated the time interval (hours) from ingestion to blood sampling.

During the study period, intravenous NAC was the mainstay treatment for acute paracetamol overdose. The standard regimen for NAC administration was 150 mg/kg in one hour, 50 mg/kg in four hours and 100 mg/kg in 16 hours, consecutively. Oral administration was used only when the patients had a contraindication to IV NAC or could not tolerate the intravenous regimen. NAC prolongation was carried out by the administration of 150 mg/kg/24 hours of NAC intravenously. In actual clinical settings, the decision to start and then discontinue the prolonged NAC therapy was based on each clinician's perception of whether a significant elevation and subsequent decline of aminotransferase had occurred.

Statistical analysis

Descriptive data were displayed as frequencies with percentages and means with 95% confidence intervals (CI). However, medians with interquartile ranges (IQR) were used for variables with non-normal distributions. Differences were tested with Student's t-test or Mann-Whitney U test. Proportions were tested with a chi-squared test or Fisher's exact test. Factors or co-variates with $p \geq 0.05$ were further tested with multiple logistic regression in order to predict cases that required NAC prolongation. Multiple logistic models were assessed using backward stepwise multiple logistic regression. Receiver operating characteristics (ROC) curve and area under the curve (AUC) with 95% CI were used to assess the accuracy of Psi in predicting the outcome. The optimal cutoff was selected using the highest Youden index.[13] Validities of the predictions were evaluated by sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) with 95% CIs. Statistical analyses were performed using PASW 18 (Release version18.0.0) statistical program.

The sample size estimation for this study was performed based on the "rule of 10 for logistic regression".[14] Since we expected no more than four factors or co-variates in the predicting model, the minimal number of events in this study was estimated to be 40. Therefore, we required at least 40 cases that fulfill the indication for NAC prolongation to achieve a desirable statistical power.

RESULTS

During the study period, 1,286 patients presented to Siriraj Hospital due to paracetamol overdose. Among these, 883 cases were excluded. Therefore, we enrolled 403 into the analyses. (Fig 2) The subjects consisted of 332 females (82.4%) with a median age of 23 years (IQR 2028, range 13-62). Compared with the group receiving standard NAC duration, the NAC prolongation group had significantly higher extrapolated four-hour paracetamol concentrations,

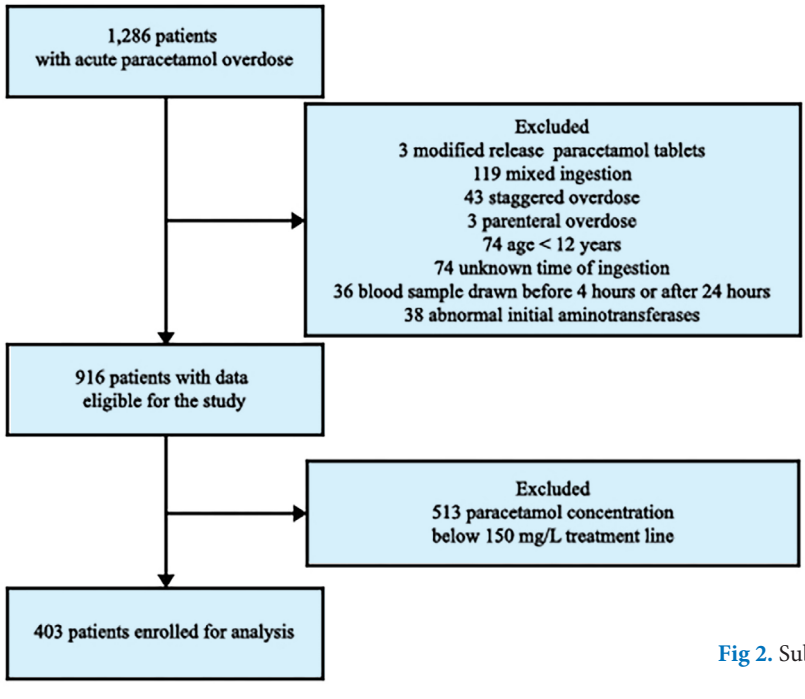

Fig 2. Subject enrollment flow

Psi values, peak aminotransferase concentrations and proportion of hepatotoxicity and longer time-to-NAC-therapy, while having a significantly lower proportion of patients who received decontamination with activated charcoal. (Table 1) None of the patients experienced liver failure and no mortality occurred in this study.

Both the Psi parameter and the decontamination with activated charcoal were entered into the multiple logistic regression analysis. However, activated charcoal yielded no statistical significance (*p*-value 0.401) in the multiple logistic regression model (Model 1). Activated charcoal was removed since the resultant Nagelkerke R^2 of Model 2 with Psi parameter alone was higher than Model 1 (a higher score meant better fit of the model). (Table 2) When using the equation Logit P = -0.918 + (0.824 * Psi), Psi was a significant predictor of the need to prolong NAC treatment (*p*-value <0.001). Fig 3 demonstrates the scatter plots of $[APAP]_{4hour}$ and onset of NAC therapy, as classified by cases with and without the need for NAC prolongation. There is a clear pattern of the need for NAC prolongation in cases with high $[APAP]_{4hour}$ or delayed NAC onset.

The ROC curve for Psi in predicting NAC prolongation has an AUC of 0.766 (95%CI 0.721-0.806) and is shown in Fig 4. The highest Youden index was found at the Psi concentration of 1.757 mM-hour. The 1.757 mM-hour cutoff yielded a sensitivity 51.7% and a specificity 94.0%. When the cutoff was increased to 2.948 mM-hour, the specificity achieved a maximal value of 99.5%. (Table 3)

TABLE 1. Demographic and clinical characteristics of the overall subjects, groups with and without N-acetylcysteine (NAC) prolongation.

Characteristics	Overall (403 case)	NAC prolongation (203 cases)	No NAC prolongation (200 cases)	P-value
Female (frequency (%)	332 (82.4)	167 (82.3)	165 (82.5)	0.951
Age (median (IQR) (years)	23 (20-28)	24 (21-27)	23 (19-31)	0.387
Paracetamol dose (mg/kg)	281.7 (200.0-400.0)	294.1 (202.0-408.2)	256.4 (200.0-378.8)	0.250
$[APAP]_{4hour}$ (mg/L)	237.3 (181.4-355.5)	356.0 (289.3-474.1)	195.5 (170.6-222.8)	<0.001
NAC onset (hours)	7 (5-9)	8 (6-10)	5 (4-7)	<0.001
Psi (mM-hour)	0.476 (0.001-2.250)	1.873 (0.001-4.995)	0.001 (0.001-0.639)	<0.001
Initial AST (U/L)	13 (10-18)	16 (11-31)	14 (10-30)	0.742
Initial ALT (U/L)	11 (8-17)	15 (8-31)	14 (9-30)	0.861
Peak AST (U/L)	37 (22-79)	76 (54-457)	24 (19-30)	<0.001
Peak ALT (U/L)	41 (19-86)	86 (60-572)	26 (15-37)	<0.001
Peak INR	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.048
Activated Charcoal	87 (21.6)	22 (10.8)	64 (32.5)	<0.001
Hepatotoxicity	45 (11.2)	45 (22.2)	0 (0)	<0.001

Abbreviations: NAC, N-acetylcysteine; IQR, interquartile range; $[APAP]_{4hour}$, Extrapolated 4-hour paracetamol concentration; AST, aspartate aminotransferase; ALT, alanine aminotransferase

TABLE 2. Logistic regression models of Psi and activated charcoal administration as predictors of N-acetylcysteine prolongation.

Models	Factors or co-variates	Regression coefficients	P-value	-2 log likelihood	Nagelkerke R^2
1	Psi	0.786	<0.001	423.678	0.285
	Activated charcoal	-0.253	0.401		
2	Psi	0.824	<0.001	424.394	0.378

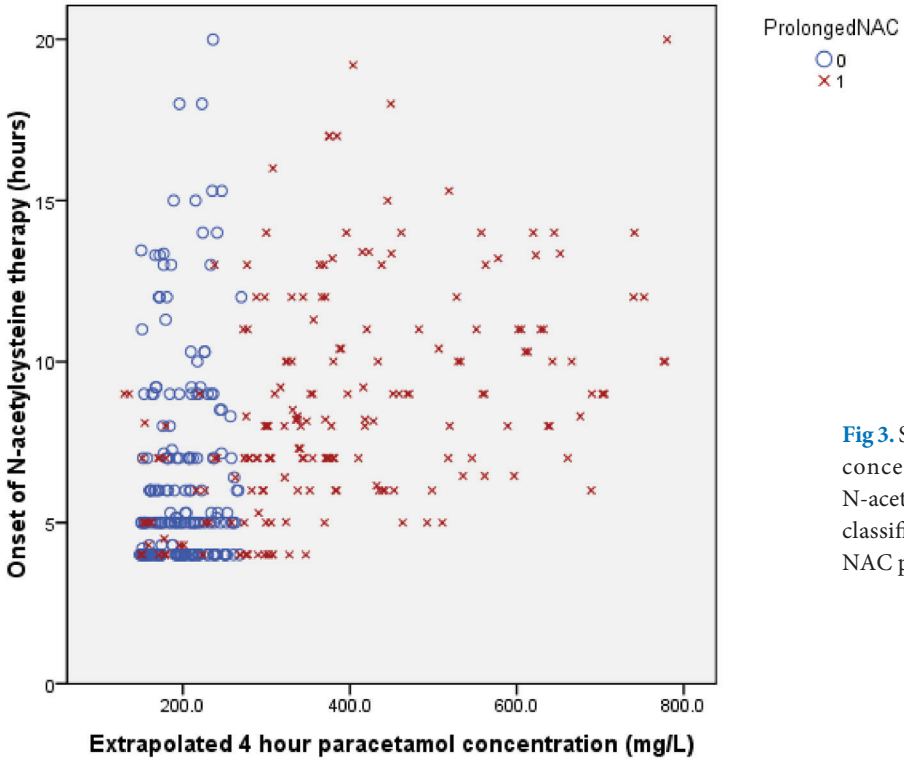

Fig 3. Scatter plots of extrapolated paracetamol concentration at 4 hours and onset of N-acetylcysteine (NAC) treatment (cases are classified as cases with (1) and without (0) NAC prolongation)

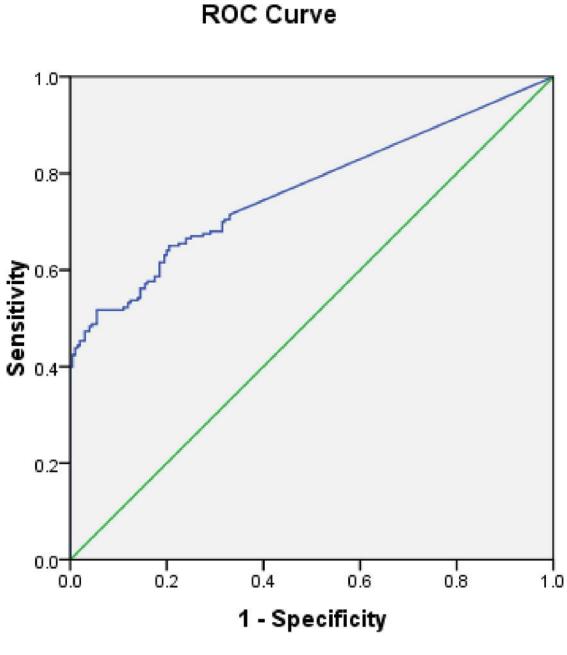

Fig 4. Receiver operating characteristics curve of Psi for predicting prolongation of N-acetylcysteine therapy

TABLE 3. Diagnostic validities of Psi for predicting N-acetylcysteine prolongation at various cutoff concentrations (* remarks cutoff psi concentration with highest Youden index).

Psi cutoff (mM-hour)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
2.948	39.9 (33.4-46.8)	99.5 (97.2-99.9)	79.80 (11.22-567.87)	0.60 (0.54-0.68)
1.757*	51.7 (44.9-58.5)	94.0 (89.8-96.5)	8.62 (4.90-15.16)	0.51 (0.44-0.60)
0.257	70.9 (64.3-76.7)	67.0 (60.2-73.1)	2.15 (1.73-2.67)	0.43 (0.34-0.55)
0.001	100.0 (98.1-100.0)	0.0 (0.0-0.019)	100.0 (100.0-100.0)	-

Abbreviations: CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio

DISCUSSION

NAC therapy for paracetamol overdose is one of the most studied antidotal treatments, as apparent by the numerous guidelines for its administration. When given early, its efficacy in preventing hepatotoxicity is well-established. Currently, it is most often given in either a two-bag (200 mg in four hours and 100 mg in 16 hours) or a three-bag (150 mg/kg in one hour, 50 mg in 4 hours and 100 mg/kg in 16 hours) regimen over a period of 21 hours.[1,2] Serum paracetamol concentration and time-to-NAC therapy are two regularly assessed clinical parameters for clinicians when prognosticating the outcome of patients with paracetamol overdose.[2,8,10] The availability of these information makes the derivation of Psi parameter possible. Because the treatment regimens are so well adopted by clinicians, the associated demands for healthcare resources such as the frequency of laboratory monitoring efforts, the amount of antidote needed, as well as the patient's length of stay can often be reasonably predicted. However, in a subset of patients, paracetamol-induced hepatotoxicity can occur despite the completion of a standard NAC administration. In these cases, the continuation of NAC has been shown to significantly reduce mortality and complications. Postulated mechanisms of the action include NAC acting as an inflammatory modulator, increasing oxygen delivery and utilization and improving blood flow in the microvasculature.[1,3,4] According to the current guideline on the treatment of acute paracetamol poisoning, NAC continuation is recommended when the aminotransferase is elevated, as determined by AST or ALT of 50 U/L or higher.[1,5] Despite the seemingly low value, we believe that this cutoff offers maximal safety for patients with paracetamol induced hepatotoxicity. Therefore, we used this value to select cases for the primary outcome of this research. NAC continuation means intravenous infusion of NAC at the rate 150 mg/kg/24hours after completing the standard 21-hours NAC regimen.

In this study, the Psi parameter is shown to be an accurate predictor of NAC prolongation. The ROC's AUC of 0.766 implies that Psi has an acceptable accuracy in discriminating cases with and without the need for NAC prolongation. Although decontamination with activated charcoal is also significantly associated with the need for NAC prolongation, we postulate the mechanism to be the reduction of serum paracetamol due to activated charcoal's effects which, in turn, affects the calculation of the Psi value. Subsequently, when activated charcoal is eliminated from the logistic regression model, the Psi parameter remains as a sole and adequate predictor of the need for NAC prolongation. Our study illustrates the tendency for increasing need of prolonging NAC therapy as a function of higher paracetamol concentration and greater delay in NAC administration (Fig 3). Similarly, Cairney et al, reported a phenomenon whereby incidences of acute liver injury, as defined by aminotransferase > 150 U/L, gradually increased as a function of paracetamol nomogram groups. The incidence was 6% in the 0-100 mg/L nomogram group and progressed to as high as 27% in the > 500 mg/L nomogram group. The rates of acute

liver injury were lower in patients who were treated with NAC within 8 hours.[15] Of note, the term 'nomogram group' in this study is similar to the $[APAP]_{4hour}$ concentration groups in our study.

We proposed that the Psi cutoff of 1.757 mM-hour be used as the criterion to predict the need for NAC prolongation, since it yielded good specificity, although the sensitivity was mediocre. (Table 3) On the other hand, the 2.948 mM-hour cutoff had very high specificity, but the sensitivity became unacceptably low. The cutoff of 0.257 is shown in Table 3 because it is the second lowest concentration cutoff, next to 0.001 mM-hour. The cutoff value of 0.001 mM-hour is also significant because it has 100% sensitivity for the need for NAC prolongation, in concordance with previous findings that Psi of 0.001 mM-hour has a very high sensitivity for hepatotoxicity (aminotransferase > 1,000 U/L).[12]

The findings in our study have relevant clinical implications. Firstly, when Psi is calculated at the onset of treatment, physicians can expect to have to continue NAC therapy beyond the standard regimen if its value is 1.757 mM-hours or higher. This has significant ramification on the expected length of stay in the hospital and suggests that, in these cases, the reimbursement scheme may need to be adjusted. Secondly, when Psi is at its lowest possible value of 0.001 mM hour the probability of requiring NAC beyond the routine protocol should be very low since the value signifies early NAC treatment and low paracetamol concentration. Furthermore, the omission of a follow-up aminotransferase level after completion of the standard NAC therapy can also be justified based on such reasoning. Thirdly, our study shows that decontamination with activated charcoal can significantly reduce the need for NAC continuation beyond the routine protocol. This recapitulates the findings of previous studies and reiterates the importance of adequate gastric decontamination.[16-18]

The limitations of this study are in its retrospective nature. The data in medical records are intended for clinical services, and some errors in information obtained from the medical records may exist. The most important piece of information that can affect the result of this study is the time of paracetamol overdose, since it is a reference point from which the time of blood sampling and NAC initiation are calculated. In this study, a large number of subjects were excluded because they did not fulfill the requirement for Psi application. However, we do not expect them to result in any distortion of the results. For the future, we suggest that the study question is re-evaluated in a prospective observational study.

CONCLUSION

Psi parameter, a composite value of paracetamol concentration, time of blood sampling and onset of N-acetylcysteine treatment, is a useful tool to help clinicians predict the need for the continuation of NAC treatment beyond the standard regimen. The Psi parameter can be derived conveniently with the use of a computer application.

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