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ORIGINAL ARTICLE

Population pharmacokinetic–pharmacodynamic modelling to describe the effects of paracetamol and N-acetylcysteine on the international normalized ratio

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SUMMARY

Paracetamol is one of the most common pharmaceutical agents taken in self-poisonings, and can increase the prothrombin time (PT) through liver injury, and in overdose without hepatic injury by reducing functional factor VII. PT is a measure of hepatic injury used to predict and monitor hepatotoxicity, reported as the international normalized ratio (INR). The antidote for paracetamol poisoning, N-acetylcysteine (NAC), has been reported to have an effect on the PT. This analysis included patients from a retrospective case series, a prospective inception cohort of paracetamol and psychotropic (control) overdoses, and a cross-over clinical trial. A population pharmacokinetic–pharmacodynamic model describing the pharmacodynamic effects of paracetamol and NAC on the INR was developed in Phoenix NLME. The dataset included 172 patients; the median age was 22 years (range 13–71 years). A one-compartment model with first-order input and linear disposition best described paracetamol pharmacokinetics. The population mean estimate of the concentration that induced a response halfway between the baseline and maximal pharmacological effect of paracetamol was 1302 μmol/L (242), the maximum effect of paracetamol was 0.534 (202; from baseline) and the maximum effect of NAC was 0.325 (9.03; from baseline). Both paracetamol and NAC contributed a pharmacological effect to the elevation of INR. The estimated paracetamol concentration that induced a response halfway between the baseline and maximal pharmacological effect was within the range of plasma paracetamol values studied, fivefold greater than the maximum therapeutic concentration, suggesting that an elevated INR would not be expected within the therapeutic range. Simulated 24 and 48 g paracetamol overdoses with NAC administration produced INR values (50th percentile) that reached the upper limit of, or exceeded, the reference range.

Key words: clinical pharmacology, international normalized ratio, modelling, N-acetylcysteine, paracetamol (acetaminophen), Phoenix NLME, population pharmacokinetic–pharmacodynamic, prothrombin time.

INTRODUCTION

Paracetamol is a widely used over-the-counter analgesic and one the most common therapeutic agents taken in overdose.[1,2] Paracetamol can cause severe hepatotoxicity in overdose.[3] Although the most significant biochemical abnormality observed in paracetamol overdose is the marked increase in alanine aminotransferases, significant effects on synthetic and metabolic liver function also occur.[3] Prothrombin time (PT) is a measure of hepatic synthetic function, and thus is used clinically as an indication for antidote treatment and monitoring.[4–6]

PT is a biochemical measure of the extrinsic pathway of coagulation, quantified as the time until there is conversion of prothrombin to thrombin and thus clot formation.[7] Clotting factors that contribute to the PT include factors I (fibrinogen), II, V, VII, IX and X, all of which are synthesized in the liver.[7] PT is standardized by calculating the international normalized ratio (INR) according to the thromboplastic reagent specific to the laboratory where ISI is the international sensitivity index of the thromboplastin used.[7]

It has been reported that paracetamol overdose prolongs the PT even when there is no detectable hepatic injury.[6,8–10] The time-course of abnormal INR in paracetamol overdose patients and reduced production of individual clotting factors, in particular factor VII, have been described.[6]

A later study also observed a decrease in the prothrombin index (equivalent to an increase in the INR) in patients with paracetamol poisoning without hepatocellular injury; however, the authors concluded that the decrease in prothrombin index was a result of the direct effects of N-acetylcysteine (NAC; rather than

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paracetamol).[11] This conclusion was largely based on the statistical correlation between the increase in INR and time of NAC infusion, but not time of paracetamol ingestion.[11] The previously documented effect of paracetamol on coagulation factor production was not explored.[11,12] As all patients received NAC, and the effect of paracetamol is delayed, more sophisticated analysis is required to differentiate the independent effects of NAC and paracetamol on the INR.[12] The study carried out by Whyte *et al.*[6] identified the increase in INR after paracetamol overdose in the absence of NAC. From this, it was concluded that the increase in INR is due to a functional factor VII deficiency as a direct result of inhibition of factor VII activation by paracetamol. The aim of the present study was to describe the effects of paracetamol and NAC on the INR.

RESULTS

Patients

Of the 172 patients, there were 198 cases (due to multiple dosing events in some patients), 76 (38%) were male, and the median age was 22 years (range 13–71 years). The median dose of paracetamol ingested was 12 g (range 0–75 g). The median paracetamol plasma concentration measured was 222 μmol/L (0–2774 μmol/L). From the 198 cases, there were a total of 908 observations; 621 paracetamol plasma concentrations and 287 INR (mean of 3.1 pharmacokinetic observations and 1.5 pharmacodynamic observations per case).

Population pharmacokinetic analysis

The pharmacokinetics of oral paracetamol were best described by a one-compartment model with first-order input and linear disposition. The population mean estimates (CV%) of the pharmacokinetic parameters lag time (t_{lag}), absorption rate constant (k_a), volume of distribution (V), and clearance (Cl) were 0.328 h (0.692 h), 4.57/h (25.4/h), 12.9 L (7.30 L) and 2.40 L/h (5.94 L/h), respectively. The population pharmacokinetic parameter estimates for the base, full and final covariate models, with CV% (and 95% CI for the final model) are given in Table 2.

Population covariate analysis

The effects of the covariates age and sex were evaluated for the final pharmacokinetic model. Neither covariate warranted inclusion in the final model after a stepwise covariate search. Imputing data (the replacement of missing data with substituted values) is a common method used when <10% of the population is missing covariate data. In the current study, two cases were missing age and sex, comprising <3% of the total dataset, therefore covariate data for these cases was imputed. Age was imputed using the population median value (22 years) and sex was imputed based on the output of a random number generator in Microsoft Excel 2007, Microsoft, Redmond, WA, USA (Table 2).

Table 1 Patient demographics

	Overdose cases		Cross-over clinical trial	All
	Paracetamol	Controls		
Patients, *n* (%)	151 (76)	8 (4)	39 (20)	198 (100)
Sex male, *n* (%)	56 (37)	1 (13)	19 (49)	76 (38)
Median (range)				
Age (years)	22 (13–71)	33 (22–49)	22 (19–31)	22 (13–71)
Dose of paracetamol ingested (g)	15 (0–75)	–	4.8 (3–7.8)	12 (0–75)

Table 2 Population mean estimates of pharmacokinetic model parameters

Model parameter Fixed effects	Final model Estimate (CV%)
t_{lag} (h)	0.328 (0.692)
k_a/(h)	4.57 (25.4)
V (L)	12.9 (7.30)
Cl (L/h)	2.40 (5.94)
Random effects	**CV% (RSE%)**
Interindividual variability	
t_{lag}	108 (13.0)
k_a	139 (12.3)
V	5.82 (13.0)
Cl	12.1 (13.0)
Residual error*	
Plasma paracetamol	77.1
Akaike Information Criterion (AIC)	7850

*Estimated residual standard deviation.

Cl, clearance; CV%, coefficient of variation; k_a, absorption rate constant; t_{lag}, lag time; V, volume of distribution.

Table 3 Population mean estimates of pharmacodynamic model parameters

Model parameter	Final model	
Fixed effects (units)	Estimate (CV%)	[95% CI]
k_{e0}/(h)	0.041 (73.4)	[–0.18–0.099]
E_0 (–)	1.06 (2.29)	[1.01–1.11]
E_{maxP} (–)	0.534 (202)	[–1.59–2.65]
EC_{50P} (μmol/L)	1302 (243)	[–4919–7522]
E_{maxNAC} (–)	0.325 (9.03)	[0.267–0.382]
EC_{50NAC} (mg/L)	0.01 (fixed)	
Random effects		**CV% (RSE%)**
Interindividual variability		
E_0		12.8 (13.3)
E_{maxP}		2.46 (18.3)
EC_{50P}		51.1 (13.5)
E_{maxNAC}		19.6 (15.2)
Residual variability*		
INR		0.00788

*Estimated residual standard deviation.

CI, confidence interval; CV%, coefficient of variation; E_0, baseline effect; EC_{50P}, concentration of NAC yielding $E = ½ E_{max}$; E_{maxNAC}, the maximum effect (E) that N-acetylcysteine can produce; E_{maxP}, maximum effect that paracetamol can produce; INR, international normalized ratio; RSE, relative standard error.

Population pharmacodynamic analysis

In this combined population pharmacokinetic–pharmacodynamic analysis, the control group was not treated differently to the paracetamol cases in the analysis of the data. The control group pharmacodynamic data were included to improve the precision of estimation of the baseline INR parameter. A modified baseline E_{max} model with effect compartment best described the inhibition of the synthesis of vitamin K-dependent coagulation factors by paracetamol. The population mean estimate (CV%) of the E_0 (baseline INR) was 1.06 (2.29), EC_{50} of paracetamol was 1302 μmol/L (242), the E_{max} of paracetamol (increase in INR from baseline) was 0.534 (202; from baseline) and the E_{max} of NAC (increase in INR from baseline) was 0.325 (9.03). The population parameter and random effects estimates for the pharmacodynamic model, with coefficients of variation (CV%) are given in Table 3.

Model evaluation

Visual fit of plots and AIC were used to discriminate between models. There was little to no apparent visual improvement in model fit with the addition of covariates nor a significant decrease in AIC. Scatter plots of plasma concentrations and INR versus population predicted (PRED) values are shown in Fig. 1, indicating goodness of fit; the data-points are mostly distributed along the line of identity. The relative standard error (RSE) of the population prediction was graphically described by conditional weighted residuals (CWRES) plotted against PRED plasma concentrations and INR, as shown in Fig. 2; both having CWRES within ± 2, indicating good model fit.[20] Percentiles (5th, 50th and 95th) of the simulated data from the final model were calculated (using the original dataset) in Phoenix NLME, and shown with observed plasma and INR data as visual predictive checks (VPC) in Fig. 3. The population estimated INR adequately predicts the observed 50th percentile. Simulations from the final model were carried out to investigate the effect of various overdoses (12, 24 and 48 g) of paracetamol and treatment with NAC on the INR, as shown in Fig. 4 (as 5th, 50th and 95th percentiles). INR values (50th percentile) after 12-g or 24-g overdose (without NAC) were within the reference range. The simulated 24-g and 48-g overdoses (with NAC) produced INR values (50th percentile) that reached the upper limit of, or exceeded, the reference range.

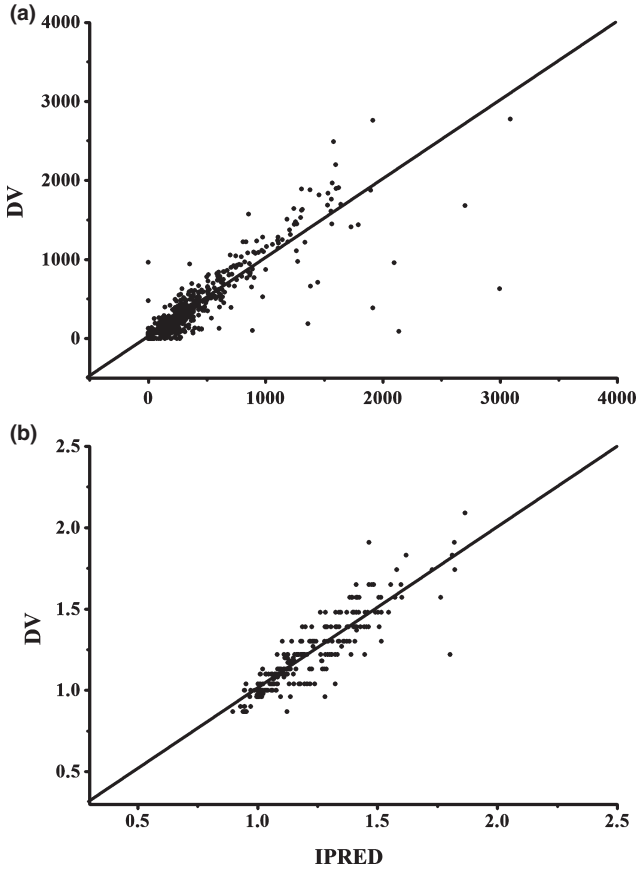

Fig. 1 (a) Observed plasma concentrations (dependent variable (DV); μmol/L) versus individual predictions (IPRED; μmol/L) of paracetamol; and (b) observed international normalized ratio values (dependent variable (DV)) versus individual predictions (IPRED).

DISCUSSION

We have developed a population pharmacokinetic–pharmacodynamic model from observed plasma paracetamol concentrations and INR values. A one-compartment model with first order input and linear disposition adequately described the population pharmacokinetic of paracetamol in overdose. The present study is the first to quantify the effect of paracetamol on INR in overdose by the estimation of the pharmacodynamic parameters, E_{maxP} and EC_{50P}.

In a previous study involving a subset of these patients Whyte *et al.* described the effect of paracetamol on INR in patients with paracetamol poisoning without hepatic injury.[6] From 143 admissions, there were 205 recorded INR observations, and 50% of all patients had an abnormal INR at some time during admission.[6] Dose ingested ($P = 0.01$) and nomogram-based risk ($P = 0.005$) were both correlated with the effect and antidote treatment with NAC was protective.[6] The amounts of antigenic and functional coagulation factors (VII, VIIIc and IX) were compared between the exposed (paracetamol overdose) patients and control (psychotropic overdose) patients. Factor VIIIc was not significantly different, and factor IX was slightly lower in the exposed patient group. Functional factor VII was much lower ($P = 0.005$), and also less than the total antigenic factor VII in exposed patients ($P = 0.03$).[6] The mechanism proposed was inhibition of the final vitamin-K dependent pathway in clotting factor synthesis.[6]

Later, another study described the same common phenomena of increased INR without hepatotoxicity after paracetamol poisoning, but attributed this to NAC, which was used as an antidote in all their cases.[11] A strong association was found between the decrease in prothrombin index (equivalent to an increase in prothrombin time or INR) and the start of NAC IV infusion.[11] The main criticism of this interpretation was that they had not considered the natural time-course of INR in paracetamol poisonings (blocking synthesis of factor VII would lead to a delayed INR rise with a potentially similar time course), and all of their 87 patients had received NAC treatment.[12]

Neither study quantified the effect by estimation of E_{max} and EC_{50}.[6,11,12] The model estimated of E_{maxP}, EC_{50P}, E_{maxNAC}, and

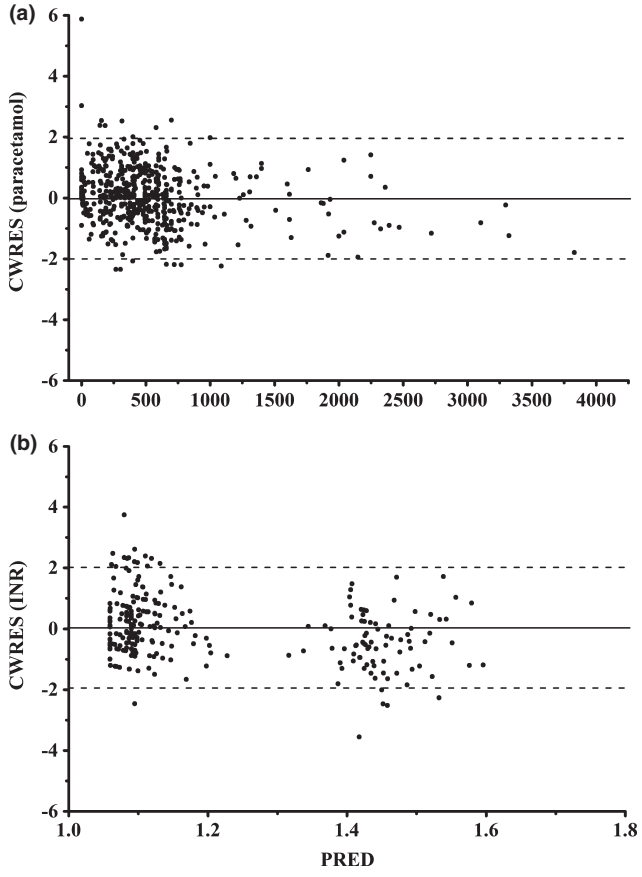

Fig. 2 (a) Conditional weighted residuals (CWRES) versus population predictions (PRED) of plasma concentrations (μmol/L) of paracetamol; and (b) conditional weighted residuals (CWRES) versus population predictions (PRED) of international normalized ratio (INR).

EC_{50NAC} adequately represent the relationship between paracetamol and NAC on the increase in INR. The estimate of EC_{50P} for paracetamol was 1302 μmol/L; more than fivefold greater than therapeutic C_{max} (29.9 μg/mL = 197.8 μmol/L), but a level commonly seen in overdose and within the range of plasma paracetamol concentrations in the study group.[21] The precision of estimation of EC_{50P} and E_{maxP} was poor because of identifiability issues in the model parameters associated with sparse sampling design, uncertainty surrounding the time of paracetamol ingestion and subsequent sampling times.

Further investigation into the estimation of paracetamol EC_{50P} is necessary in order to determine the minimum plasma concentration of paracetamol that can result in a clinically abnormal INR. Factor VII concentrations vary widely, and it is likely that the extent of paracetamol effect will be influenced by this baseline concentration. For example, those with subclinical liver disease might be anticipated to be more susceptible, and even small changes in factor VII concentrations might have important implications for those on anticoagulants. However, we were unable to explore such factors in this model, as we did not have baseline factor VII concentrations, and few people had comorbid conditions.

The effect of NAC we observed was less than paracetamol, with a maximum predicted effect of a 0.325 change in INR. Although the population mean value of paracetamol E_{max} was higher than that of NAC, the calculated 95% confidence intervals show no statistically significant difference in the magnitude of their effect on INR (Table 3). The simulations shown in Fig. 4 show the effect of paracetamol overdose and NAC treatment on INR. When comparing the 24-g overdose with the 24-g overdose with NAC treatment simulation (Fig. 4), it is apparent that NAC treatment is associated with a greater and more prolonged increase in INR.The mechanism of NAC anticoagulation is unclear, but has been hypothesized to be a result of the destabilization of disulphide bonds in clotting factors.[11,22] Further clinical studies exploring this effect in the absence of paracetamol are required for clarification.

The pharmacokinetic model broadly agreed with previously published data. The population mean (CV%) for t_{lag} was 0.328 h (0.692 h), k_a was 4.57/h (25.4/h), V was 12.9 L (7.30 L) and Cl was 2.40 L/h (5.94 L/h). The population estimate of volume of distribution is similar to that previously reported by our research group.[23] The estimate of clearance was lower than previously reported, and the estimate of absorption rate constant was greater than previously reported because of the inclusion of the absorption lag time parameter, t_{lag}.[24]

We have quantified the effect of paracetamol on INR by estimating E_{maxP} and EC_{50P}. The estimate of EC_{50P} for paracetamol was fivefold greater than therapeutic C_{max}, and within the range of plasma paracetamol values in the study group. The model supported an additional increase in INR from NAC; however, this effect is considerably smaller, and unlikely to be seen except in paracetamol overdose. Further studies exploring the effect of NAC in other settings and modelling potential paracetamol interactions with anticoagulated patients could be useful.

METHODS

Participants and study designs

Participants included in the study were from three different study groups, a retrospective case series and a prospective inception cohort study carried out in Newcastle, Australia, and a cross-over clinical trial carried out in Dunedin, New Zealand. A total of 172 patients contributing 198 cases were included in the dataset. Cases were defined as specific patient occasions; for example, a paracetamol overdose (exposed) case patient who had another occasion of poisoning that was also reviewed for the retrospective study would be two cases. Of these cases, 151 were from paracetamol overdoses, eight from psychotropic overdose (control) cases and 39 from a cross-over clinical trial.

The prospective inception cohort study (defined as the inclusion of patients at a common time point, e.g. at presentation of paracetamol overdose) included paracetamol overdose patients and psychotropic overdose patients as a control group.[6] After patients gave informed consent, blood samples were taken for coagulation factor analysis and to confirm the absence of hepatotoxicity, and to determine plasma paracetamol concentration.[6] The retrospective case series examined all admissions from January 1987 to March 1999, and patients who had ingested paracetamol and had a PT measured were included. Patients who had any biochemical evidence of hepatic injury (aspartate aminotransferase

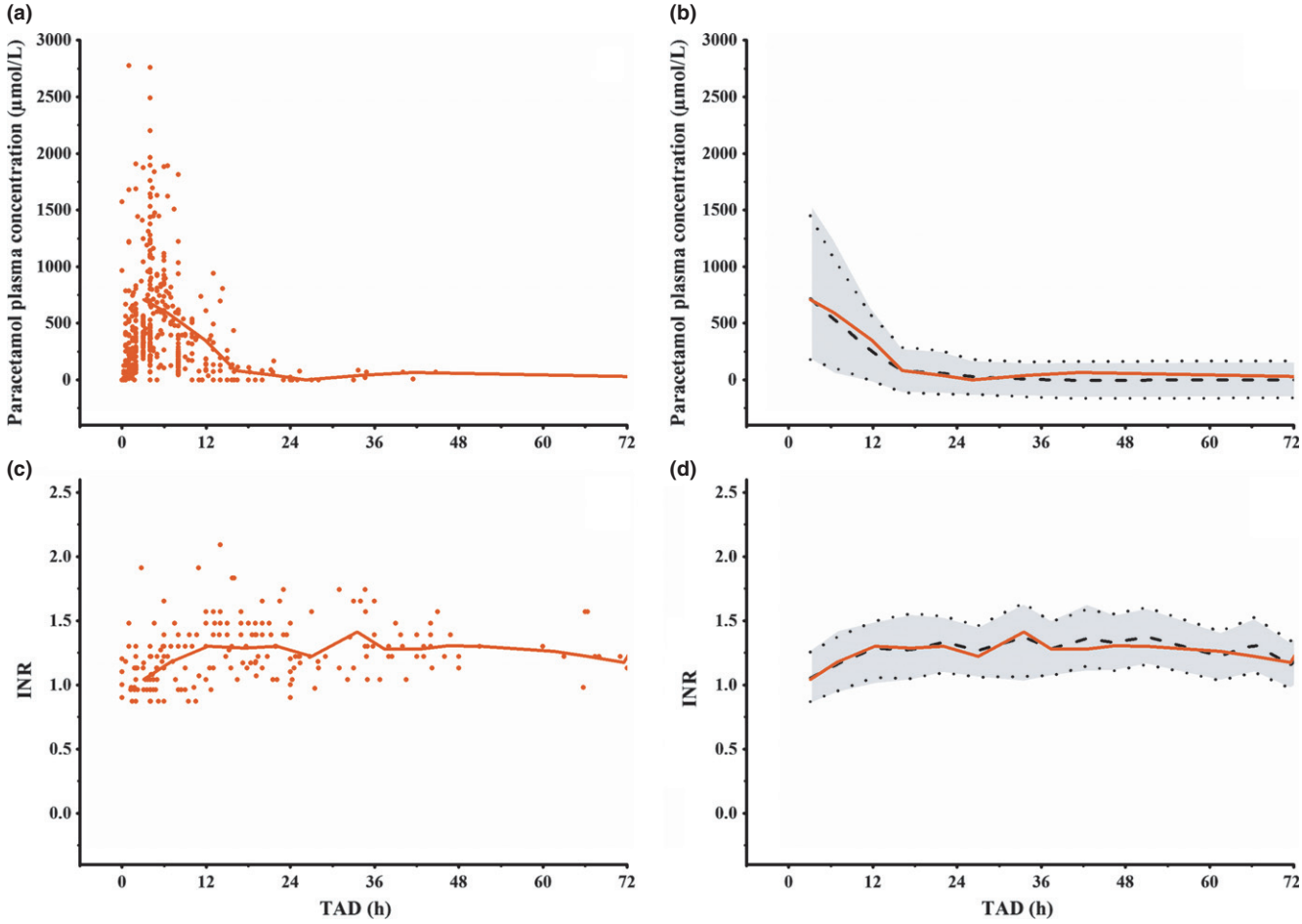

Fig. 3 Visual predictive check (VPC) for final pharmacokinetic–pharmacodynamic model. (a) Observed plasma paracetamol concentrations (µmol/L) (●), with 50th percentile (—) versus time (h). (b) Observed 50th percentiles (—), model predicted plasma concentrations 50th (—) 5th and 95th (····) percentiles with 95% confidence intervals (shaded area) versus time (h). (c) Observed international normalized ratio (INR; ●), with 50th percentile (—) versus time (h). (d) Observed 50th percentiles (—), model predicted INR 50th (—) 5th and 95th (····) percentiles, with 95% confidence intervals (shaded area) versus time (h). TAD, time after dose (h).

(AST) >35 U/L (reference range 1–35 U/L) or alanine aminotransferase (ALT) >40 U/L (reference range 1–40 U/L)) at any time during admission were excluded.[6] Patients taking anticoagulants (or coingested substances known to affect PT in overdose) were also excluded.[6,13,14] Whether patients received antidote treatment with NAC after paracetamol ingestion was recorded. The study was approved by the Hunter Area Research Ethics Committee.

The clinical trial included healthy adults aged 18–50 years scheduled for surgical removal of bilateral, symmetrically impacted, lower or lower and upper third molars (wisdom teeth).[15] The study had a randomized, double-blind, single-dose, cross-over design.[15] Patients were randomized to receive a single large dose (60 or 90 mg/kg) of oral paracetamol for the first surgery, and then received the other dose for the second (3 weeks later).[1,15] To ensure there was no paracetamol toxicity, blood concentrations were taken at 4 h as per the National Poisons Centre recommendations.[15,16] Blood samples were also taken at 24 h for full blood count, factor VII activity, PT, ALT and AST.[15] The trial was approved by the New Zealand Lower South Ethics Committee and registered with the Australian Clinical Trials Registry.

Bioanalytical methods

The Newcastle studies measured PT using Australasian Reference Thromboplastin (Westmead Hospital, Sydney, NSW, Australia; ISI of 0.98) or Innovin Thromboplastin (Dade-Bearing; Brisbane, QLD, Australia; ISI of 1.00). The PT were reported as INR using in-house pooled normal plasma for reference PT, and the laboratory normal range for INR was 0.87–1.26.[6] In the Dunedin study, all biochemical, haematological and coagulation tests (haemoglobin concentration, platelet count, ALT, AST, PT, factor VII activity and paracetamol plasma concentration) were carried out in the hospital laboratories by standard commercial methods.[15]

Population pharmacokinetic analysis

All modelling was carried out in Phoenix NLME (version 6.1; Pharsight, Mountain View, CA, USA) using quasi-random parametric expectation maximization as an approximation method.[17] One- and two-compartment models with first-order input and lag time were tested to describe the pharmacokinetics of orally

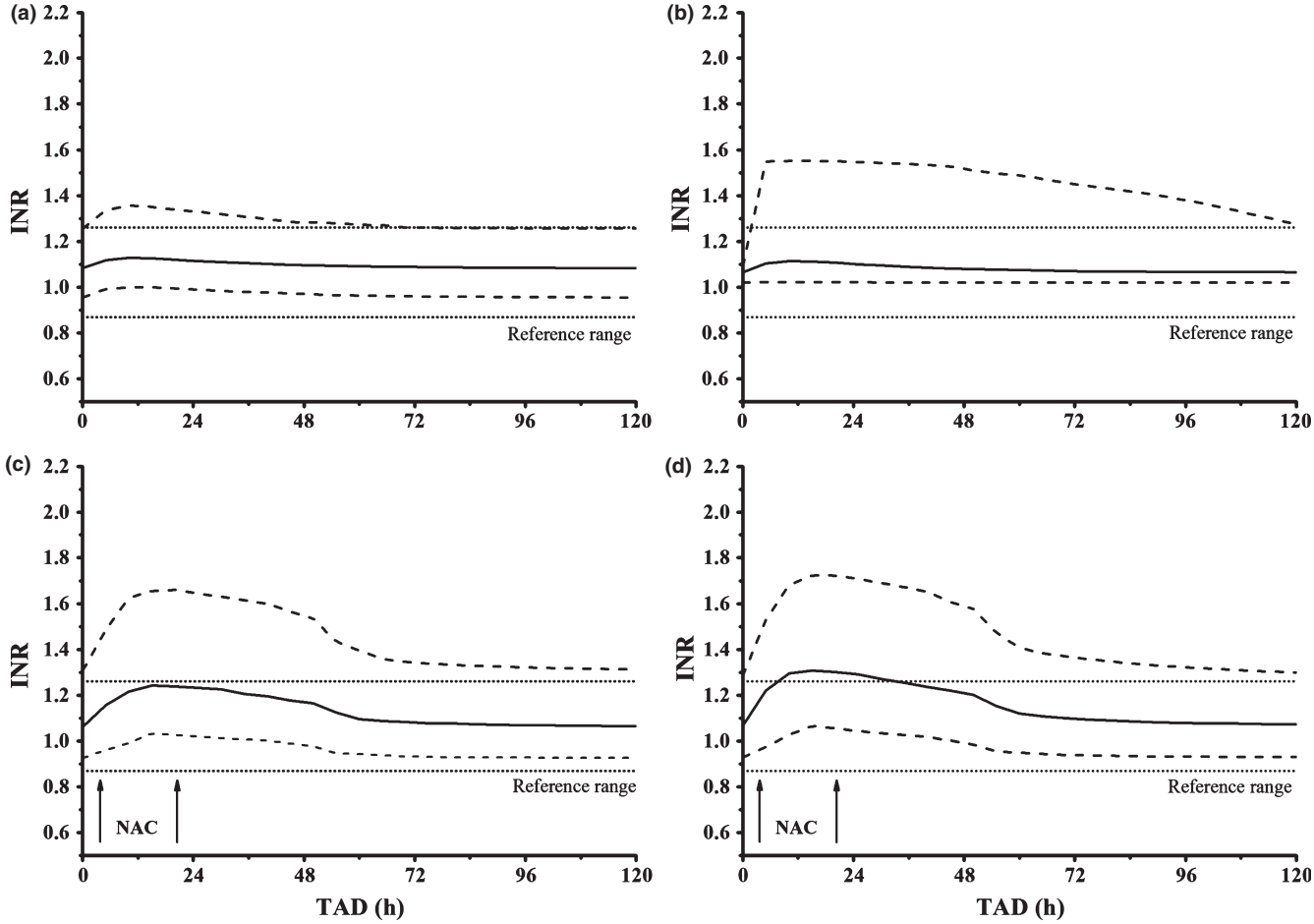

Fig. 4 Model simulated international normalized ratio (INR) values (dashed lines: 5th and 95th percentiles, solid lines: 50th percentiles) after paracetamol overdose of (a) 12 g, (b) 24 g and (c) 24 g with N-acetylcysteine treatment; (d) 48 g with N-acetylcysteine treatment. TAD, time after dose (h).

administered paracetamol plasma concentrations. Initial population parameter estimates for volume of distribution and clearance were obtained from non-compartmental analysis in Phoenix NLME. Interindividual variability of the pharmacokinetic parameters was modelled using an exponential random effects model. A mixed error model was used to describe the residual variability.

Population covariate analysis

The effects of the covariates of age and sex were evaluated for the final model. Age, a continuous covariate, was centred at the median value and was included in the model using a linear relationship. Sex, a categorical covariate, was incorporated using indicator variables. For the final pharmacokinetic model, stepwise forward addition followed by backward deletion was used. A covariate was considered significant when the addition of this covariate resulted in a decrease in the Akaike information criterion (AIC) of >6.635 ($P < 0.05$), and elimination of this covariate resulted in an increase in the AIC of >10.828 ($P < 0.01$). It was decided *a priori* that if >10% of study patients were missing any covariate data, that covariate was excluded from the covariate analysis. All pharmacokinetic estimates were fixed during pharmacodynamic modelling.

Population pharmacodynamic analysis

Potential pharmacodynamic measures for establishing the association between paracetamol and coagulation in overdose included INR, prothrombin complex activity (PCA) and activated factor VII. Each of these was assessed for an identifiable relationship in the modelling, and INR was found to be the most reliable. The pharmacodynamic relationship between paracetamol and INR was best described by a modified baseline E_{max} model with an effect compartment describing the time delay for clotting factor synthesis. To account for any change in INR as a result of treatment with NAC, a second E_{max} block was included in the equation, shown below.

$$E = E_0 + E_{maxP} \times C_{eP}(EC_{50P} + C_{eP}) + E_{maxNAC} \times C_{eNAC}(EC_{50NAC} + C_{eNAC})$$

where, E is the pharmacodynamic effect (INR); E_0 is the baseline effect (existing INR); E_{maxP} is the maximum effect (E) that paracetamol can produce (maximum increase in INR); EC_{50P} is the concentration of paracetamol yielding $E = ½\ E_{max}$; C_{eP} is the effect compartment concentration of paracetamol; E_{maxNAC} is the maximum effect (E) that NAC can produce (maximum change in INR); EC_{50NAC} is the concentration of NAC yielding $E = ½\ E_{max}$; and

C_{eNAC} is the effect compartment concentration of NAC. Interindividual variability on the pharmacodynamic parameters was modelled using an exponential random effects model. A mixed error model was used to describe the residual variability.

Patients treated with NAC during their hospital admission were included in the dataset. The time of beginning the NAC series of infusions (as per protocol) was recorded, but plasma samples were not collected or analysed for NAC concentrations. Subsequently, it was not possible to model the pharmacokinetics of NAC. Instead, a pharmacokinetic link model was used, with literature values for parameter estimates. The pharmacokinetics of NAC have been extensively studied. Studies by Brown *et al.* and Shen *et al.* have both shown that NAC displays three-compartment kinetics after intravenous infusion.[18,19]

Model evaluation

The improvement of fit of the model was evaluated using the AIC. Visual model evaluation was carried out by inspection of scatter plots of plasma concentrations and INR versus individual (IPRED) and population (PRED) predicted values. The relative standard error of the mean was graphically described by conditional weighted residuals (CWRES) plotted against population predicted (PRED) plasma concentrations and urinary amounts. To further evaluate the model, simulations of the final model were carried out in Phoenix NLME using the study dataset. Visual predictive checks (VPC) were created in OriginPro (version 8.5; OriginLab, Northhampton, MA, USA) showing the observed data and the simulated percentiles (5th, 50th and 95th) of model predictions. Simulations from the final model were carried out to show the effect of various overdoses (12, 24 and 48 g) of paracetamol and treatment with NAC on the INR.

Statistical analysis

Descriptive statistics of clinical data and patient demographics were carried out using STATA (version 11.2; StataCorp, College Station, TX, USA) Table 1.

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