

Population analysis of paraquat toxicokinetics in poisoning patients



THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Klinton Wunnepuk (1,2) , Fahim Mohammed (3), Indika Gawarammana (3), Xin Liu (1), Roger K. Verbeeck (4), Nicholas A. Buckley (3,5), Michael S. Roberts (1,6), Flora T. Musuamba (4)

(1) Therapeutics Research Centre, School of Medicine, University of Queensland, Brisbane, QLD, Australia, (2) Department of Forensic Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, (3) South Asian Clinical Toxicology Research Collaboration, Faculty of Medicine, University of Peradeniya, Sri Lanka, (4) Louvain Centre for Toxicology and Applied Pharmacology, Catholic University of Louvain, Brussels, Belgium, (5) Professorial Medicine Unit, University of New South Wales, NSW, Australia, (6) School of Pharmacy & Medical Science, University of South Australia, Adelaide, SA, Australia



Background and Objectives

Paraquat (PQ) is a commonly used herbicide that has caused many accidental or intentional deaths. Only a few studies have been done on PQ toxicokinetics (TK) in humans (1, 2). In this study a population TK analysis was performed to estimate the typical TK parameters and interindividual variability of PQ distribution in intoxicated patients. Potential covariates were explored as well.

Methods

- PQ plasma concentrations from 78 poisoning patients were used.
- A two-compartmental TK model with first-order absorption and first-order elimination was fitted to the data when choosing the basic structural model.
- An exponential model and combined model were used for inter-individual variability (IIV) and residual errors, respectively.
- The varying doses were imputed as covariates on the bioavailability factor.
- The median dose of PQ (10 g) was given as the amount administered to each patient.
- The logit of bioavailability factor (XF) was first estimated, and the bioavailability factor was subsequently regenerated using the following formula: $F=XF/(1+XF)$.
- K_a was fixed to 1 h^{-1} given that the reported mean T_{max} in human was 3 h.
- Model selection was based on objective function values, bootstrap derived standard errors, graphics and visual predictive checks (VPC).
- A TK model for PQ was developed using Phoenix NLME version 1.2.

Results

A total of 698 plasma concentrations from 78 PQ poisoning patients were included in TK analysis.

Table 1 Demographics of the patients enrolled in the population toxicokinetic

Characteristics	Toxicokinetic study Median (Range)
Male/Female (n)	52/26
Age (y)	28 (14-76)
Weight (kg)	51 (35-66)
sCr (mg/dl)	2 (0.3-12.6)
CL _{cr} (L/h)	1.89 (0.29-13.25)
Ingestion volume (ml)	50 (5-750)
Ingestion dose (g)	10 (1-150)

Fig. 1 Population toxicokinetics, goodness-of-fit/diagnostic plots.

- (A) Conditional weighted residuals versus time after ingestion
- (B) Conditional weighted residuals versus population predicted concentration
- (C) observed versus individual predicted concentrations
- (D) Observed versus population predicted concentrations

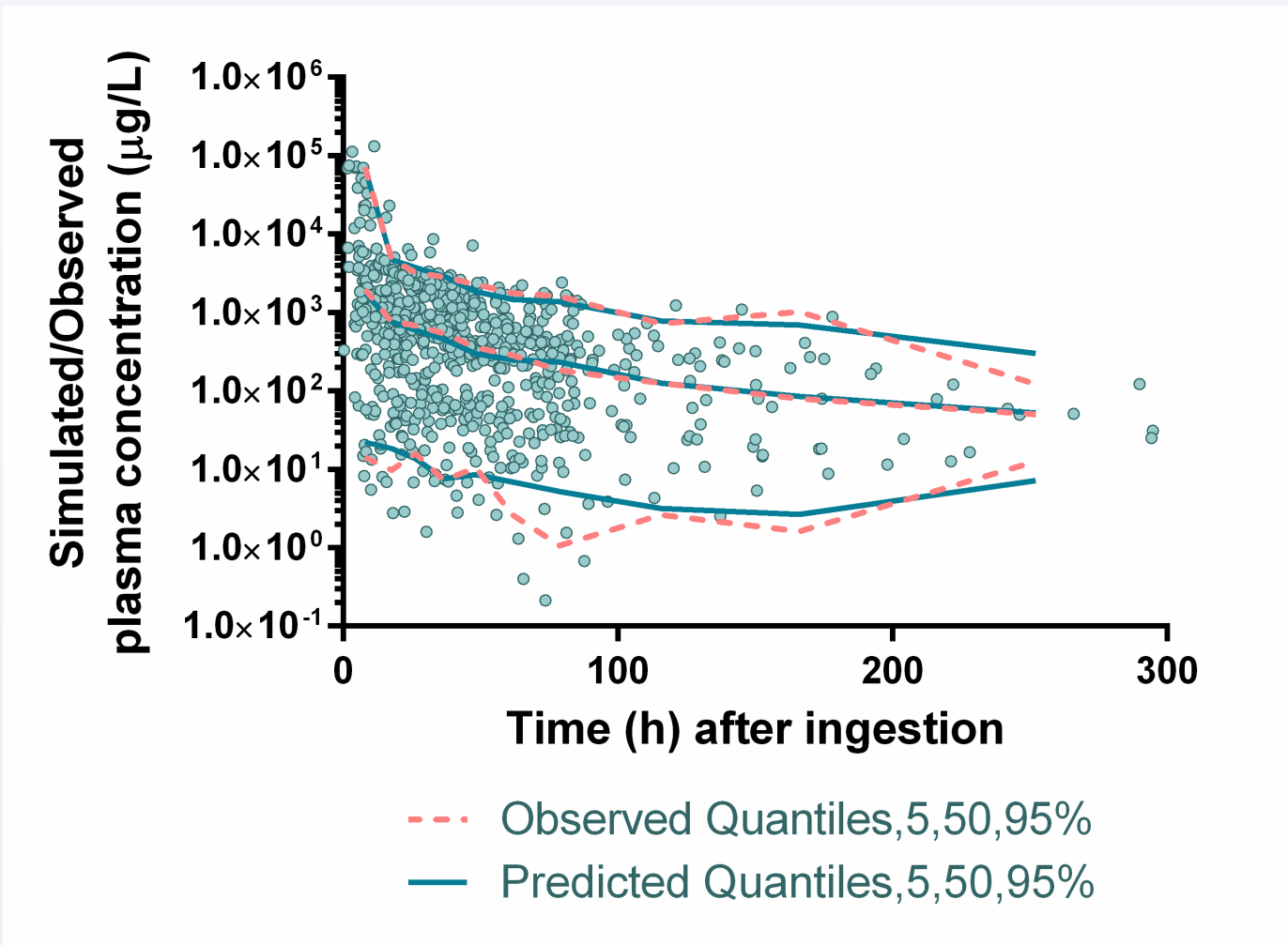
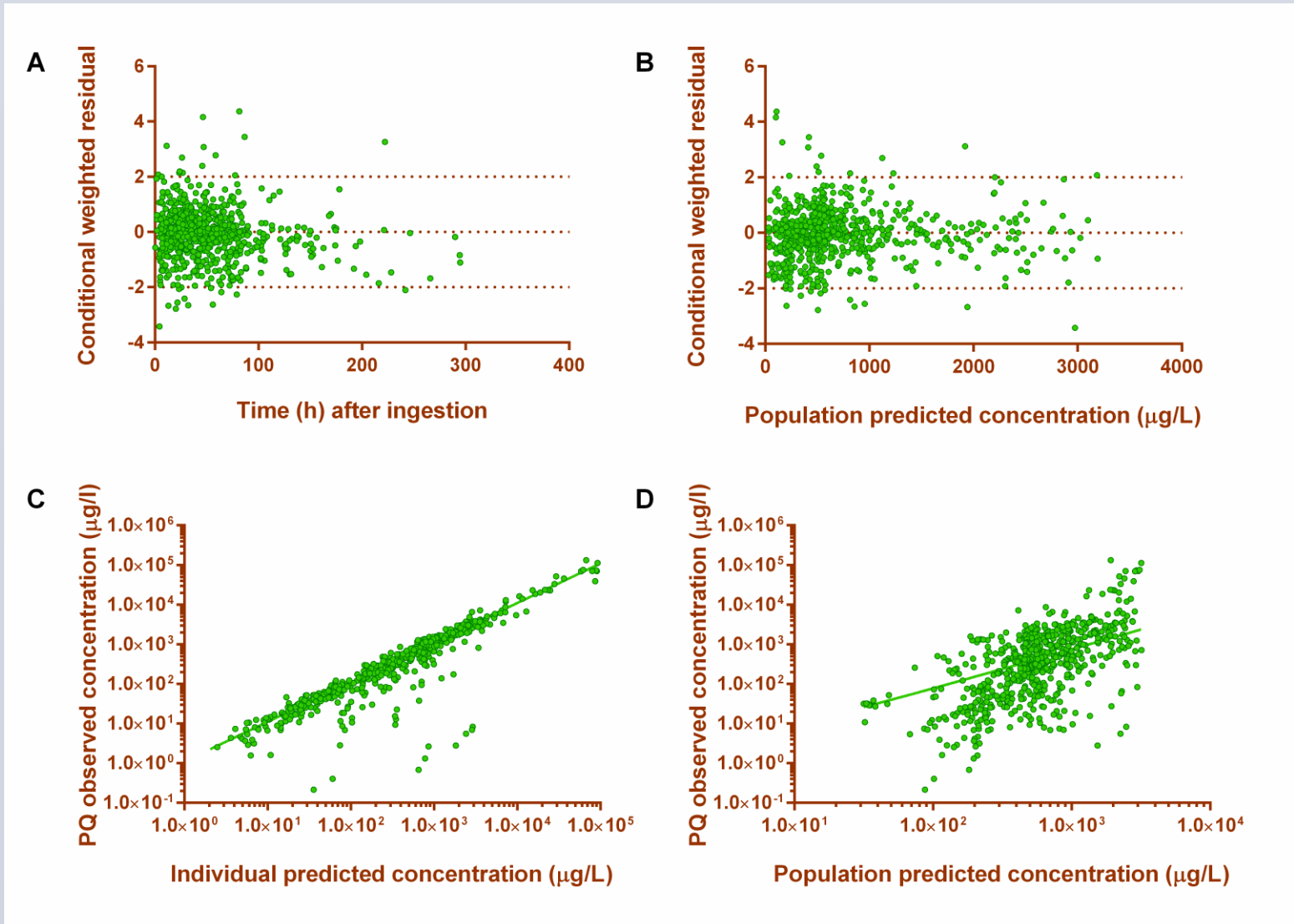


Fig.2 Scatter plot for Visual predictive check generated from the final model

Table 2 Bootstrap analysis of PQ population toxicokinetics

Parameter	Final model				Bootstrap				
	Mean	%CV	2.5%	97.5%	Mean	%CV	Median	2.5%	97.5%
Θ_v (L)	13.63	16	9.28	17.98	14.64	36	13.59	6.62	27.32
Θ_{CL} (L/h)	0.15	31	0.06	0.24	0.22	86	0.16	0.02	0.73
Θ_Q (L/h)	0.84	11	0.67	1.02	0.87	27	0.85	0.48	1.35
Θ_{XF}	0.01	16	3.67E-03	0.01	0.01	35	0.01	2.83E-03	0.01
Proportional error (%)	48	39	0.12	0.84	80	148	0.44	0.11	4.38
Additive error (µg/L)	0.89	-	-	-	1.26	77	0.98	0.1	3.7

Table 3 Bayesian estimation of population toxicokinetic parameters

Parameter	Mean	SD	2.5% CI	97.5% CI
V_1 (L/kg)	0.34	0.21	0.05	1.00
V_2 (L/kg)	2.06	1.74	0.46	7.6
K_a (h ⁻¹)	0.93	0.40	0.02	1.9
CL _{PQ} (L/h)	1.17	3.52	0.003	16.4
$t_{1/2\beta}$ (h)	86.93	189.2	0.20	1042

Conclusions

- PQ toxicokinetics were characterised using a 2-compartment disposition model with first order absorption and elimination.
- The discrepancy between the estimated value of V/F and those previously published could be due to the uncertainty in the ingested doses.
- The low CL_{PQ} reflects the PQ induced renal impairment at long time after swallowing.

Acknowledgement

This work was supported by the National Health and Medical Research Committee of Australia. KW was supported by Faculty of Development Fund, Faculty of Medicine, Chiang Mai University and Graduate School International Travel Award (GSITA), the University of Queensland.

Reference

1. Houze P, Baud FJ, Mouy R, Bismuth C, Bourdon R, Scherrmann JM. Toxicokinetics of paraquat in humans. Hum Exp Toxicol. 1990;9(1):5-12. Epub 1990/01/01.
2. Baud FJ, Houze P, Bismuth C, Scherrmann JM, Jaeger A, Keyes C. Toxicokinetics of paraquat through the heart-lung block. Six cases of acute human poisoning. J Toxicol Clin Toxicol. 1988;26(1-2):35-50. Epub 1988/01/01.