The pharmacokinetics of sertraline in overdose and the effect of activated charcoal

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SUMMARY

Aims: To investigate the pharmacokinetics (PK) of sertraline in overdose and the effect of single dose activated charcoal (SDAC).

Methods: Patients presenting to a toxicology unit with sertraline overdoses had demographic and clinical information recorded, and serial serum collected for measurement of sertraline concentrations. Monolix® version 4.2 was used to develop a population PK model of sertraline overdose and the effect of SDAC. Uncertainty in dose time was accounted for by shifting dose time using lag time with between subject variability (BSV). BSV on relative fraction absorbed was used to model uncertainty in dose.

Results: There were 77 timed sertraline concentrations measured in 28 patients with sertraline overdoses with a median dose of 1550mg (250–5000 mg). SDAC was given to seven patients between 1.5 and 4h post-overdose. A one compartment model with lag time of one hour, and first order input and elimination adequately described the data. Including BSV on both lag time and relative fraction absorbed improved the model. The population PK parameter estimates for absorption rate constant, volume of distribution and clearance were $0.895h^{-1}$, 5340L and 130L/h respectively. The calculated half-life of sertraline following overdose was 28hours (IQR:19.4 –30.6h). When given up to 4h post-overdose, SDAC significantly increased the clearance of sertraline by a factor of 1.9, decreased the area under the curve and decreased the maximum plasma concentration (Cmax).

Conclusions: Sertraline had linear kinetics in overdose with parameter values similar to therapeutic use. SDAC is effective in increasing clearance when given 1.5 to 4h post-overdose.

What is already known about this subject:

- There are no data available to describe the pharmacokinetics of sertraline in overdose.
- Currently, single dose activated charcoal is recommended up to one hour post drug ingestion.

What this study adds:

- The pharmacokinetics of sertraline in overdose are similar to therapeutic use.
- Activated charcoal given up to 4h post-overdose of sertraline increases the clearance of sertraline and reduces the AUC.

INTRODUCTION

Antidepressant drugs are one of the major groups of drugs taken in overdose for deliberate self-poisoning. The types of antidepressants prescribed, and therefore available and taken in overdose, have changed over the last 20 years. The selective serotonin reuptake inhibitors (SSRIs) - citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline - are now one of the most commonly prescribed groups of drugs for psychiatric disorders, particularly depression.[1-3] They are also one of the most common groups of drugs seen in deliberate self-poisoning. [4] The major toxic effect of these drugs is serotonin toxicity with approximately 15% of SSRI overdoses resulting in serotonin toxicity requiring hospital admission and medical treatment. [5] Serotonin toxicity, often termed 'Serotonin Syndrome', is potentially life-threatening and presents as neuromuscular excitation (clonus, myoclonus, hyperreflexia and/or tremor), autonomic hyperactivity (tachycardia, fever, diaphoresis and/or mydriasis) and altered mental status (confusion, agitation and/or excitement). Severe serotonin toxicity may require urgent medical intervention and intensive monitoring. [5-7]

Despite the importance of antidepressant overdose there are limited studies investigating the pharmacokinetics (PK) and pharmacodynamics (PD) of antidepressant drugs in overdose. An understanding of the PK and PD of drugs in overdose is important to quantify and understand the likely effects of these drugs in overdose over time and guide risk assessment and treatment.[8] There is no information on the PK of sertraline in overdose, despite being one of the most commonly taken SSRIs in overdose, [5] .

In recent years, there has been significant debate over the use of single dose activated charcoal (SDAC) in the management of overdose patients. Recommendations suggest that administration is ineffective in improving clinical outcomes, particularly if given more than one hour post-overdose. [9, 10] However, recent PK and PD studies investigating

decontamination procedures in antidepressant and antipsychotic overdose have found that the use of SDAC may have benefit when administered more than one hour post ingestion. [11-14] In citalopram overdose the fraction absorbed was reduced by 22% and the clearance increased by 72% when SDAC was administered between one and four hours post ingestion. [11] Similarly, in quetiapine overdose, the fraction of drug absorbed was reduced by 35% following the administration of SDAC more than one hour following overdose. [12] In the case of citalopram overdose, this translated into a meaningful clinical effect with the administration of SDAC up to four hours post-overdose reducing the risk of QT prolongation. [13] Similar beneficial effects have been shown in studies of escitalopram and venlafaxine. [14-16]

There is limited information available on the PK of sertraline following therapeutic dose studies. Following oral administration the drug is slowly absorbed with the maximum concentration (C_{max}) occurring 4 to 6 hours after oral administration.[17] It undergoes extensive first pass metabolism via a number of cytochrome P450 (CYP) isoenzymes (CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4), to produce a weakly active metabolite for serotonin reuptake, N-desmethylsertraline. [17-20] The half- life of the parent compound, sertraline is approximately 26 hours, and is approximately 98% protein bound. [21, 22] Sertraline appears to follow linear kinetics in therapeutic use, with the measured plasma sertraline concentration proportional to dose over the range of 50 – 200mg per day. [23]

This study aims to describe the pharmacokinetics of sertraline in overdose using a population analysis approach to quantify the relationship between dose and the time course of drug concentrations, and to investigate the effect of SDAC administration on the PK of sertraline overdose.

METHODS

Study design and setting

This was a population pharmacokinetic study of sertraline using drug concentration data collected prospectively from patients who had taken an overdose of sertraline from February 2001 to February 2010. Written informed consent was obtained from patients for collection of blood samples for analysis of sertraline. The study was approved by the Hunter Area Research Ethics Committee and the University of Newcastle Human Research Ethics Committee. The study was conducted in a regional toxicology unit which accepts referrals and admissions for all poisoning and overdose patients from a population of over half a million people.

Patients

Demographic and clinical information is collected for all patients admitted to the toxicology unit during their admissions and is maintained in a clinical database. Details include age, sex and information relating to the drug overdose (timing of the overdose event, quantity [strength and amount] of medication), co-ingestants, clinical effects and any treatments administered (single-dose activated charcoal [SDAC]). Treatment is determined by the admitting clinical toxicologist. A proprietary SDAC product was used which was formulated as a suspension of 50g activated charcoal in 250 mL of purified water, with sucrose, propylene glycol, glycerol, citric acid and sodium hydroxide as excipients (Carbosorb®, Phebra Pty Ltd, NSW, Australia). Blood samples were collected from patients on admission and during their hospital stay. The number of samples collected was dependent upon the duration of the hospital stay and the willingness of the patient to provide blood samples. The exact times were recorded.

Dosing history was obtained from the patient on admission and then on subsequent occasions when reviewed by the attending toxicologist. This was also corroborated where possible by friends/relatives, the ambulance officer record and by tablet counts when available. In this study drug overdose was defined as any dose greater than the maximum daily dose where the intention was self-harm. Uncertainty in the reported dose was assessed based on the reliability of the history using a previously described veracity score [11]. The veracity was scored using a 5-point categorical scale ranging from an accurate history (score = 0; exact dosing) to a very poor history (score = 4; large error in reported dose allowed). There were no patients with an accurate history in this study, so a score of 1 was taken as if it were an exact dosing history. Uncertainty in the overdose time (termed mod-time) was also included in the analysis and was based on allowing a range in the time of ingestion using the earliest possible ingestion time (last contact with family or friends) and the latest possible ingestion time (e.g. ambulance call time). The range in mod-time in this study was 5 minutes to 2 hours.

Drug analysis

Samples collected were centrifuged and the serum taken from the tube was frozen at minus 20 degrees Celsius prior to analysis. Measurement of sertraline concentration was performed using high-performance liquid chromatography (HPLC) in the method described by Kristensen et al, with the limit of detection of sertraline of 0.005mgL^{-1}. [24] The measured concentrations of sertraline in our study were between 0.016 and 0.896mgL^{-1}.

Pharmacokinetic analysis

Population pharmacokinetic analysis was performed using the nonlinear mixed effect modelling software Monolix® version 4.2 (Lixoft, Orsay, France. www.lixoft.com) which utilises the Stochastic Approximation Expectation Maximization algorithm (SAEM) and a Markov chain Monte-Carlo (MCMC) procedure to compute the maximum likelihood

estimates of the population means and between-subject variances for the PK parameters. [25] The number of chains was fixed to 15 for all computations with convergence demonstrated.

One- and two-compartment models, with zero- and first-order oral absorption kinetics and models with and without Michaelis-Menten elimination were assessed and compared to determine the best structural model. For the residual unexplained variability, additive and proportional models and a combination of the two were evaluated. Between-subject variability (BSV) included in the model was assumed to have log-normal distribution. Initial parameters estimated using the model were the absorption rate coefficient (Ka), bioavailability (F), shifted lag time (T_{slag}), volume of distribution (V) and clearance (CL). Shifted lag time with BSV was used to shift the dose time to allow for uncertainty in dose time both before and after the reported dose time, rather than estimating a true lag time.

Initial estimates of parameters were taken from previous pharmacokinetic studies of sertraline. [17, 22, 26] An initial value of Ka of 0.5 h^{-1} was based on multiple dose administration of the therapeutic use of sertraline from published literature. [22] Similarly, the initial estimates used in the model for CL (100 L/h) and V (3500L) were based on a 70kg adult [22].

Uncertainty in overdose history

We attempted to include both uncertainty in the reported dose (veracity score) and the reported time of ingestion (mod-time), similar to previous analyses. [11, 12, 27, 28] However, previously veracity was included in the model by allowing the uncertainty in dose (Δdose) to be drawn from a normal distribution with a mean of zero and precision that incorporated an additive and proportional component based on veracity [11]. This was not possible in Monolix and uncertainty in dose amount was instead modelled by allowing between subject variability (BSV) in the relative bioavailability (F) which could then be

modified by the veracity score. Firstly the relative bioavailability was fixed to 1 and the BSV estimated for each patient to account for uncertainty in dose. The BSV on F for each veracity score was then plotted to determine if veracity provided any additional information (i.e. the BSV was smaller for smaller veracity scores). The BSV for patients with the lowest veracity score (1 in this study) was then set to zero. The BSV was then constrained less for increasing veracity scores to account for increasing uncertainty. Models were compared with and without the veracity score.

Similarly, the uncertainty in time of dose time (mod-time) could not be incorporated in the model using a distribution form as previously reported [12] because it caused instability during modelling. Uncertainty in the dose time was therefore incorporated by using a shifted lag time parameter (T_{slag}) in the model and using BSV on this shifted lag time parameter to represent uncertainty in dose time. To do this all dose times and times of drug concentration measurements were advanced by 1 hour to allow a 'negative' time effect (i.e. drug taken prior to the reported ingestion time) because the traditional lag time parameter can only be positive. It should be noted that the shifted lag time parameter was not used as the traditional lag time parameter (i.e. to represent a lag in gastrointestinal absorption) but as uncertainty in timing of the overdose.

Effect of covariates

The effect of covariates, including age and sex, were explored by visual inspection of the individual parameter estimates vs the covariate of interest. Age and sex were not included in final model evaluation due to the absence of an association visually. Weight was not considered because it was not available for the majority of patients. Weighing overdose patients during a hospital admission is not performed routinely and therefore not possible to include in the model.

The administration of SDAC was included after considering uncertainty in dose and dose time. The effect of SDAC was evaluated as a fractional effect on relative bioavailability ($f_{F\text{-}char}$) and a fractional effect on CL ($f_{CL\text{-}char}$). This factor was set to 1 for patients who were not administered charcoal i.e. no effect on bioavailability or clearance.

Thus in the model the estimation of the effect of charcoal on clearance is:

$$CL = \theta_{CL} \times f_{CL\text{-}char}$$

Where θ_{CL}, is the typical value of clearance. Similar reasoning was used to estimate the effect of charcoal on the relative fraction absorbed (F).

Final model selection and evaluation was based a number of criteria including goodness of fit plots which included observations versus predictions, plots of the weighted residuals and the visual predictive check (VPC).The log likelihood was computed using importance sampling and was used to discriminate between models through the difference in log likelihood (−2 LL). A p-value of 0.05 was considered statistically significant. For the inclusion of covariates in the model a change of 20% in the parameter (F or CL) was regarded as clinically significant change, as per previous studies. [11] We also examined the between subject variability estimates, deviance distribution errors, and the reduction in the log likelihood ratio test.

Derived pharmacokinetic parameters, including half-life ($t_{1/2}$), maximum serum concentration (C_{max}), time to maximum serum concentration (T_{max}) and area under the curve (AUC), were calculated for each patient from their individual predicted patient parameters in the final model. The derived parameters were then presented as a median and range for the whole group. A typical concentration time plot for the median dose taken in the study was created by simulating 1000 patients and plotting the median concentration versus time.

RESULTS.

Patient Data

There were 28 patients recruited during the study period, 21 were female and the median age was 32 years (15 to 55y). The median reported dose was 1550mg (250 to 5000mg). Patient demographic information is provided in Table 1. Twenty one patients co-ingested other drugs and/or alcohol as part of their overdose. None of the co-ingested drugs were known to either inhibit or induce the metabolism of sertraline, so co-ingested medications were not considered further. Seven of the 28 patients (25%) of the patients developed serotonin toxicity. Four patients (14%) had a Glasgow coma score (GCS) < 15, but only one had a GCS < 10. One patient was admitted to intensive care and required intubation and ventilation for a sedative co-ingested drug. There were no deaths or other major complications including seizures, arrhythmias and hypotension.

Seven patients were administered SDAC, although one of these received approximately a quarter of the dose only. The administration of charcoal for these seven patients was timed between 1.5 and 4 hours (median time 3 hours) after the reported time of overdose. The median overdose of sertraline ingested by these seven patients was 1900mg (250 – 2800 mg).

There were a total of 77 blood samples collected from the 28 patients with a median of 2 samples per patient (Range: 1 to 6). The times of blood sampling for analysis of sertraline concentration ranged from 1.17 to 68 hours after the reported time of the drug ingestion. Each patient presented following an overdose on one occasion only.

Pharmacokinetic analysis

The dose normalised plasma concentration-time profiles for the 28 patients are shown in Figure 1. A one compartment model with first order absorption and linear elimination

kinetics adequately described the data. A proportional error model provided the best error model, as a combined additive and proportional error model produced negligible additive error or improvement.

The inclusion of BSV on F improved the model. Plots of the BSV on F versus the veracity score showed no relationship between veracity and BSV on F (Supplementary Figure 1) and attempts to incorporate veracity did not improve the model. The inclusion of shifted lag time (T_{slag}) improved the model and T_{slag} was initially estimated to be close to 1 (i.e. confirming that the actual dosing time was shifted by one hour), T_{slag} was then fixed to 1 in subsequent models and BSV on T_{slag} estimated. The effect of SDAC on CL and F was considered separately. Administration of SDAC was estimated to increase the CL by a factor of 1.9 ($p < 0.05$). In contrast, the administration of SDAC decreased F by 27% ($p > 0.05$) which was not statistically significance.

The final model was a one compartment first order input model with shifted lag time and proportional residual error model. The final model incorporated BSV on the relative fraction absorbed (F), which was fixed to 1 and BSV on shifted lag time, which was also fixed to 1, to allow variability between patients in dose and dose time respectively. Finally the model incorporated SDAC as a covariate with a fractional effect on relative clearance (f CL-char). Figure 2 shows the goodness-of-fit plots for the final model. The typical mean population PK parameter estimates from the base and final models with modelling decisions and final model parameters are described in Table 2.The derived pharmacokinetic parameters for sertraline are included in Table 3. The median half-life for patients given SDAC was 15.02hr (IQR: 10.74-22.19hr) compared to 29.39hr (IQR: 26.44-30.79hr) in those not given SDAC. The median AUC for patients given SDAC was 5.63 mg.h/L (IQR: 3.86-8.82 mg.h/L) compared

to 15.13mg.h/L (IQR: 7.63-20.84mg.h/L) in those not given SDAC. Plots showing the effects of SDAC on the PK parameters from the final model are shown in figure 2.

DISCUSSION

The study has defined the pharmacokinetics of sertraline in overdose and the effect of SDAC. The PK profile of sertraline in overdose was best described by a one compartment model with linear elimination using Monolix ®, and was similar to previous pharmacokinetic studies of sertraline in therapeutic doses. Decontamination with SDAC had a beneficial effect by increasing the clearance of sertraline by a factor of 1.9 which reduced the AUC, and the median value of Cmax (Figure 2). This suggests there may be benefit in administering SDAC but further study is required to determine if this effect on the pharmacokinetics translates to clinical benefit.

Following oral administration, sertraline reaches a peak plasma concentration four to six hours after administration.[17] The drug undergoes extensive first pass metabolism via several metabolic pathways. [17, 18, 19] Previous studies of the pharmacokinetics of drugs in overdose have found that SDAC has a variable effect on CL and F. SDAC is able to bind unabsorbed drug and thus can affect relative bioavailability, in addition it is possible that activated charcoal is able to remove some drugs from the circulation via gastric dialysis. In citalopram overdose SDAC increased CL and decreased F, [11]. In contrast, in quetiapine overdose SDAC was observed to decrease F but had no significant effect on CL.[12] The reasons for these differences are not easily explained. It has been previously suggested that SDAC is more likely to have an effect on CL for drugs with longer half-lives, such as citalopram [11] compared to drugs with shorter half-lives such as quetiapine. [12] We found a significant effect of SDAC on CL of sertraline in overdose, and no effect on relative bioavailability (F), consistent with the fact that sertraline has a long half-life. It remains probable that SDAC affects both F and CL in most cases but that the influence varies based

on the PK properties of the drug in question and the study designs and sparseness of the data may in many cases be insufficient to disentangle these effects.

SDAC was administered between one and four hours post overdose, which is similar to other pharmacokinetic studies of drugs in overdose where SDAC is rarely given within 1 hour, and usually between 2 and 4 hours post overdose. [11, 14, 15] Previous studies found that the incidence of toxic effects, such as seizures following venlafaxine overdose, [29] or prolongation of the QT interval with citalopram or escitalopram,[13, 16] can be reduced if charcoal is administered more than one hour following the overdose. Similarly, in quetiapine overdose there is a potential for benefit when SDAC is given up to six hours post-overdose. [12] Although current treatment guidelines only recommend the use of SDAC within one hour of overdose, [9, 10] our findings add further support for the administration of SDAC beyond this time. However, it will be important to demonstrate that the use of SDAC also results in a significant effect on the pharmacodynamics of sertraline, such as a reduction in serotonin toxicity.

Published values for the PK estimates for sertraline is available in only limited single-dose or short term therapeutic studies. Our estimated V of approximately 76L/kg is similar to values reported in the literature, [17] and our estimate for CL of 1.9L/kg/hr is not dissimilar to that seen in young males (1.41 L/h/kg [±0.36]). [22] As sertraline is highly protein bound and V is relatively large, indicating much of the drug is bound to tissue outside of the circulation, it is expected that haemodialysis or haemoperfusion is unlikely to remove significant amounts of drug. However, sertraline is relatively safe in overdose with no significant ECG changes and no deaths have been reported from ingestion of sertraline as a single agent. Serotonin toxicity may require treatment depending on symptom severity. The use of SDAC may assist in

increasing the clearance of sertraline and potentially limiting adverse effects of serotonin excess.

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Table 1: Patient demographic and overdose information

	Median (range)	Number of patients (%)
Age (years)	32 (15 – 55)	28 (100)
Male		7 (25)
Prescribed therapeutic dose (mg) for patients on sertraline prior to the overdose event	100 (25 – 200)	24 (86)
Overdose reported (mg)	1550 (250 – 5000)	28 (100)
Co-ingested medications/substances:		
Alcohol		10 (36)
Analgesics (paracetamol, codeine, ibuprofen)		6 (21)
Anticoagulants (warfarin)		1 (4)
Antiepileptics (sodium valproate)		1 (4)
Antihistamines (dexchlorpheniramine, doxylamine)		3 (11)
Antihypertensives (atenolol, candesartan)		2 (7)
Antipsychotics (olanzapine, quetiapine, risperidone)		3 (11)
Benzodiazepines		4 (14)
Decongestants (phenylephrine, pseudoephedrine)		2 (7)
Herbal preparations (valerian)		1 (4)
Unknown substances		1 (4)
Nil		9 (32)
Measured sertraline concentration range (mg L^{-1})	0.016 – 0.896	
Veracity score		
1		14 (50)
2		11 (39)
3		3 (11)
4		0 (0)
Single dose activated charcoal (SDAC);		7 (25)*
Median overdose in patients treated with SDAC (mg) ;	1900(250-2800)	
Median overdose in patients not treated with SDAC (mg)	1500 (300-5000)	

* One patient received a partial dose of SDAC of approximately 12.5g

Table 2: Parameter estimates using Monolix® version 4.2 and the effect of single dose activated charcoal on bioavailability and clearance

	Base Model Mean value (RSE%)	Model 1 – SDAC $f_{F\text{-}char}$ Mean value (RSE%)	Model 2 - Final SDAC $f_{CL\text{-}char}$ Mean value (RSE%)
Structural model (θ)			
T_{slag} (h)	1 (fixed)	1 (fixed)	1 (fixed)
Ka (h^{-1})	1.06 (83)	1.02 (95)	0.895 (42)
F	1 (fixed)	-	1 (fixed)
V (L)	5130 (15)	4730 (14)	5340 (18)
CL (L h^{-1})	151 (20)	144 (19)	-
$f_{F\text{-}char}$	-	0.731 (178)	-
θ_F	-	1 (fixed)	-
$f_{CL\text{-}char}$	-	-	1.92 (70)
θ_{CL}	-	-	130 (34)
Between subject variance (ω)			
T_{slag}	0.849 (45)	0.794 (51)	0.922 (52)
Ka	1.51 (139)	1.63 (104)	1.02 (77)
F	0.321 (40)	0.275 (43)	0.303 (48)
V	0.087 (95)	0.146 (80)	0.085 (219)
CL	0.18 (77)	0.109 (134)	0.126 (103)
Coefficient of variation for proportional residual error (CV%)	11.8	11.9	11.7
Objective Function *(-2 log-likelihood value)*	-207.10	-208.09	-212.04

T_{slag} = shifted dose time (estimated time plus one hour), Ka = absorption rate constant, F = relative bioavailability, V = volume of distribution, CL = clearance,
f F-char = fractional effect of SDAC on bioavailability, f CL-char = fractional effect of SDAC on clearance .
$CL = \theta_{CL} \times f_{CL\text{-}char}$

$$F = \theta_F \times f_{F\text{-}char}$$

Table 3: Pharmacokinetic data for sertraline following overdose in 28 patients, and the effect of SDAC, based on the median overdose of 1500mg.

	Total (n=28) median [Range]	No SDAC (n=21) median [Range]	SDAC (n=7) median[Range]
$t_{1/2}$ (h)	27.64 [19.34-30.60]	29.39 [26.44-30.79]	15.02 [10.74-22.19]
C_{max} (mg/L)	0.25 [0.18-0.42]	0.33 [0.18-0.43]	0.22 [0.18-0.42]
T_{max} (h)	2.8 [2.1-3.6]	2.9 [2.3-3.6]	2.5 [1.9-3.6]
AUC (mg.h/L)	8.96 [6.45-19.08]	15.13 [7.63-20.84]	5.63 [3.86-8.82]

Figure 1: Observed dose-normalised sertraline concentration (to the median therapeutic dose of 100mg) versus time post overdose.

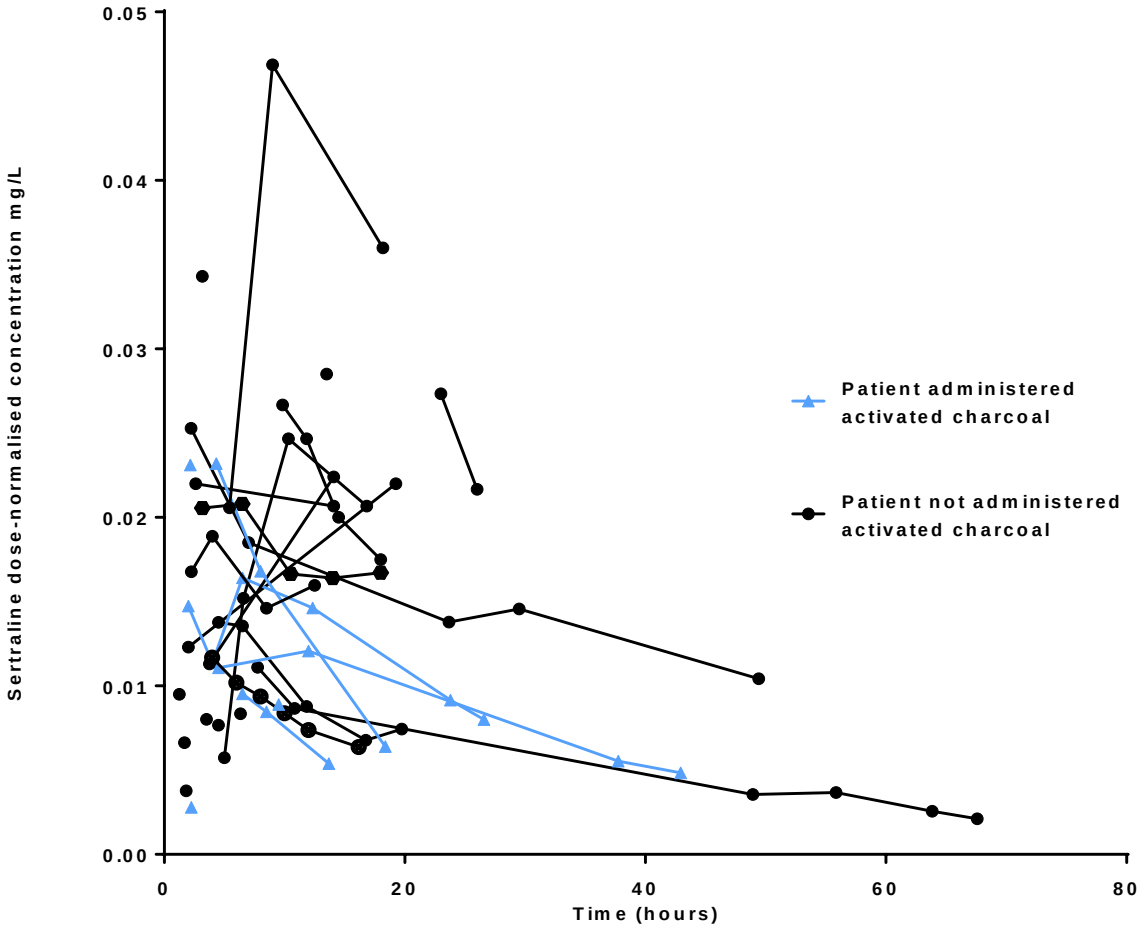
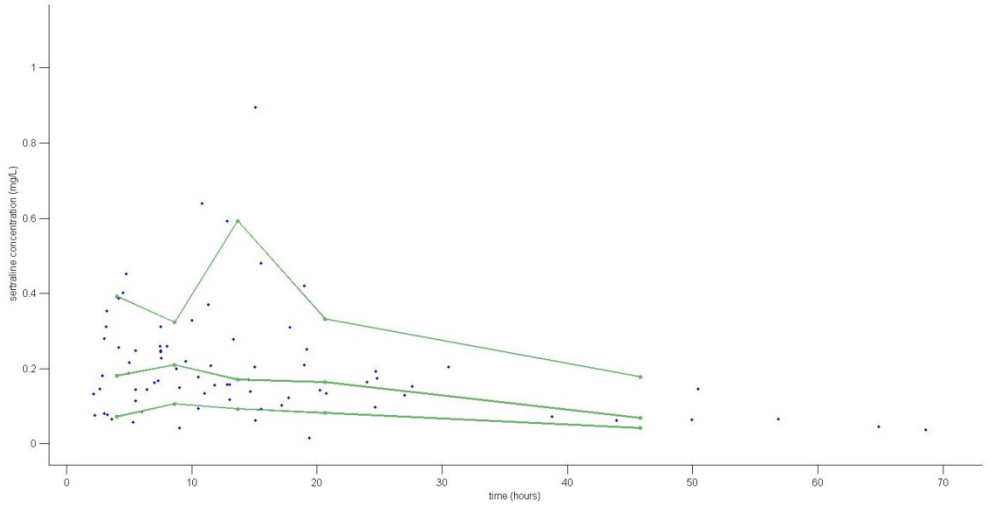


Figure 2: Goodness-of-fit plots including (a): a visual predictive check (VPC) showing the observed data with the 10th, 50th, and 90th percentiles and (b): a plot of observations versus individual predictions from the final model.

a



b

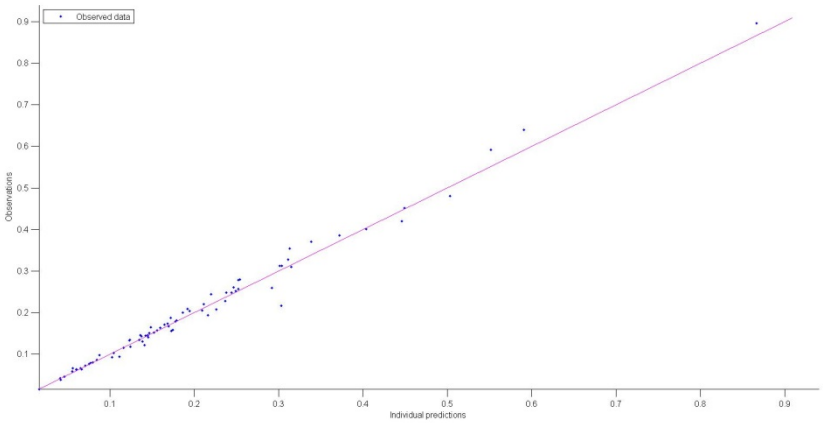
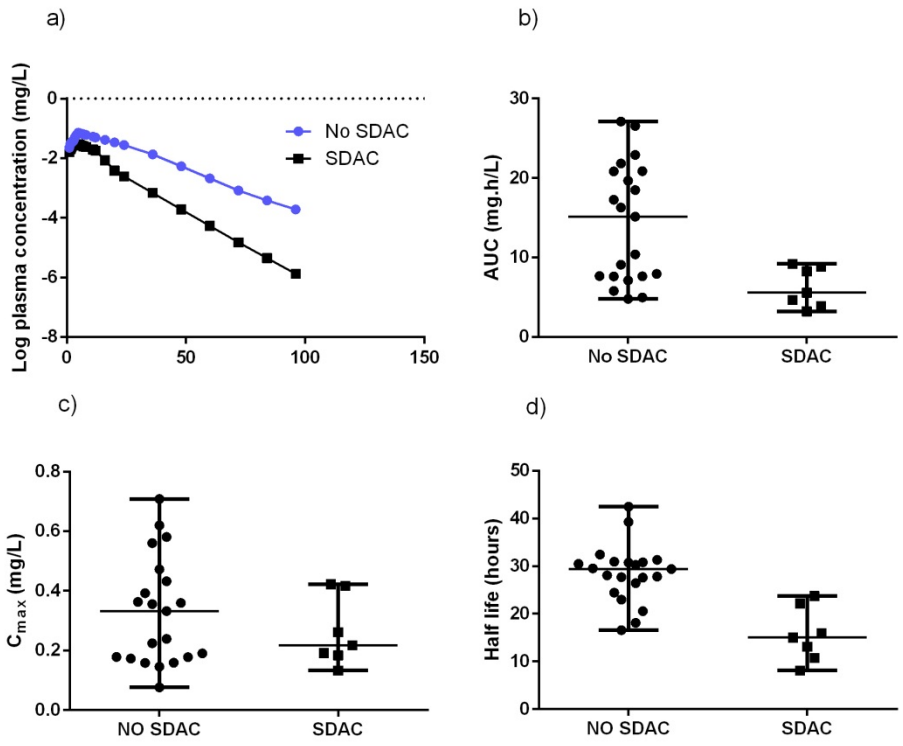


Figure 3: Plots showing the effect of single dose activated charcoal decontamination, on: a) log median values of the plasma concentration–time course for an overdose of 1500mg, b) the area under the curve (AUC) (showing median and range), c) the maximum plasma concentration (C_{max}) (showing median and range), and d) half- life (showing median and range) following sertraline overdose.



Supplementary Figure 1: Plot of between subject variability (BSV) on relative fraction absorbed (F) as a standard deviation (SD) versus the veracity score.