Pharmacokinetic–pharmacodynamic modelling of QT interval prolongation following citalopram overdoses

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Aims

To develop a pharmacokinetic–pharmacodynamic model describing the time-course of QT interval prolongation after citalopram overdose and to evaluate the effect of charcoal on the relative risk of developing abnormal QT and heart-rate combinations.

Methods

Plasma concentrations and electrocardiograph (ECG) data from 52 patients after 62 citalopram overdose events were analysed in WinBUGS using a Bayesian approach. The reported doses ranged from 20 to 1700 mg and on 17 of the events a single dose of activated charcoal was administered. The developed pharmacokinetic–pharmacodynamic model was used for predicting the probability of having abnormal combinations of QT-RR, which was assumed to be related to an increased risk for torsade de pointes (TdP).

Results

The absolute QT interval was related to the observed heart rate with an estimated individual heart-rate correction factor [$\alpha = 0.36$, between-subject coefficient of variation (CV) = 29%]. The heart-rate corrected QT interval was linearly dependent on the predicted citalopram concentration (slope = 40 ms l mg⁻¹, between-subject CV = 70%) in a hypothetical effect-compartment (half-life of effect-delay = 1.4 h). The heart-rate corrected QT was predicted to be higher in women than in men and to increase with age. Administration of activated charcoal resulted in a pronounced reduction of the QT prolongation and was shown to reduce the risk of having abnormal combinations of QT-RR by approximately 60% for citalopram doses above 600 mg.

Conclusion

Citalopram caused a delayed lengthening of the QT interval. Administration of activated charcoal was shown to reduce the risk that the QT interval exceeds a previously defined threshold and therefore is expected to reduce the risk of TdP.

Introduction

Determining the probability of developing toxicity and the required observation period are fundamental issues for the clinical management of the poisoned

patient. Drug concentration is usually related to the degree of toxicity and clinical severity of poisoning. Therefore, a pharmacokinetic–pharmacodynamic (PKPD) model would be valuable for understanding

the relationship between dose ingested, drug concentration and the time course of outcomes in patients who have taken a drug overdose. The proposed model would be a valuable tool in improving treatment guidelines.

Although central nervous system toxicity is more common in drug overdose, cardiovascular effects, and importantly pro-arrhythmic effects, are more problematic and there is significant benefit in patients having cardiac monitoring in hospital. The management of the cardiovascular toxicity is determined by two assessments: the likelihood of cardiovascular toxicity and the duration of monitoring that may be required. An electrocardiogram (ECG) is often used to assess the risk of cardiac toxicity by assessing ECG parameters such as the QRS width or the QT interval. It is assumed that drug concentration correlates with these ECG measures in a predictable way. The advantage of an ECG is that it can be repeated frequently and rapidly compared with drug assays that are not commonly available in the clinical setting.

One important marker of cardiac toxicity on the ECG is the QT interval, which is defined as the period from the beginning of the QRS complex to the end of the T-wave. Prolongation of the QT interval has been associated with an increased risk of torsade de pointes (TdP), a potentially fatal ventricular tachyarrhythmia [1]. Drug-induced QT prolongation is associated with blockade of potassium channels and hence ventricular repolarization is delayed [2]. Although it is recognized that the QT interval is an imprecise predictor for proarrhythmia, there are no other established ECG measures for assessing the risk of TdP [3].

Currently there appear to be insufficient data to describe adequately the relationship between the absolute or heart rate-corrected QT interval and TdP and it is not clear how QT should be corrected for heart rate when predicting the risk for development of TdP. Fossa *et al.* have suggested that QT–RR combinations outside the 95% ‘normal’ range of QT–RR combinations may be associated with an increased arrhythmogenic risk [4]. In their article they propose a joint distribution of QT and RR that represents the normal range of these values for a typical subject.

More than 70 marketed noncardiovascular drugs have been reported to cause an increased QT [5], with citalopram, a selective serotonin reuptake inhibitor (SSRI), included on this list. Citalopram has been reported to cause prolongation of the absolute QT interval and QTc (Bazett’s) interval after overdose to a higher degree than other SSRIs [6]. Citalopram, although rarely, can induce TdP [7, 8], which has been postulated as a likely cause

for observed fatalities after citalopram overdoses [9, 10].

We have recently presented a method for analysing PK data arising from drug overdoses by using a population approach and a fully Bayesian methodology [11]. In Bayesian analysis the posterior distributions of the parameters are determined by a combination of the prior distributions of the parameters and the likelihood for the data, compared with the ‘standard’ maximum likelihood methods where only the likelihood is used. See Duffull *et al.* [12] for an overview of using Bayesian analysis in PK analysis. In the PK analysis of citalopram (see [11] for details) informative prior information was needed to characterize accurately the absorption phase as there were few early PK samples in the dataset. In addition, the Bayesian methodology allowed uncertainty in dose and time to be incorporated into the model. A substantial effect on the PK after administration of a single dose of activated charcoal was found (on average a 22% reduction in the fraction absorbed and a 72% increase in clearance). It remains unknown if administration of activated charcoal also reduces the magnitude and/or duration of QT prolongation associated with citalopram overdose to a clinically important degree.

The aim of the present study was to develop a PKPD model that describes the time-course of the QT interval after citalopram overdoses with specific reference to the effects of decontamination procedures. This modelling was performed using a Bayesian approach in the program WinBUGS version 1.4 [13]. We also aimed to determine if activated charcoal reduced the risk of having abnormal QT–RR combinations, a clinically important effect.

Patients and methods

Patients

Recruitment Clinical data for the PKPD modelling were available from 52 patients who presented to a tertiary toxicology unit. All patients had taken an overdose of citalopram to deliberately self-harm (deliberate self-poisoning). The patients were recruited prospectively over a total of 62 overdose occasions. The study was approved by the institutional ethics committee. After consent 1–12 (median two per occasion) PK samples were drawn. The PK modelling, which has been presented elsewhere [11], included one additional patient who lacked ECG measurements. All patients recruited to the clinical study for citalopram overdose, based on their history, had citalopram detected in their blood.

Table 1

Patient and overdose event characteristics

	Median (range)	Number of patients	Number of events
Reported overdose (mg)	280 (20–1700)		
Age (years)	30 (13–72)		
Males/females		16/36	16/46
<i>Co-ingested drugs with possible effect on QT</i>			
No known risk (cat. = 0)		31	13
Intermediate risk (cat. = 1)		8	41
High risk (cat. = 2)		13	8
Activated charcoal		16	17
Absolute QT interval (ms)	400 (280–560) ^a		
RR interval (ms)	760 (410–1730) ^a		
QTcB (ms)	459 (365–550) ^a		
QTcF (ms)	438 (367–515) ^a		

^aAll observed QT and RR observations.

On admission, demographic information was recorded including age and gender, and information on the overdose including dose amount, time of overdose and coingested drugs (Table 1). Thirty-nine of the patients used citalopram regularly and their baseline concentration was estimated in the PK modelling (see below). The treatment of each patient was recorded and performed according to the admitting clinical toxicologist, including the use of activated charcoal.

Activated charcoal Sixteen patients received a single dose of activated charcoal (SDAC; 50 g as a suspension) on a total of 17 occasions. The reported median dose of citalopram on these charcoal occasions was 480 mg (range 80–1700 mg), while the reported median dose was 280 mg (range 20–1200 mg) on occasions where no charcoal was administered. The time of decontamination was recorded and then categorized as less than 1 h (for one overdose event), 1–2 h (for nine overdose events), or 2–4 h (for seven overdose events). Charcoal was not administered to any patient at a time greater than 4 h after the reported time of the overdose. One patient took only a partial dose of SDAC and the remainder were recorded to have taken the full SDAC dose. SDAC was administered in 10 overdose events at the time of the first concentration measurement and for the remainder between 1 and 70 h before the first blood sample. No concentration measurements were taken before SDAC was administered. The majority of ECGs were taken after the administration of SDAC except for on admission in some cases, where the ECG was taken in the 15 min prior to SDAC. Four patients (one before

SDAC administration and three who were not decontaminated) vomited after the overdose. No effect of vomiting was considered in the modelling. No other method of decontamination was used in this study.

Electrocardiograph (ECG) measurements For each ECG, the RR and QT intervals were measured manually using a standardized approach. More comprehensive QT–RR measurements using a Holter monitor, digital storage of data and measurement software [14] are not available in the clinical setting of overdose patients. Electrocardiographic intervals were measured on a 12-lead ECG manually with a ruler by one of the authors (G.K.I.). The QT interval was measured from the beginning of the Q wave until the end of the T wave. The end of the T wave was taken as the point where the trace returned to baseline. The QT was measured in multiple leads (at least six leads including chest and limb leads) and the median QT interval was used for the study. The RR length was measured from the same point in one complex to the next complex for at least six RR intervals in the rhythm strip (lead II); usually the tip of the R wave or the tip of the S wave. The median RR interval was used for the study. There were no patients in the study with congenital or acquired cardiac disease that would have resulted in atypical ECG morphology.

A total of 166 ECGs were recorded after citalopram overdoses (median two per patient, range 1–9) between 0.45 and 81.5 h after the reported time of the overdose (Figure 1, Table 1). From 16 patients an additional 24 ECG recordings (median one, range 1–

Figure 1

Observed QT intervals vs. time (top) and vs. RR intervals (bottom). Measurements from the same overdose event are connected with dotted lines. The solid line in the bottom graph are approximately the 97.5th percentile of normal QT-RR combinations illustrated by Fossa *et al.*, Figure 1 [4]. The observed QT-RR combinations above the lines would therefore be associated with an increased risk of torsade de pointes

4) were available from previous hospital admissions where a noncardiotoxic drug was taken in overdose or the admission was not for an overdose. These were also included in the dataset. There was no case of TdP in this dataset.

Co-ingested drugs Co-ingested drugs taken in overdose were rated by the clinical investigator on a 3-point ordinal scale; 0 = no known influence on the QT interval ($n = 41$), 1 = potential influence on the QT interval, but based on limited reports and no cases of arrhythmias associated with QT prolongation ($n = 13$), and 2 = known potential for prolongation of the QT interval, including cases of TdP ($n = 8$). Drugs classified as

2 in this study were tricyclic antidepressants and venlafaxine.

Pharmacokinetic model

The population PK model building was performed in WinBUGS version 1.4. The procedure and final model have been presented elsewhere [11]. In summary, the concentration–time course was described by a one-compartment structural model with first-order absorption and elimination and an estimated baseline concentration added at time zero for those patients who were taking citalopram therapeutically. The population mean estimates were 22.1 l h^{-1} , 1280 l , 1.48 h^{-1} and 0.097 mg l^{-1} for apparent (oral) clearance, apparent volume of distribution, absorption rate constant and the concentration at baseline, respectively. Between-subject variability ranged from 27% for clearance to 52% for the volume of distribution. The clinical investigator graded the dosing history veracity of each patient and the final model allowed the reported dose amount ingested to be estimated with limits defined by the clinician's veracity grading and a defined maximum error in dose amount (see [11] for details). Patients who had been administered SDAC were estimated to have a 72% higher clearance and a 22% lower fraction absorbed.

The same structure of the PK model was kept here in the PKPD modelling. All PK and PD parameters were estimated simultaneously. The estimated actual dose taken by each patient was fixed in this study to that of the posterior mean values estimated from the PK model [11].

Pharmacokinetic–pharmacodynamic modelling

Model building The QT interval is dependent on heart rate and the relationship is most commonly described by a hyperbolic formula

$$QT = QT_c \cdot RR^\alpha \quad (1)$$

In Bazett's formula (QTcB) $\alpha = 1/2$ while in the Frid-ericia formula (QTcF) $\alpha = 1/3$. Allowing an individual heart-rate correction factor, α_i (i.e. the relationship between QT and RR varies for each individual) has been found to decrease substantially the bias and unexplained variability in evaluation of drug-induced QT prolongation [14, 15]. Therefore the QT interval which is heart rate-corrected with an α specific to each individual was used in this study and denoted by QT_{ci} . It was assumed in using a patient-specific heart rate correction that the value of the correction factor for each individual applies in both overdose and non-overdose scenarios.

The absolute QT interval was assumed to be dependent on the observed RR interval according to Equation 1. The patients' observed RR intervals were therefore treated as independent variables and assumed to be measured without significant error. The predicted concentration of citalopram (C) was allowed to change $QTci$ from the value when no citalopram is present ($QTci_0$), i.e. the baseline, via a model denoted $f(C)$

$$QTci = QTci_0 + f(C) \quad (2)$$

$f(C)$ was allowed to be a linear function,

$$f(C) = Slope \cdot C \quad (3)$$

an E_{max} model,

$$f(C) = \frac{E_{max} \cdot C}{Ec_{50} + C} \quad (4)$$

or an exponential model,

$$f(C) = \Delta QT_{max} \cdot (1 - e^{-k_{DaQT} \cdot C}) \quad (5)$$

Reparameterized versions of the E_{max} model were also tried [16, 17]. A potential delay in the effect of citalopram on the QT interval in relation to the plasma concentration was also evaluated, for example the QT prolongation could be related to an unmeasured toxic metabolite. This was considered by introduction of a hypothetical effect compartment [18]. Log-normally distributed parameters were assumed unless otherwise stated.

Prior distributions

Population mean parameters The prior mean and the precision (the inverse of the variance) of the prior distribution need to be defined in a Bayesian analysis. Priors

with high precision are called informative and priors with very low precision are called uninformative. When uninformative priors are used the information in the data alone will in principle determine the posterior distribution. The prior distributions for the PK parameters were the same as previously reported [11]. The priors used for the PD parameters were in most cases vague but could generally be considered 'biologically plausible', i.e. the 95% intervals of the priors were constructed to include plausible values with regard to previous reports on the QT interval. In other cases the priors were more informative (details provided below).

ECGs from a previously developed group of 318 poisoned patients who had taken single ingestions of paracetamol, temazepam, oxazepam or diazepam (these drugs have no known effect on the QT interval) [6] were used to provide prior information on $QTci_0$. The prior mean value of $QTci_0$ was 423 ms and based on the QTcB measurement in these patients (Table 2). The prior distribution was constructed so that the 95% prior interval also included the previously reported mean QTcB for healthy men and women, 410 and 420 ms, respectively [19]. This relatively high precision of $QTci_0$ was used as normal QT values have been well documented previously and are generally not highly variable. ECGs at baseline were available only for 35% of the patients in our study.

Fridericia's coefficient, $1/3$, was used as the prior mean for the heart-correction factor, α . The 95% prior distribution interval was constructed to cover the extremes of the study means earlier reported (0.25–0.60) in Table 4 in Fenichel *et al.* [20].

In a first step, we assumed we had no prior information on the effect of citalopram exposure on $QTci$, i.e.

Table 2

Prior (log-normal) distributions of PD parameters

	Population mean parameters				BSV ² (CV ²) Mean
	Mean	Precision	2.5th	97.5th	
$QTci_0$ (ms) ^a	423	2474	407	440	0.0056
α	0.333	11	0.19	0.60	0.1
t_{eq} (h)	1	0.36	0.039	26	0.25
$Slope$ (ms l mg ⁻¹)	5	0.28	0.125	200	0.25
E_{max} (ms)	20	0.72	2	200	0.25
Ec_{50} (mg/l ⁻¹)	0.2	0.72	0.02	2	0.25
$\Delta QTci_{max}$ (ms)	100	2	25	400	0.25
$k_{\Delta QTci}$ (mg l ⁻¹)	1	1.48	0.2	5	0.25

^aThe same prior distribution was used for men and women when gender-specific $QTci_0$ was evaluated.

the prior for *Slope* (Equation 3) was assumed to be normally distributed with a mean of zero and a standard deviation of 100 (precision = 0.0001). However, this uninformative prior distribution resulted in convergence problems. At least 97.5% of the samples from the posterior distribution were above zero, indicating an increasing QT interval with increasing citalopram concentration. Therefore, in the following models we used a somewhat less vague prior for parameters describing $f(C)$; the *Slope*, $E_{\max}$ and $\Delta QT_{\max}$. These were constrained to arise from log-normal distributions with the 2.5th percentiles close to zero, allowing for an essentially no-effect relationship between citalopram and QT prolongation (Table 2). It was therefore assumed that if citalopram had an effect on the QT interval it would be a lengthening (not a shortening) of the interval. The prior mean for *Slope* was set to 5 ms l mg⁻¹, which for the highest observed concentration of 1.8 mg l⁻¹ would lead to a QT interval prolongation of less than 10 ms.

A prior mean of 20 ms was used for $E_{\max}$, i.e. a small but clinically significant effect. For EC_{50} we used a prior mean just below the average of all observed concentrations with a 95% prior distribution covering the observed concentration range. Other prior distributions of $E_{\max}$ and EC_{50} were also evaluated. The prior distributions used for $f(C)$ in the later part of the PD-modelling process are presented in Table 2.

The mean of the prior distribution of the half-life of effect delay, t_{eq} , was set to 1 h, predicting the maximum effect to occur after approximately 6 h ($C_{\max}$ for citalopram occurs at approximately 3 h). A relatively low prior precision was used for t_{eq} , allowing for an estimated nondelay (Table 2).

Between-subject variability Between-subject variability (BSV) in the parameters was evaluated and the parameters were assumed to have a log-normal distribution. For $QTci_0$ the mean was set to a CV of 7.6%, a value previously reported in patients who have taken drug overdose of noncardiotoxic drugs [6]. The between-subject variance in α was assumed to have a mean prior variance of 0.10, while t_{eq} and the parameters describing the relationship between the concentration and effect (e.g. *Slope*, $E_{\max}$ and EC_{50}) were all assigned a mean prior variance of 0.25. Relatively non-informative distributions were chosen for the variance-covariance matrix; the degrees of freedom for the Wishart-distribution were 7 for a 3 × 3 matrix and 8 for a 4 × 4 matrix. These numbers of degrees of freedom result in a 97.5th percentile of approximately 200% variability for those between-subject variances with a prior mean of 0.25.

Figure 2

Distribution of age for men (Gender = 0) and women (Gender = 1) (left panel) and for the occurrence of taking coingestant drugs with no (rating = 0), intermediate (rating = 1) and high (rating = 2) risk for QT prolongation (right panel). The 'box' represents the interquartile range with the median. The whiskers are extended to points that are less than 1.5 times the interquartile range below (above) the first (third) quartile. Values outside this range are indicated separately (—●—)

Covariates The available covariates were age, gender and coingested drugs (Table 1). The women were on average younger than men (31.0 vs. 35.7 years), while the median age was lower for men (Figure 2). The average age was highest in those patients with an occurrence of coingested drugs with a rating of 2 (33.4, 23.6 and 39.1 years for a coingestant rating of 0, 1 and 2, respectively), while the average and median ages (Figure 2) were lowest for the patients with a coingestant rating of 1. Relationships between the covariates and the unexplained differences between individuals' parameter values and the typical values in the population were explored by graphical inspection. The significance of any potential relationships was evaluated by incorporation into the population PKPD model using prior distributions with means that predicted no influence of covariates (i.e. the priors were centred on a no-covariate effect). The heart rate corrected QT interval when no drug is present is well documented to be higher in females than in males [19] and has been reported to be increased in the elderly [21, 22]. Therefore, first gender and then age were evaluated as predictors of $QTci_0$ in the model, prior to evaluation of other covariate relationships.

A gender-specific $QTci_0$ (male: *Gender* = 0, female: *Gender* = 1) and the influence of age (centred on the median age of 30) were evaluated in the log-domain of the parameters

$$\ln(QTci_0) = \ln(QTci_{0,men}) \cdot (1 - Gender) + \ln(QTci_{0,women}) \cdot Gender + \ln(\Delta QTci_{0,age}) \cdot \ln\left(\frac{age}{30}\right) \quad (6)$$

$QTci_{0,men}$ and $QTci_{0,women}$ were assumed to have the same prior distributions (Table 2). The prior distribution of $\Delta QTci_{0,age}$ was assumed to have a prior mean of 1 [i.e. $\ln(\Delta QTci_{0,age}) = 0$] and a 95% prior distribution interval ranging between 0.6 and 1.6.

The influence of coingested drugs ($\Delta QTci_{coingest}$) was evaluated as an additive estimated parameter when time was greater than 0.01 h (i.e. not at time zero such that the estimate of $QTci_0$ remains identifiable and independent of potential QT prolongation associated with other drugs taken in overdose),

$$QTci = QTci_0 + f(C) + \Delta QTci_{coingest} \quad (7)$$

$\Delta QTci_{coingest}$ was assumed normally distributed with a prior mean of 0. A relatively uninformative 95% prior distribution interval was used as it ranged between -200 ms and 200 ms.

Parameter estimation WinBUGS version 1.4 [13] was used to fit the PK and PD data simultaneously. The program generates posterior means and credible intervals of the estimated parameters using Markov chain Monte Carlo (MCMC) numerical simulation methods. A proportional residual error was used for the PK data [11] and an additive residual error was used for the QT data. During the model building the posterior distributions of the parameters were determined by two chains of 20 000 samples each after convergence was achieved. The final model was run for 200 000 iterations after convergence but only every 10th sample was used for the posterior distribution to reduce potential influence of autocorrelation between the samples. Convergence was assessed by visual inspection of the history of the two chains and by Gelman–Rubin diagnostics [23].

Model selection Model selection was based on a combination of the following:

- 1 A reduction in the BSV in the parameters and/or a reduction in residual error magnitude.
- 2 The mean of the deviance distribution (equivalent to $-2 \log$ likelihood) and/or the deviance information criterion, DIC, which is the mean of the deviance distribution plus a penalty function for the number of parameters [24].
- 3 The magnitude of an estimated parameter, e.g. the magnitude of the delay in effect.

- 4 The convergence properties of the model given a finite number of iterations of the sampler.
- 5 When 1–4 gave unclear or contradictory outcomes, two models were run simultaneously as mixture models with an extra estimated parameter, *mix*, to indicate which model was preferred [25]. The parameter *mix* was drawn from a uniform distribution between 0 and 1. The proportion of samples that was above or below 0.5 was taken as the posterior probability in favour of either model. The PK model was not altered when considering mixture models for the PD.
- 6 Inclusion of covariates was based on the posterior probability for a clinically significant change in the parameter. A posterior probability >0.5 for a difference of at least 5 ms in $QTci$ was regarded as a significant difference, as the regulatory authorities define QT prolongations <5 ms as clinically unimportant [26]. For the continuous covariate age the two extremes in the population were compared, i.e. the youngest and the oldest.

Sensitivity analysis

The influence of using informative PK priors on the posterior distribution of the PD parameters was assessed in a sensitivity analysis. The prior precision of the PK parameters was decreased by doubling the standard deviation, i.e. reducing the precision by 4, and for BSV by decreasing the number of degrees of freedom of the Wishart distribution for the variance–covariance matrix to a number that increased the 75th percentiles of the distribution of BSV by approximately 50%.

The influence on the PD parameters by the use of a relatively informative prior distribution of $QTci_0$ was also tested by reducing the prior precision on this parameter by 4. For some parameters the influence on the posterior distributions on the choice of the prior mean was also tested.

Prediction of risk for having abnormal QT/RR combinations

The final model was coded in MATLAB (Version 6.5, The MathWorks, Natick, MA, USA) in order to compute the relative decrease in hazard for having abnormal QT-RR combinations by charcoal. The means of the posterior distributions in the final model were used as point estimates of the model parameters. The increased risk of developing an arrhythmia (assumed to be equal to an increased risk of developing TdP) was defined as combinations of QT and RR that exceeded the 97.5th percentile of the normal combinations of QT and RR intervals as presented as the upper bound of the ‘cloud’ by Fossa *et al.* [4]. Since we did not have access to the

models used to develop the diagram presented in Fossa's work, we approximated their upper bound by two linear 'threshold' lines which are illustrated in Figure 1 (bottom panel) together with our observed QT and RR combinations. For the 10th, 50th and 90th percentiles of the observed RR intervals in our study (540, 760 and 1060 ms) we used the 'threshold' lines to obtain the corresponding QT intervals associated with an increased risk for TdP (375, 447 and 480 ms, respectively). From the final model 2000 individuals were simulated and all patients were assumed to be females, 30 years of age, had taken the nominal dose they reported and were taking citalopram therapeutically (i.e. they were assumed to have a baseline concentration). The simulated dose levels were 5, 10, 20, 30, 40, 50, 60, 70, 80 and 90 times the defined daily dose of 20 mg. The probability (equal to the proportion of patients) for being above the QT interval related to an increased risk for TdP was evaluated from the simulation QT-time course profiles for each of the three RR intervals.

For an RR interval of 760 ms, for which the threshold QT interval was 447 ms, patients were simulated as either having received charcoal or not. The instantaneous hazard was set to be the fraction of patients at any given time that had a predicted QT interval ≥ 447 ms. The cumulative hazard was taken to be the integral of the instantaneous hazard (i.e. the area under the curve for the probability for having a QT ≥ 447 ms vs. time) from 0 to 96 h. The relative decrease in cumulative hazard associated with administration of activated charcoal was then computed.

In the model the effect of charcoal was assumed to be constant over time and therefore the estimated effects on clearance and the fraction absorbed were averaged over the observation period for all patients who were administered charcoal. In the simulations the same model and assumptions were applied.

However, the effect of charcoal on the overall fraction absorbed will decrease with time after the overdose as the majority of the drug has already been absorbed when charcoal is administered. The later that charcoal is administered, the less effect it will have on early high concentrations. Therefore a 'worst-case' scenario was also simulated. In these simulations it was assumed that all patients were administered charcoal at 4 h after the overdose (no patient in our study had been administered charcoal after this time point). The previously estimated effect of charcoal on the fraction absorbed was assumed to be negligible. We also assumed that the charcoal effect on clearance, i.e. gastrointestinal dialysis, only lasted for 12 h after administration because after this time charcoal may not still be in the gastrointestinal

tract. By doing this the previously estimated effect of clearance (a 72% increase) was regarded as the maximum impact charcoal can have on clearance rather than an average effect over the whole observation period. Apart from the charcoal effect, all simulation conditions in this scenario were as described above.

Results

Final model

The final model included an individual-specific heart-rate correction factor, α_i , a linear concentration–effect relationship (Equation 3) that included an effect-compartment model and a gender-specific value of $QTci_0$ which increased with age to the same degree for both men and women (Figure 3). The model described the data accurately (Figure 4). The final parameter distributions are presented in Table 3 and the critical model building steps are described below in Model selection.

The data contained information on all parameters as the posterior means were shifted from the prior and the 95% posterior distribution intervals were narrower than the 95% prior distribution intervals (Figure 5). For an individual with typical PK and PD parameter values the maximum prolongation of the QT interval was predicted to occur at 7.8 h after the overdose, while the maximum plasma concentration was predicted to occur after 2.9 h (Figure 6, top panel). The final model predicted a pronounced reduction of the QT prolongation after administration of activated charcoal (Figure 6, bottom panel). The *Slope* was estimated to 40 ms l mg^{-1} , i.e. the $QTci$

Figure 3

Estimated relationship between the baseline heart rate corrected QT ($QTci_0$) and age for men (dotted line) and women (solid line)

Table 3

Means (95% CI)^a of the posterior parameter distributions

	Population mean (95% CI) ^a	BSV ^b (CV%) (95% CI)
$QTci_{0, \text{women}}$ (ms)	429 ^c (420–439)	5.3 ^d (4.0–7.0)
$QTci_{0, \text{men}}$ (ms)	420 ^c (409–432)	5.3 ^d (4.0–7.0)
$Slope$ (ms l mg ⁻¹)	40.0 (18.8–65.8)	70.2 (37.8–116.4)
α	0.364 (0.313–0.415)	28.5 (18.8–39.2)
t_{eq} (h)	1.43 (0.0847–4.42)	Not estimated
$\Delta QTci_{0, age}$	1.07 (1.03–1.12)	–
Residual error (ms)	16.8 (14.8–19.1)	–

^aCI, Credible interval of posterior distribution, i.e. the interval covering 95% of the MCMC samples. ^bApproximated to the square root of the estimated between-subject variance. ^cFor a 30-year old patient. ^dForced to be the same value for men and women.

Figure 4

Observed QT intervals vs. individual predicted QT intervals with the line of identity (—)

will for a typical patient increase 40 ms for an effect-compartment concentration increase of 1 mg l⁻¹. Interpretation of this $Slope$ value for a standard therapeutic steady-state concentration of 0.05–0.1 mg l⁻¹ results in a predicted increase in $QTci$ of 2–4 ms for a typical patient, which is clinically insignificant. This finding is expected since citalopram is considered noncardiotoxic after usual therapeutic doses [27].

The PK parameter means were similar to the estimates based on analysis of the PK data only [11]. The between-subject variance parameters and the proportional residual error were all 2.0–5.3% lower than in the PK analysis.

Model selection

An individual estimate of the heart rate correction factor α resulted in a decrease in deviance and DIC by 40 and 22 units, respectively, as well as a reduction in the residual error and the BSV in $f(C)$.

The nonlinear models for describing $f(C)$, which used two parameters (Equations 4 and 5), led to convergence problems which we believe were due to over-parameterization. The problems remained when other parameterizations were tried and when BSV in E_{max} was omitted. In addition, the deviance and DIC were similar for the more complex models as for linear concentration–effect models. The linear model was therefore chosen.

The between-subject variance in $Slope$ was reduced from 0.54 to 0.49 when an effect-compartment was added; while the deviance and the DIC were similar to a model without an effect-compartment. A mixture-model approach for model selection was applied and the posterior probability in favour of an effect-compartment model was 0.6. Consideration of both the mixture model and the significant reduction in unexplained between subject variance in the other parameters, in conjunction with the magnitude of the estimated effect-delay ($t_{eq} = 1.4$ h), supported the choice of an effect-compartment model. However, the data contained too little information for estimation of BSV in t_{eq} .

The posterior probability for a 5 ms difference in $QTci_0$ between men and women was 0.74. The corresponding probability for at least a 5 ms difference between the youngest and the oldest individuals was >0.99 for both men and women. Other relationships between $QTci_0$ and age were also explored, but the

Figure 5

Ninety-five percent prior intervals (Prior) and 95% credible intervals for the final model (Final model), when using reduced prior precision on the PK parameters (Prior Prec PK↓), and when using reduced prior precision on QTc_0 (Prior Prec QTc_0 ↓), i.e. when the 95% prior interval for QTc_0 was increased and ranged between 392 and 457 ms. Men (♂) and women (♀) were allowed to have different distributions of QTc_0 . Note that because of the vague prior distributions used, the distributions of t_{eq} and Slope are on log-scale

model described in Patients and methods (Equation 6) gave the best results with the lowest deviance and DIC. No other covariate relationships were found to influence the PD parameters. When $\Delta QTc_{coingest}$ was tried in the model, the posterior probability was 0.46 for a $\Delta QTc_{coingest}$ of 5 ms (coingested drug rating = 2) with the posterior mean estimated to 4.2 ms. This effect was regarded as clinically insignificant.

Sensitivity analysis

Less informative PK parameter prior distributions did not affect the posterior distributions of the PD population mean parameters (Figure 5), including the age-dependent effect (data not shown) and the BSV parameters (data not shown).

A lower precision of the prior distribution of QTc_0 decreased the posterior mean of QTc_0 for men from 420 to 418 ms (Figure 5). Other changes in the parameter distributions were negligible.

Widely dispersed values of the mean of the prior distribution of t_{eq} were tried, and although a mean of the posterior distribution was influenced, the differ-

ence was <20%, suggesting that the posterior mean was relatively insensitive to the choice of the mean of the prior.

Prediction of increased risk for TdP

The probability of an abnormal QT value following various sized overdoses of citalopram at the median RR value of 760 ms (79 bpm) is shown in Figure 7. It was found that the effect of citalopram on QT prolongation was less pronounced at this heart rate than the other heart rates evaluated (57 and 111 bpm; data not shown). Administration of activated charcoal reduced the probability for having a QT associated with increased risk of TdP (Figure 7, bottom panel, compared with the upper panel). The relative decrease in the cumulative hazard for TdP was approximately 60% for overdoses of 600–1800 mg after administration of charcoal (Figure 8). For the ‘worst-case’ scenario, i.e. where charcoal was assumed to affect clearance only between 4 and 16 h after the overdose by the previously estimated average effect on clearance, and to have no effect on the total fraction absorbed, a relative decrease of 20% in risk by

Figure 6

Simulated plasma concentrations (.....) and QT intervals (—) vs. time for a patient with typical PK and PD parameters after an overdose citalopram, without taking charcoal (top panel). The bottom panel shows the predicted effect on QT interval prolongation without (—) and with (.....) administration of activated charcoal. In both panels the dose was 1200 mg and the RR interval was 760 ms

Figure 7

Simulated probability over time for having a QT $\geq$ 447 ms for a given RR interval of 760 ms. Ten different dose levels are shown, ranging from 100 mg to 1800 mg. The top panel shows the probability without charcoal administration and the lower panel the probability if charcoal is administered. In the simulations all patients were assumed to be 30-year-old women who were also taking citalopram therapeutically

administration of charcoal was predicted for doses of 600–1800 mg (Figure 8).

Discussion

A PKPD model predicting QT prolongation after citalopram overdose was successfully developed. The model showed a delayed prolongation of the QT interval compared with the plasma concentrations and, most importantly, it demonstrates that administration of activated charcoal produced a clinically beneficial reduction in citalopram-induced QT prolongation. Administration of charcoal was also shown to reduce the risk of having

abnormal combinations of QT–RR that are associated with increased risk for TdP by approximately 60% (Figure 8). When administered late (e.g. 4 h after the overdose) the effect of charcoal is likely to be reduced because most of the drug will have been absorbed. However, gastrointestinal dialysis by charcoal [28], that is postulated to be the mechanism for increased citalopram clearance, remains an important decontamination process that was of significant clinical benefit (Figure 8). Citalopram has a long half-life, a low hepatic extraction ratio and unrestrictive protein binding, which are typical PK characteristics for drugs potentially affected by gas-

Figure 8

Relative decreases in cumulative hazard for having an abnormal QT interval (≥ 447 ms) at an RR interval of 760 ms associated with administration of charcoal for different dose levels of citalopram when the average effect of charcoal estimated in the PK modelling was used (solid line) and for the 'worst-case' scenario where the previously estimated charcoal effect is only present on clearance at 4–16 h after the overdose (dashed line)

trointestinal dialysis [29]. The true charcoal effect on the decreased risk of TdP is time dependent. From the results from this study we believe the true effect is probably at least 20% when charcoal is administered within 4 h after the overdose and may be greater than 60% if administered within 1 h after the overdose.

As there was a time delay between plasma concentrations of citalopram and the time-course of QT prolongation, it would be difficult to predict the risk of toxicity without a PKPD model. QTc prolongation has previously been modelled with a delay for other drugs (see, for example, [30, 31]). A delay could be due to formation of metabolites that affect cardiac conduction and/or because of a delay due to drug distribution to the myocardium, as suggested for tacrolimus and quinidine in a guinea pig model [32]. However, the half-life of effect-delay estimated here was relatively long, suggesting the contribution of a metabolite. QT prolongation after citalopram administration paralleled the concentrations of the metabolite didemethylcitalopram (DDCT) in dogs [33]. DDCT has approximately a three times longer half-life than citalopram [34]; however, the parent compound seems itself to be able to block potassium channels [35]. The PK of DDCT is poorly characterized, as concentrations of DDCT are relatively low and difficult to quantify. DDCT concentrations were not available in the present study. In humans the reported $t_{\max}$ for DDCT

has varied from approximately 7 h [36] to 18 h [34]. The latter value would correspond to an approximate t_{eq} of 5 h, much longer than our estimated value of 1.4 h. From these results the influence of both citalopram and its metabolites on QT prolongation cannot be excluded.

In most previously presented PKPD models of QT interval prolongation, QTcB or QTcF have been used as the dependent variable. However, the limits of using a fixed population value of the heart rate correction factor have been demonstrated on numerous occasions and estimating an individual heart rate correction factor reduces the residual variability in QTc and thereby increases accuracy with which the drug-induced effect on QTc can be quantified [14, 15, 37]. The data included information about α as the posterior interval was narrower than the prior interval (Figure 5). Allowing an individual heart rate correction factor improved the fit of the model to our data, compared with when only a single value was estimated for the whole population. There was no apparent estimation correlation between α and *Slope*, i.e. both parameters could be identified in the population analysis despite the sparse baseline data. When the individual estimates of α were plotted vs. dose there was no trend for any relationship (data not shown).

We did not include concentration–effect relationships for the RR interval which may also be plausible. Citalopram has been reported to cause bradycardia but in our study the RR interval showed a slight decrease with increased predicted plasma or effect-compartment concentrations. A similar relationship was also seen when excluding observations arising from occasions with cardiotoxic coingestant drugs (data not shown).

The baseline value of QT corrected to 60 bpm (QTc_{i0}) was found to be 9 ms (2.2%) longer in females than in males, which is in the range of the gender differences in QTc found in other studies of healthy volunteers (1.6–5%) [21]. A trend for increasing QTcB with age has also been found (average was 397 ms for 20–40-year-olds and 412 ms for >70-year-olds) [21]. In another study the QTcB increased with age from 407 ms for a 40-year-old to approximately 440 ms for a 100-year-old [22].

As the relationship between the absolute QT interval (or the heart rate-corrected QT interval) and the risk for TdP is not yet defined and there was no case of TdP in the present study, we used a previously described threshold level for assessment of being at increased risk of an arrhythmia, i.e. for having abnormal QT-RR combinations [4]. We computed the relative risk decrease for being above the threshold QT interval related to a specific RR interval when activated charcoal is administered. Unfortunately, the true relationship between QT prolongation and the absolute risk for TdP is not known.

The absolute risk is not likely to be threshold related but dependent on the time-course of QT prolongation and the degree of QT prolongation. The relationship might also be drug specific and is known to be dependent on several other risk factors [38, 39].

We demonstrated at least a 20% relative risk reduction (worst-case scenario) and up to a 60% relative risk reduction following a low-risk intervention which is of clinical relevance. There is only one previously published example which has demonstrated a real clinical benefit of SDAC in overdose patients (paracetamol [40]); and therefore its use, especially at times greater than 1 h after ingestion, has been debated [41]. Our study showed a significant effect of SDAC on the QT interval after citalopram overdose and a predictive model was developed that described this charcoal effect.

In conclusion, a PKPD model was developed which demonstrated delayed QT prolongation following citalopram overdose. Administration of activated charcoal was shown to cause a pronounced effect on reducing citalopram-induced QT prolongation and thereby decreasing the risk for having abnormal QT-RR combinations and hence the risk for development of TdP.

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