Individual clearance and therapeutic drug monitoring of Quetiapine in clinical practice

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Abstract

OBJECTIVE: Quetiapine is one of the most frequent prescribed antipsychotics. Based on the consensus guidelines of therapeutic drug monitoring (TDM) in clinical practice, TDM of Quetiapine is "useful". In this pilot study, using a natural sample, we investigated the influence of co-medication, age and gender on the serum concentrations and clearance of Quetiapine. Also we compared the individual clearance in our sample with the expected clearance for healthy subjects, obtained in controlled studies.

METHODS: 150 blood samples were collected anonymously under clinical conditions, Quetiapine trough serum levels were determined using HPLC. Additional information about gender, age, co-medication and dosage was obtained.

RESULTS: There was a significant, positive, but weak correlation between daily dose and serum levels of Quetiapine (r=0.44; p=0.01). When Carbamazepine was co-administered, the clearance was significantly higher (p=0.01). 83% of the serum levels were outside the therapeutic range, only 28% were within the expected clearance.

CONCLUSIONS: In addition to the therapeutic range the individual clearance related to the expected clearance may help to optimize individual pharmacotherapy, especially for combination therapy or in case of incompliance or abnormal metabolism.

Abbreviations :

Cl	- clearance
CYP	- cytochrome P-450 enzyme
c_{ss}	- serum concentration in steady state
D	- daily dose
EC	- expected clearance
F	- oral bioavailability
HPLC	- high pressure liquid chromatography
SD	- standard deviation
SPC	- summary of product characteristics
TDM	- therapeutic drug monitoring
TR	- therapeutic range

ORIGINAL ARTICLE

INTRODUCTION

In the recent years there has been a shift in the prescribing pattern of antipsychotics with an increase in usage of the newer atypical antipsychotics. Quetiapine has been demonstrated to be one of the most frequently prescribed antipsychotics not only for schizophrenia and bipolar disorders, but also in off-label-use for other psychiatric disorders (Wittmann *et al.* 2007; 2009). Although initial doses of 300 mg and more are common, an acute overdose of Quetiapine can lead to coma, respiratory insufficiency and severe hypotension (Ngo *et al.* 2008). A recent cohort study showed the highest overall mortality rate for Quetiapine, compared to other second-generation antipsychotics (Tiihonen *et al.* 2009). Based on the consensus guidelines for the use of therapeutic drug monitoring (TDM) in clinical practice, TDM of Quetiapine is "useful", as suggested therapeutic ranges are serum concentrations at therapeutically effective doses obtained from steady-state pharmacokinetic studies (Baumann *et al.* 2004). In spite of the obvious advantages of TDM in psychiatry, utilization in practise is poor, although numerous studies indicated high incompliance rates.

The evaluation of serum concentrations for TDM to avoid adverse events is based on the therapeutic range (TR). Also poor compliance could be implicated if the daily dose is associated with a measured low concentration or if a previous measurement suggested that the plasma concentration should be higher for the given dose. But for daily doses outside the recommended dosage the therapeutic range (TR) is not suitable to detect relevant drug interactions or incompliance, as the dose of the administered drug remains unconsidered.

As the final rationale for TDM is actual or suspected overdose with pharmacologic substances we investigated in this study, how the individual clearance may give additional information about possible reasons for elevated or lowered serum levels like incompliance, abnormal individual metabolism or interactions (Haen *et al.* 2008; Haen 2005; De Vane & Nemeroff 2001; Ereshefsky 1996; Markowitz *et al.* 1999).

MATERIAL AND METHODS

A laboratory for therapeutic drug monitoring is attached to the Dpt. of Psychiatry, University of Regensburg, Germany, where by this time the serum concentrations of 47 different psychotropic drugs are routinely determined for TDM in clinical practise. Additional to data about the daily dose of the determined substance information about complete co-medication, age and gender is included in the form which goes along with the blood specimen, afterwards a special programme for TDM was used for collecting and managing the data. In this study we evaluated 150 specimens of patients treated with Quetiapine. The physicians, who collected the specimens, were briefed to take trough serum levels of Quetiapine.

High pressure liquid chromatography (HPLC) was used for analyzing. Samples with missing information on the daily dose were dropped out from study evaluation. Co-medication was classified according to drugs which induce CYP3A4, inhibit CYP3A4, that are only substrates of CYP3A4 or are supposed to have no relevant interactions with Quetiapine. The co-administered inhibitors were all assumed to be no potent inhibitors, in detail Haloperidol, Omeprazole, Esomeprazole, Sertraline and Paroxetine (Cozza *et al.* 2003). Extended release-tablets of Quetiapine (Seroquel XR® / Seroquel prolong®) were not prescribed in any case. The data were initially made anonymous and then evaluated statistically using SPSS®.

Based on clearance data of Quetiapine obtained in controlled steady-state pharmacokinetic studies (McConville *et al.* 2000) and using the term $D^*F=Cl\pm SD^*c_{ss}$ (D=daily dose; F=oral bioavailability; Cl= Clearance; c_{ss}=serum concentration in steady state; SD=Standard deviation), we calculated the expected clearance (EC) $=Cl\pm SD/F=c_{ss}/D$ for Quetiapine mono-therapy in healthy subjects to be between 0.29 and 0.61 [µg/L]. To get the upper and lower limit for this range, standard deviation was added and subtracted from the mean clearance. Thus, the expected clearance (EC) represents 68.27% of the serum levels of healthy subjects (Haen *et al.* 2008).

According to the summary of product characteristics (SPC) of Quetiapine the Clearance in the elderly is about 30–50% lower. Quetiapine is mostly metabolized by the Cytochtrome-P450-enzyme 3A4, the enzymatic activity and genetic expression of this enzyme shows a high interindividual variability (Guengerich, 1999; Shimada *et al.* 1994; Watkins 1994). The therapeutic range of Quetiapin is between 70 and 170 µg/L (Baumann *et al.* 2004).

In this study we described the distribution of both serum levels and individual clearance related to the therapeutic range and the expected clearance of Quetiapine in a natural sample, obtained in clinical practice. The primary goal was to investigate, how using both the individual and the expected clearance may help to optimize pharmacotherapy in clinical practice.

RESULTS

Sample

From 150 samples (=100% of Q_{all}), 64 samples (=42.7% of Q_{all}) were from male patients and 72 from female patients (=48.0% of Q_{all}). In 9.3% (n=14) gender information was missing. The mean age was 41±15 years, the Quetiapine daily dose was 611±352 mg. 46 samples were from patients who received Quetiapine as a drug mono-therapy (=100% of Q_{mono}). The mean daily dose in this subpopulation was 677±375 mg without significant differences to the samples with co-medication (=$Q_{co\text{-}med}$; n=104; p=0.13). The mean age of Q_{mono} was 39±16 years, also without significant differences com-

pared to $Q_{co\text{-}med}$ (p=0.3). Gender ratio in Q_{mono} was male:female = 26:13 (67%:33%).

Age-related differences (Q_{all})

Eight patients were older than 65 years, 129 younger. For the rest of the cases information about age was missing.

The daily dose was significant lower in patients elder than 65 years (281 mg vs. 624 mg; p=0.03). The mean clearance showed large age-related differences (> 65 y.: 52 L/h; <= 65 y.: 198 L/h; p=0.17). The difference was not significant, but probably due to the low number of cases older 65 (Figure 1).

Gender differences (Q_{all})

Female subjects got a significant lower mean daily dose (500mg) of Quetiapine than male subjects (718 mg; p=0.00), whereas there was no significant difference in the clearance (m: 195L/h; f: 174L/h; p=0.71). This finding corresponds to the SPC.

Serum concentrations (Q_{all})

The correlation of dose and serum concentration was r=0.44 (p=0.01), the serum concentrations varied widely between 10 and 1715 µg/L. The mean total Clearance Cl/F was 200±376 L/h (Q_{all}).

Table 1 shows the serum concentrations of Quetiapine related to the therapeutic range (TR) and the expected clearance (EC) for Q_{all}. Each serum concentration, related to the associated dose, corresponds to an individual clearance.

83% (n=125) of the samples (Q_{all}) were outside the therapeutic range (TR) and 72% (n=108) deviated from the expected clearance (EC). In 8 of 78 cases, in which the measured Quetiapine serum concentrations were lower than the therapeutic range, Carbamazepine was co-administered. The rest of these cases were thought to be ultra-rapid metabolizers or to be of poor compliance. As in case of non- or poor compliance the assumed daily dose is (much) higher as in fact, the calculated clearance data could be wrongly misinterpreted as an indication for high activity of the drug-metabolising enzyme.

Table 1 shows the distribution of the serum levels that are below, within or above the therapeutic range and/or the expected clearance, respectively. The samples e.g. in field [B2] are both within the therapeutic range. That is, for these 6 cases, a sufficient therapeutic effect can be expected without a high probability for dose-related adverse events. These cases are within the expected clearance and also the patient seems to be compliant. In addition, in case of co-medication, there is probably no relevant drug interaction and in case of a drug mono-therapy, the patient probably is an extensive metabolizer. Serum levels e.g. in the field [A3] are below the therapeutic range, but the clearance is lower than expected. This is a typical finding for poor metabolizers at very low therapeutic doses. If the dose is increased, high serum levels with possible side effects will be expected. Only 25 cases of Q_{all} were within the therapeutic range, as the values varied widely. As 72% were outside the expected clearance (EC) and drug interactions could be a possible reason for this finding, we afterwards analysed the samples in which Quetiapine was prescribed as a drug mono-therapy.

Monotherapy (Q_{mono})

If Quetiapine was prescribed without co-medication as a drug mono-therapy (=Q_{mono}; n=46), there was a weak correlation between dose and serum concentration (r=0.47; p<0.01). The mean serum concentration was 438±379 µg/L, and the mean clearance 211±387 L/h. There were no significant differences between the Clearance of Q_{mono} and $Q_{co\text{-}med}$ (p=0.6).

Age differences (Q_{mono})

As only three subjects of Q_{mono} were older than 65, the age difference was not significant (p=0.43), but in absolute numbers, the clearance of the elderly was about 8-fold lower than in the rest. (>65 y: 28 L/h; ≤65 y: 213 L/h).

Tab. 1. Serum concentrations related to the therapeutic range (TR) and individual clearance values compared to the expected clearance (EC) (Q_{all}).

Q_{all}; n=150		Therapeutic range (TR)		
		c<TR	c=TR	c>TR
Individual clearance (Cl) and expected clearance (EC)	Cl>EC	n=24 (16%) [A1]	n=9 (6%) [B1]	n=7 (5%) [C1]
	Cl=EC	n=3 (2%) [A2]	n=6 (4%) [B2]	n=33 (22%) [C2]
	Cl<EC	n=0 (0%) [A3]	n=10 (7%) [B3]	n=58 (39%) [C3]

c= serum concentration; Cl = individual clearance

Tab. 2. Monotherapy (Q_{mono}): Serum concentrations related to the therapeutic range (TR) and individual clearance values, compared to the expected clearance (EC).

Q_{mono}; n=46		Therapeutic range (TR)		
		c<TR	c=TR	c>TR
Individual clearance (Cl) and expected clearance (EC)	Cl>EC	n=4 (9%)	n=4 (9%)	n=1 (2%)
	Cl=EC	n=0 (0%)	n=0 (0%)	N=11 (24%)
	Cl<EC	n=0 (0%)	n=3 (6%)	n=23 (50%)

c= serum concentration; Cl = individual clearance

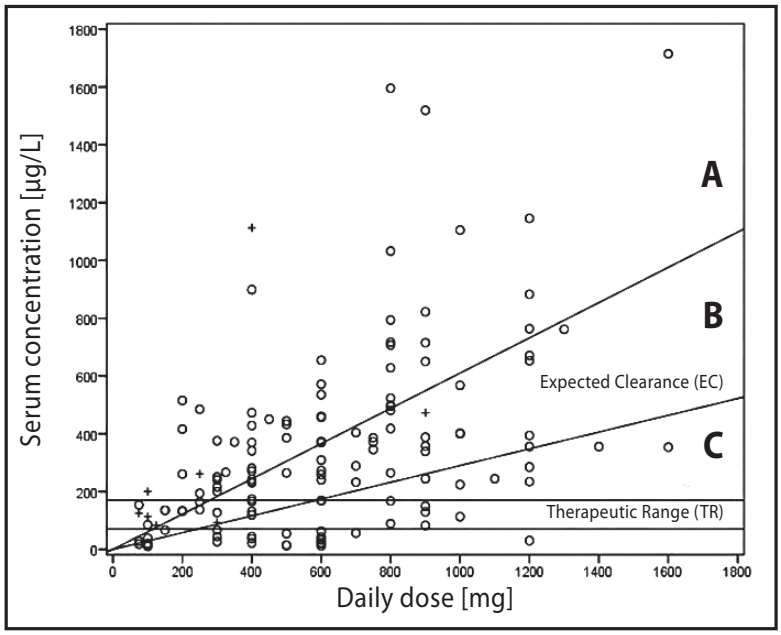

Fig. 1. Serum concentrations of Q_{all} (n=150); **+** = age > 65 years. Each serum concentration, related to the associated dosage, corresponds to an individual clearance. The serum concentrations within '**B**' represent an individual clearance which is within the expected clearance (EC) of Quetiapine. Serum concentrations in '**A**' represent a clearance which is lower than expected and serum levels in '**C**' a clearance that is higher as the expected. These concentrations may also indicate a possible incompliance. Only one of the samples of subjects >65 yrs. was within the expected clearance (EC). The serum levels of 3 samples (>65 yrs.) were within the therapeutic range, but only at very low daily doses.

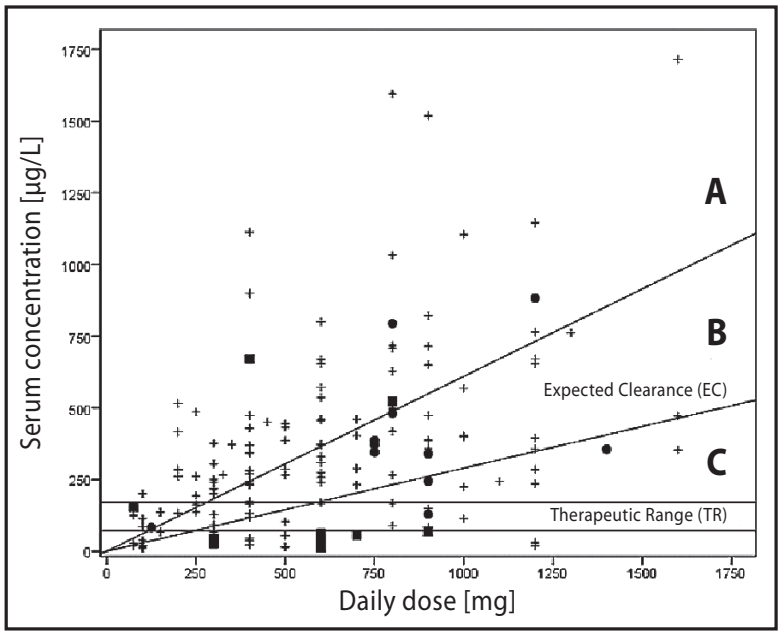

Fig. 2. Drug interactions (n=150; Q_{all}); **+**: no relevant interaction; ●: co-administered inhibitor; ■: co-administered inducer; The serum concentrations within '**B**' represent an individual clearance which corresponds to the expected clearance of Quetiapine. Serum concentrations in '**A**' represent a clearance, which is lower than expected, serum levels in '**C**' a clearance that is higher as the expected clearance (EC), also they may indicate a possible incompliance.

Gender differences (Q_{mono})

In contrast to Q_{all}, the clearance of the female subjects in Q_{mono} was much lower (73 L/h) than that of the male subjects (255 L/h), but only negligibly (p=0.06).

In Q_{mono} 15% of the samples were within the therapeutic range and 11% of the samples within the expected clearance (Table 2).

Simultaneous therapy with a CYP3A4-Inducer (Q_{ind}) or Inhibitor (Q_{inh})

In 11 cases (of Q_{all}), a CYP3A4-Inducer was co-administered (=$Q_{ind;}$ in all cases Carbamazepine), Cl/F was significantly higher in Q_{ind} than in Q_{mono} (p=0.01). There were no significant differences in age (p=0.36) and daily dose (p=0.24). The clearance values of 3 sam-

ples were within or lower than the expected clearance (EC), although Carbamazepine was co-administered. In the rest of Q_{ind}, the clearance of Quetiapine was higher, how expected.

In 12 cases a CYP3A4-Inhibitor was co-administered (Q_{inh}). There were no significant differences in dose (p=0.22), age (p=0.45) and clearance (p=0.88). This was probably because no potent inhibitor was co-administered (Figure 2).

DISCUSSION

Only the minority of the samples was within the expected clearance (EC) or the therapeutic range. This result could be reproduced in the subpopulation Q_{mono}, which got Quetiapine as a pharmacologic single-treatment regimen. Factors like (yet unknown) drug interactions, individual metabolism or incompliance may be the basis for those findings. Therefore in clinical practice for defined doses of Quetiapine, the resulting steady-state serum concentration c_{ss} is very difficult to predict. Except when Carbamazepine was co-administered, no relevant influence of co-medication could be found. This finding, however, should be put into perspective, as the broad distribution of the serum concentrations can be a sum effect of drug interactions and individual metabolism. The distribution of the serum levels in Q_{mono}, however, indicates a high number of rapid or poor metabolizers, which is a typical finding for drugs that are metabolized mostly by CYP3A4. In 8 of 11 cases of co-administered Carbamazepine, the individual clearance of Quetiapine was higher than the expected clearance (EC), which was expected, but in two cases it was even lower. This demonstrates that factors like individual metabolism may antagonize an expected interaction and underlines the importance of therapeutic drug monitoring in clinical practice.

Using clearance data could fill a gap in TDM: Both at very low and very high dosages, incompliance can be indicated as well as relevant drug interactions or abnormal metabolism. Although by using the clearance for TDM it is not possible to distinguish e.g. between a rapid metabolizer and incompliance, or a poor metabolizer and a co-administered inhibitor, it could be a useful and early indicator for these factors.

In the SPC (summary of product characteristics) of Quetiapine, the clearance of the elderly is mentioned to be about 30 to 50 % lower. Our findings, however, indicate that the clearance in a natural sample may probably be even much lower. The therapeutic benefit using the individual clearance of Quetiapine for TDM is limited for the elderly, because there is no valid clearance data for this population as controlled trials to evaluate representative clearance data of Quetiapine are missing.

Quetiapine is thought to have a large therapeutic spectrum. Sachse *et al.* found a definite increase of dose related adverse events not till a serum concentration of about 500 µg/L (Sachse *et al.* 2003). As the majority of the cases in our sample showed a serum concentration higher than the therapeutic range, at least the upper limit of the reference range of Quetiapine (170 µg/L) is disputable in the authors' opinion.

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