Psychiatr Q (2013) 84:329–335
DOI 10.1007/s11126-012-9248-9

ORIGINAL PAPER

Use of High Doses of Quetiapine in Bipolar Disorder Episodes are not Linked to High Activity of Cytochrome P4503A4 and/or Cytochrome P4502D6

Yasser Khazaal · Martin Preisig · Anne Chatton · Nadine Kaufmann · Romain Bilancioni · Chin B. Eap

Published online: 15 November 2012

Abstract The use of quetiapine for treatment of bipolar disorders at a higher dosage than the licensed range is not unusual in clinical practice. Quetiapine is predominantly metabolised by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by CYP2D6. The large interindividual variability of those isozyme activities could contribute to the variability observed in quetiapine dosage. The aim of the present study is to evaluate if the use of high dosages of quetiapine in some patients, as compared to patients treated with a dosage in the licensed range (up to 800 mg/day), could be explained by a high activity of CYP3A4 and/or of CYP2D6. CYP3A4 activities were determined using the midazolam metabolic ratio in 21 bipolar and schizoaffective bipolar patients genotyped for *CYP2D6*. 9 patients were treated with a high quetiapine dosage (mean ± SD, median; range: 1467 ± 625, 1200; 1000–3000 mg/day) and 11 with a normal quetiapine dosage (433 ± 274, 350; 100–800 mg/day). One patient in the high dose and one patient in the normal dose groups were genotyped as *CYP2D6* ultrarapid metabolizers. CYP3A4 activities were not significantly different between the two groups (midazolam metabolic ratio: 9.4 ± 8.2; 6.2; 1.7–26.8 vs 3.9 ± 2.3; 3.8; 1.5–7.6, in the normal dose group as compared to the high dose group, respectively, NS). The use of high quetiapine dosage for the patients included in the present study cannot be explained by variations in pharmacokinetics parameters such as a high activity of CYP3A4 and/or of CYP2D6.

Keywords Bipolar disorder · Quetiapine · Pharmacokinetics · CYP3A4 · CYP2D6

Y. Khazaal (✉) · A. Chatton
Geneva University Hospitals, Grand pré, 70 C, 1206 Geneva, Switzerland
e-mail: yasser.khazaal@hcuge.ch

M. Preisig · N. Kaufmann · R. Bilancioni
University Hospital Center and University of Lausanne, Lausanne, Switzerland

C. B. Eap
Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, University Hospital Lausanne, Prilly-Lausanne, Switzerland

Introduction

Quetiapine was found to be effective in the treatment of acute bipolar mania, both as monotherapy [1–3] and in combination with other mood stabilizers [4, 5] as well as monotherapy in bipolar depression [6]. The quetiapine dosage in mania studies was usually up to 800 mg/day [1–6] and up to 600 mg for the treatment of bipolar depression [6]. The response rates of groups receiving quetiapine in those studies varied between 43 and 58 % [1]. Part of the non-response may be due to an inadequate dosage. The use of high-dose of quetiapine (>800 mg/day) is not unusual in clinical practice, but there are few published data regarding its efficacy or safety [7]. In a retrospective analysis of 94 patients with bipolar or schizoaffective bipolar disorder treated in the Department of Psychiatry (Lausanne, Switzerland) between December 1999 and February 2005, more than thirty percent received quetiapine at a dosage higher than 800 mg [8]. One can hypothesize that such dosage variability may be due, in part, to the inter-individual variability of drug pharmacokinetics.

Quetiapine is predominantly metabolised by cytochrome P450 3A4, whereas CYP2D6 only contributes to a small extent, via quetiapine 7-hydroxylation [9]. Accordingly, quetiapine pharmacokinetics was affected when administered with potent CYP3A4 inhibitors or inducers such as ketoconazole or carbamazepine [10]. The large interindividual variability of CYP3A4 [11] and/or of CYP2D6 [12] activities could thus contribute to the variability in quetiapine dosage.

The aim of the current study was to evaluate if high dosages of quetiapine (>800 mg), when used under routine clinical conditions in a sample of bipolar and schizoaffective bipolar patients, could be explained in part by high CYP3A4 and/or of CYP2D6 activities, in comparison with patients treated with a dosage of quetiapine within the licensed range (≤800 mg).

Methods

Patients were recruited from the Department of Psychiatry, Lausanne, Switzerland. During a 6 months period, all adult patients with bipolar or schizoaffective bipolar disorder, who were receiving or had received treatment for a major affective episode with quetiapine, were identified and the study was proposed. Quetiapine was usually introduced during hospitalization, with a rapid titration scheme (200 mg at day 1, 400 mg at day 2) or less frequently with a slower titration scheme (50 mg at day 1, 100 mg at day 2). The dosage was thereafter adjusted (increased or decreased) every 2–7 days, in order to optimize efficacy and tolerability. The patients were classified respectively as high (>800 mg/day) and normal quetiapine dosage (≤800 mg/day), in accordance with the highest dosage prescribed to each patient during an actual or past episode.

Hepatic and renal functions were assessed using standard clinical laboratory tests (alanine amino transferase, aspartate amino transferase, alkaline phosphatase, ϒ-glutamyltransferase, and creatinine concentrations). Blood samplings for quetiapine serum/plasma concentration determinations were performed before the morning medication intake. The concentrations of quetiapine were determined using a high-pressure liquid chromatography column (analytical column: EC 125/2 Nucleosil 100-5 C18, 5 μm silica gel, 125 × 2 mm, Astec, Basel, Switzerland) with a mass spectrometry detector (HP 1100 series, Agilent Technologies, Palo Alto, CA, U.S.A.) after a liquid–liquid extraction step. The LC conditions were: mobile phase: 35 % tetrahydrofuran: 65 % 4 mM NH_4NO_3: 1.5 % methanol;

flow rate: 0.3 ml/min. Analyses were performed in the selected-ion monitoring mode for the ions at *m/z* 384.2. The limit of quantification was 0.4 ng/ml. Intra- and interday coefficients of variation determined at three concentrations ranged from 0.9 to 1.8 % (Eap et al., unpublished method, detailed method available on request).

CYP3A4 activity was measured using the midazolam metabolic ratio (MR) as previously described [13, 14]. In summary, following oral administration, midazolam is oxidized to 1′-OH midazolam by CYP3A4. The test measures the 1′OH-midazolam/midazolam plasma MR half an hour after oral intake of 0.075 mg of midazolam (8). Genomic DNA was extracted from EDTA blood samples with the FlexiGene DNA Kit (Qiagen, Hombrechtikon, Switzerland). Genotyping of *CYP2D6* was performed by real-time polymerase chain reaction with the use of 5′-nuclease allelic discrimination assays (ABI PRISM 7000 Sequence Detection System; Applied Biosystems, Rotkreuz, Switzerland) with primers and probes obtained from Applied Biosystems for alleles **3*, **4*, and **6*, and as previously described for the allele **5* and **xN* [15, 16].

The following data were recorded from medical charts: baseline demographic and clinical characteristics, psychiatric diagnosis, concurrent medical illness, current and past doses of quetiapine. Psychiatric diagnosis was made according to DSMIV criteria by psychiatry residents and confirmed by a senior psychiatrist. Concomitant medication and grapefruit juice intake were checked in order to detect potential biases due to inhibition or induction of CYP3A. The study protocol was approved by the appropriate Ethical committee and the institutional review board and all subjects gave written informed consent to participate.

Analysis

Statistical analysis was performed using the SPSS 12.0 program. Group to group comparisons were made using the Mann–Whitney *U* Test. Spearman correlations were carried out when appropriate. The two sample-binomial test of equal proportion (two-sided) was used to compare frequencies of variables between the two groups. A p value of less than 0.05 was considered as statistically significant.

Results

Twenty-two patients were identified, but one of them refused to participate in the study. Consequently, twenty-one patients were included, 9 in the high dose group, 12 in the normal dose group. All but 3 (1 Black African 2 North Africans) patients were Caucasian, with 11 female (52 %), and a mean age of 43.5 years (SD: 12 years), all meeting criteria for bipolar disorder type I ($n = 13$; 62 %), type II ($n = 3$; 14 %) or for schizoaffective bipolar disorder ($n = 5$; 24 %). A diagnosis of dependence on a substance other than nicotine was observed in 19 % of the population sample (cannabis, heroin) whereas 76 % of patients were smokers. Patients with heroin dependence were abstinent during the study, as assessed by urine screening. Two patients had a history of C hepatitis infection (one in each dose group), both of them being without symptoms at the time of inclusion. Hepatic and renal functions were either normal or slightly disturbed (values of alanine amino transferase, aspartate amino transferase, alkaline phosphatase and ϒ-glutamyltransferase less than threefold the normal range, value of creatinine less than twofold the normal range). All but 4 patients received quetiapine at the time of inclusion in the study. Reasons related to quetiapine cessation were the occurrence of side effects (akathysia, one normal

dose patient), dizziness (one normal dose patient), refusals of the treatment (one normal dose patient, one high dose patient).

All patients were taking 1 or more comedications (alprazolam, amisulpride, anetholtrithione, atorvastatin, bisacodyl, carbamazepine, chlorprothixene, chlortalidonum, clorazepate, citalopram, eletriptan, esomeprazole, flurazepam, lamotrigine, lansoprazole, lithium, lorazepam, macrogolum, methylphenidate, mirtazapine, norfenedrine, olanzapine, oxazepam, paroxetine, pinaverium, procyclidine, propranolol, simvastatin, sulcrafate, tolperisone, topiramate, triethylperazine, valproate, venlafaxine, zolpidem, zuclopenthixol). With the exception of carbamazepine (one normal dose patient), a strong inducer of CYP3A4 [11], none of the reported comedications were known to be strong CYP3A4 inhibitors or inducers. The patient treated with carbamazepine had a MR of 6.2, i.e. in the normal range and not increased as expected [14], associated with a very low quetiapine serum/plasma concentration (4 ng/ml). He was therefore considered to be non-compliant to both treatments at the time of the study. For patients who were still treated with quetiapine at inclusion, quetiapine dosage was correlated with quetiapine trough plasma concentration ($r^2 = 0.61$, $p = 0.0004$).

Demographic and metabolic data measured in the high and normal dose groups are shown in Table 1. The two groups did not differ with regards to the age of the patients (44 vs 43 years, respectively, $p = 0.86$) nor to the proportion of smokers (78 % vs 75 %, respectively, $p = 0.6$. As expected quetiapine doses and blood levels, measured at the maximum dosage for each patient, were higher (1468 vs 433 mg/day, $p = 0.002$; 303 vs 64 ng/ml, $p = 0.006$ respectively) in the high dose group. A higher proportion of patients in the high dose group were male (78 % vs 25 %, $p < 0.0001$).

The MR [mean ± standard deviation; median; (range)] in the whole group was: [7.0 ± 6.8; 5.5; (1.4–26.8)]. There was a trend ($p = 0.06$) towards higher CYP3A activity in the normal dose group as compared to the high dose group MR: 9.4 versus 3.9, respectively. Excluding the analysis of the four patients who stopped quetiapine or the patient considered as non-compliant during the study period, did not change the results.

Table 1 Demographic and metabolic data as determined in the normal and high dose group

	High dose ($n = 9$)	Normal dose ($n = 12$)	p
Age, years	44 ± 12	43 ± 12	0.86
Female (number, frequency)	2 (22 %)	9 (75 %)	<0.0001
Smokers (number, frequency)	7 (78 %)	9 (75 %)	0.6
Quetiapine maximum dosage, mg/day	1467 ± 625	433 ± 274	0.002
	1200	350	
	1000–3000	100–800	
Quetiapine serum/plasma concentrations, ng/ml	303 ± 210	64 ± 46	0.006
	287	44	
	14–673	4–126	
Midazolam metabolic ratio	3.9 ± 2.3	9.4 ± 8.2	0.06
	3.8	6.2	
	1.5–7.6	1.7–26.8	
CYP2D6 ultrarapid metabolizer (number, frequency)	1 (11 %)	1 (8.3 %)	0.28

Data are given as mean ± standard deviation, median, range unless otherwise specified

When correcting for multiple tests, only the proportion of male, and the quetiapine doses and blood concentrations remained significantly different between the normal dose as compared to the high dose groups.

Finally, when considering the whole group, there was a trend ($r = 0.40$, $p = 0.10$) between quetiapine serum/plasma concentration and CYP3A4 activity, with a decrease in quetiapine serum/plasma concentration with increasing CYP3A4 activity.

Discussion

The use of quetiapine at doses higher than the licensed range (i.e. >800 mg/day) is not unusual in clinical practice and the present study aimed to investigate whether the use of such high doses could be due, at least in part, to a high activity of the two main enzymes involved in quetiapine metabolism, namely CYP3A4 and CYP2D6 [9]. Two groups of patients were therefore included, the normal and high dose group having previously received, or receiving at the time of inclusion, quetiapine at a maximum mean dose of 433 ± 274 mg/day and of 1467 ± 625 mg/day, respectively. At the time of inclusion all patient received comedications and the two groups did not differ with regards to smoking habit and age. The higher proportion of female patients in the normal dose (75 %) as compared to the high dose group (22 %) could tentatively be explained by the fact that, in the presence of non-response, clinicians will more easily increase quetiapine doses beyond the licensed range in male than in female. On the other hand, such a difference in the proportion of female between the two groups is not expected to influence the clearance of quetiapine, as it has been shown that gender has no effect on the pharmacokinetics of quetiapine [17, 19].

Our results show that a high CYP2D6 activity cannot explain the use of high quetiapine dosages as one patient in each group was genotyped as being *CYP2D6* ultrarapid metabolizer. It should however be mentioned that the presently available genotyping methods allows to detect about only one-fourth of all *CYP2D6* ultrarapid metabolizer [18]. An unequal repartition of ultrarapid metabolizers not detected by the currently used method can therefore not be excluded. With regard to CYP3A4, the main enzyme involved in quetiapine metabolism [9], the use of high quetiapine doses can also not be explained by a high activity of this isozyme. Finally, the correlation observed between the quetiapine dosage and its serum/plasma concentrations are in agreement with previous reports [9].

Conclusion

In summary, the present study shows that, at least in the population treated in our hospital, the use of higher than licensed range of quetiapine cannot be explained by a high activity of CYP3A4 and/or CYP2D6, the two main enzymes involved in quetiapine metabolism. The present results did not contest that individual patients may receive a high quetiapine dose in relation to high activity of CYP3A4 and/or of CYP2D6, as suggested by the trend towards significant negative correlation between quetiapine serum/plasma concentration and CYP3A4 activity, and by case observations of non-response to quetiapine associated with very high CYP3A4 and CYP2D6 activities and very low quetiapine plasma levels (Eap et al. unpublished observation). Further studies are needed to explore the influence of other genetic variability (e.g. genetic polymorphism of receptors or transporters possibly involved in quetiapine mechanisms of action) [20, 21] and of clinical factors (e.g. episode types, episode severity, clinical practice) which could contribute to the interindividual

variation of administered quetiapine doses for bipolar disorders and for schizoaffective episodes. As a final comment, it should be stressed that the prescription of drugs at a higher dosage than the licensed range should be performed only after careful examination of risk/benefit ratios, and also after taking all necessary measures to ensure their safety (e.g. Electrocardiogram).

Acknowledgments The authors thank the editorial assistance of Mrs. V. Sari, and the bibliographical help of Mrs. M. Gobin and Mrs. E. Retamales. Prof Eap received during the period 1995-2012 research support from Astra Zeneca, Eli Lily, Fujisawa, Janssen Cilag, Novartis, Sandoz, SmithKline Beecham, Bristol-Myers Squibb and Wyeth. He received honoraria for conferences or teaching CME courses from Astra Zeneca, Bristol-Myers Squibb, Eli Lily, Essex Chemie, Glaxo-Smith Kline, Janssen-Cilag, Lundbeck, Novo Nordisk, Organon, Sandoz, Advisis. Dr Yasser Khazaal received during the period 2002-2012 research support from Astra Zeneca and Eli Lily. He received honoraria for conferences or teaching CME courses from Astra Zeneca, Bristol-Myers Squibb, Eli Lily and Lundbeck.

Conflict of interest The other authors declare that they have no competing interests in relation to the present study.

References

1. Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, Vagero M, Svensson K: A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. Journal of Clinical Psychiatry 66:111–121, 2005
2. McIntyre RS, Brecher M, Paulsson B, Huizar K, Mullen J: Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial. European Neuropsychopharmacology 15:573–585, 2005
3. Vieta E, Mullen J, Brecher M, Paulsson B, Jones M: Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. Current Medical Research and Opinion 21:923–934, 2005
4. Sachs G, Chengappa KN, Suppes T, Mullen JA, Brecher M, Devine NA, Sweitzer DE: Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disorder 6:213–223, 2004
5. Yatham LN, Paulsson B, Mullen J, Vagero AM: Quetiapine versus placebo in combination with lithium or divalproex for the treatment of bipolar mania. Journal of Clinical Psychopharmacology 24:599–606, 2004
6. Calabrese JR, Keck PE, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J: A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. The American Journal of Psychiatry 162:1351–1360, 2005
7. Pierre JM, Wirshing DA, Wirshing WC, Rivard JM, Marks R, Mendenhall J, Sheppard K, Saunders DG: High-dose quetiapine in treatment refractory schizophrenia. Schizophrenia Research 73:373–375, 2005
8. Khazaal Y, Tapparel S, Chatton A, Rothen S, Preisig M, Zullino D: Quetiapine dosage in bipolar disorder episodes and mixed states. Progress in Neuropsychopharmacology and Biological Psychiatry 31:727–730, 2007
9. DeVane CL, Nemeroff CB: Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. Clinical Pharmacokinetics 40:509–522, 2001
10. Grimm SW, Richtand NM, Winter HR, Stams KR, Reele SB: Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. British Journal of Clinical Pharmacology 61:58–69, 2006
11. Lamba JK, Lin YS, Thummel K, Daly A, Watkins PB, Strom S, Zhang J, Schuetz EG: Common allelic variants of cytochrome P4503A4 and their prevalence in different populations. Pharmacogenetics 12:121–132, 2002
12. Meyer UA: Pharmacogenetics—five decades of therapeutic lessons from genetic diversity. Nature Reviews Genetics 5:669–676, 2004
13. Eap CB, Bouchoux G, Powell Golay K, Baumann P: Determination of picogram levels of midazolam, and 1- and 4-hydroxymidazolam in human plasma by gas chromatography-negative chemical ionization-mass spectrometry. Journal of Chromatography B 802:339–345, 2004

14. Eap CB, Buclin T, Cucchia G, Zullino D, Hustert E, Bleiber G, Golay KP, Aubert AC, Baumann P, Telenti A, Kerb R: Oral administration of a low dose of midazolam (75 microg) as an in vivo probe for CYP3A activity. European Journal of Clinical Pharmacology 60:237–246, 2004
15. Lovlie R, Daly AK, Molven A, Idle JR, Steen VM: Ultrarapid metabolizers of debrisoquine: characterization and PCR-based detection of alleles with duplication of the CYP2D6 gene. FEBS Letters 392:30–34, 1996
16. Schaeffeler E, Schwab M, Eichelbaum M, Zanger UM: CYP2D6 genotyping strategy based on gene copy number determination by TaqMan real-time PCR. Human Mutation 22:476–485, 2003
17. FDA: 2006. www.fda.gov/cder/foi/label/2001/20639s11lbl.pdf
18. Zanger UM, Fischer J, Raimundo S, Stuven T, Evert BO, Schwab M, Eichelbaum M: Comprehensive analysis of the genetic factors determining expression and function of hepatic CYP2D6. Pharmacogenetics 11:573–585, 2001
19. Cotreau MM, von Moltke LL, Greenblatt DJ: The influence of age and sex on the clearance of cytochrome P450 3A substrates. Clinical Pharmacokinetics 44:33–60, 2005
20. Arranz MJ, Bolonna AA, Munro J, Curtis CJ, Collier DA, Kerwin RW: The serotonin transporter and clozapine response. Molecular Psychiatry 5:124–125, 2000
21. Arranz MJ, Munro J, Owen MJ, Spurlock G, Sham PC, Zhao J, Kirov G, Collier DA, Kerwin RW: Evidence for association between polymorphisms in the promoter and coding regions of the 5-HT2A receptor gene and response to clozapine. Molecular Psychiatry 3:61–66, 1998

Author Biographies

Yasser Khazaal, MD is a specialist in psychiatry and psychotherapy. He is Deputy Head of the Division of Addictology at the University Hospitals of Geneva, Switzerland. He has more than 100 scientific publications, mainly on internet-related behaviors, cognitive behavior therapy and pharmacotherapy.

Martin Preisig, MD is a specialist in psychiatry and psychotherapy and epidemiology. He has a high number of scientific publications, mainly on epidemiology.

Anne Chatton, MA is a researcher involved in several publications in the field of mental health. She has a master's degree in econometrics, a post-graduate diploma in statistics and a master of advanced studies in public health.

Nadine Kaufmann, MD is a specialist in psychiatry and psychotherapy.

Romain Bilancioni, MD is a specialist in psychiatry and psychotherapy.

Chin B. Eap, PhD is a specialist in psychopharmacology and psychoparmacogenetics. He is the head of Unit of Pharmacogenetics and Clinical Psychopharmacology of the Centre for Psychiatric Neuroscience, Department of Psychiatry in Lausanne, Switzerland. He has more than 100 scientific publications, mainly on Pharmacotherapy and Pharmacokinetics and Pharmacogenetics.