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How long does the pharmacokinetic interaction between carbamazepine and quetiapine last after carbamazepine withdrawal?

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Abstract

OBJECTIVES: Carbamazepine and quetiapine are drugs that are used as mood stabilizers in the treatment of bipolar disorders. A series of studies has shown that concurrent use of carbamazepine decreases quetiapine serum level due to induction of CYP3A enzymes by carbamazepine.

METHODS: In a 30-year-old bipolar patient with mania treated with quetiapine 1200 mg and carbamazepine 900 mg per day, we measured quetiapine serum level before and after carbamazepine withdrawal.

RESULTS: No serum quetiapine was detected during concurrent use of carbamazepine and was lower than the therapeutic range almost 2 weeks after carbamazepine withdrawal. The patient suffered from sedation when her serum level of quetiapine was 181 ng/ml and because she was quiet we started slowly to decrease to a quetiapine dose of 600 mg. Her serum level (45 ng/ml) was again below therapeutic levels after 3 weeks of carbamazepine withdrawal.

CONCLUSION: We hypothesize that induction of CYP3A lasts even after carbamazepine withdrawal. Our hypothesis was confirmed during the next treatment of mania. The patient had been off carbamazepine for 1 year and her serum level was four times higher (210 ng/ml) on 600 mg of quetiapine than 3 weeks after carbamazepine withdrawal. The influence of carbamazepine on CYP3A enzymes lasted at least 3 weeks after carbamazepine withdrawal which is in accordance with CYP3A de-induction lasting 3 weeks. This could be important information for psychiatrists to know that in some patients it is better to use a minimum washout period of 3 weeks for carbamazepine before new treatment with quetiapine.

Abbreviations:

AUC	- area under curve
CBZ	- carbamazepine
CYP3A	- cytochrome P450 3A4 enzyme
Li	- lithium
p.d.	- per diem
QUE	- quetiapine

CASE REPORT

INTRODUCTION

Bipolar affective disorder is a serious medical condition that is often difficult to treat despite recent progress in psychopharmacology and some improvement of medical, psychological and social care given to patients suffering from mania and/or depression. Quetiapine is a second-generation antipsychotic drug used for treatment of schizophrenia and all phases of bipolar disorders with a good tolerability profile (Muneer 2015). Quetiapine is metabolized in the liver mainly by CYP3A (cytochrome P450 3A4) enzymes (Spina *et al.* 2016a). Carbamazepine is an antiepileptic drug and mood stabilizer suited for long-term pharmacotherapy of bipolar disorder (Hubenak *et al.* 2015; Nasrallah *et al.* 2006; Rybakowski 2007). Carbamazepine is a strong inducer of CYP3A enzymes (Spina *et al.* 2016b). The average elimination half-life of unchanged carbamazepine is approximately 36 h following a single oral dose, whereas after repeated administration of carbamazepine its biological half-life is only 16–24 h. The decrease is due to auto-induction of hepatic monooxygenases by carbamazepine and depends also on the duration of the medication. Theoretically the complete elimination of carbamazepine from the human body after long-term pharmacotherapy and after complete withdrawal of carbamazepine should not last more than 5–7 days, because the time needed to achieve a steady state concentration of carbamazepine is 5–7 days (Vajda & Eadie 2014). In a pharmacokinetic study performed on 18 psychiatric patients carbamazepine 600 mg daily decreased quetiapine maximal blood concentration (Cmax) by 80% and increased its clearance 7.5-fold (Grimm *et al.* 2006). Therapeutic drug monitoring studies provided similar results (Castberg *et al.* 2007; Hasselstrom & Linnet 2004). The clinical implications were also demonstrated in three patients taking carbamazepine 400–800 mg/day in which serum quetiapine concentration could not be detected (<25 ng/ml) despite taking 700 mg quetiapine daily (Nickl-Jockschat *et al.* 2009). This interaction is explained by the potent inducing effect of carbamazepine on CYP3A4-mediated quetiapine metabolism. The mood stabilizing therapeutic plasma levels of carbamazepine and quetiapine are 4–10 μg/ml (17.2–43 μmol/l) and 100–500 ng/ml, respectively (Hiemke *et al.* 2011).

DESCRIPTION OF PATIENT'S CASE

A 30-year-old female was treated for bipolar disorder with lithium 600 mg and carbamazepine 900 mg per diem (p.d.) for more than 3 months. A manic episode developed in the patient despite her compliance with the pharmacologic treatment that was approved by recurrent appropriate carbamazepine serum levels of 45.7 and 38.8 μmol/l, respectively. She was hospitalized in the National Institute of Mental Health, Czech Republic due to mania and quetiapine was then added to the previous treatment and titrated up to 1200 mg p.d. We surpassed the recommended maximal dose of 800 mg of quetiapine daily because of an absence of clinical improvement and because of knowledge of interaction and the necessity to use higher doses. The morning sample of blood was drawn at least 9 h after the last carbamazepine and quetiapine dose and then was sent to the laboratory. The liquid chromatography-tandem mass spectrometry method was used and validated according to the international standards for determination of quetiapine and carbamazepine levels. Because the patient took 1200 mg of quetiapine daily and no serum quetiapine was detected (<20 ng/ml) after achievement of expected steady state the psychiatrist decided to withdraw carbamazepine. The quetiapine serum level increased after carbamazepine withdrawal (see Table 1) on the 4th, 11th and 16th day when she received an unchanged dose of quetiapine 1200 mg/day. The patient suffered from sedation when her serum level of quetiapine was 181 ng/ml and because she was quiet we started slowly to decrease to a dose of 600 mg of quetiapine. Her serum level (45 ng/ml) was again below therapeutic serum levels after 3 weeks of carbamazepine withdrawal. Despite low quetiapine serum level she was euthymic. The patient was released from hospitalization to outpatient care in a euthymic state. She was again hospitalized due to mania one year after carbamazepine withdrawal and her serum level on 600 mg of quetiapine was within the treatment range (see Table 1).

DISCUSSION

The treatment range of quetiapine serum level was not reached during the first hospitalization even when the patient had been taking 1200 mg quetiapine daily. The probable reason was strong induction of CYP3A liver enzymes by carbamazepine. The low serum level of quetiapine lasted almost 2 weeks after carbamazepine withdrawal. We hypothesize that induction of CYP3A lasted even after carbamazepine withdrawal. Based on our measurements and observations we conclude that the consequences of pharmacokinetic interactions lasted longer than could be predicted only from the pharmacokinetic rule that after 5 biological half-lives the remaining amount of drug applied is only approximately 3% of the drug amount at the time application of drug is stopped; in the case of carbamazepine the time period is 5 days (5×24 h). The half-life of CYP3A4 was estimated to be 70 h using a turnover model (Magnusson *et al.* 2008), which is in accordance with our observation because the effect on the quetiapine serum concentration lasted longer than could be estimated from the plasma elimination half-life of carbamazepine (Magnusson *et al.* 2008). A typical finding for drugs metabolized mostly by CYP3A4 is great variability of biotransformation between individuals, thus we could also hypothesize that the very high quetiap-

Tab. 1. Quetiapine serum level before and after carbamazepine withdrawal.

Course of pharmacotherapy	Before CBZ withdrawal	4 days after CBZ withdrawal	11 days after CBZ withdrawal	16 days after CBZ withdrawal	25 days after CBZ withdrawal	1 year after CBZ withdrawal
Daily dose (mg)	CBZ 900 QUE 1200 Li 1200	CBZ 0 QUE 1200 Li 900	CBZ 0 QUE 1200 Li 1200	CBZ 0 QUE 1200 Li 1200	CBZ 0 QUE 600 Li 1200	CBZ 0 QUE 600 Li 600
QUE serum level (treatment range 100–500 ng/ml)	Not detected	38 ng/ml	67 ng/ml	181 ng/ml	45 ng/ml	210 ng/ml
CBZ serum level (treatment range 17.2–43 µmol/l)	33.0 µmol/l	N.A.	N.A.	Not detected	N.A.	N.A.
Lithium serum level (treatment range 0.5–1.2 mmol/l)	1.3 mmol/l	0.6 mmol/l	0.87 mmol/l	1.1 mmol/l	0.87 mmol/l	0.68 mmol/l

CBZ – carbamazepine, Li – Lithium, N.A. – not assessed, QUE - quetiapine

Tab. 2. Cytochrome P450 enzymes involved in the biotransformation of carbamazepine and quetiapine.

Metabolizing enzyme of applied drugs	1A2	2B6	3A4/ 3A5	2C8/ 2C9	2D6	Reference
Carbamazepine	+	+	+, inducer	+	–	Hilal-Dandan & Brunton 2014a; Thorn *et al.* 2011
Quetiapine	–	–	+	–	+ in vitro + minor role in vivo	Hiemke *et al.* 2011
Is the enzyme genetically polymorphic?	1A2 yes	2B6 no	3A4 no 3A5 yes	2C9 yes	2D6 yes	Djordjevic *et al.* 2016; Hilal-Dandan & Brunton 2014b; Ragia *et al.* 2016

ine metabolic clearance in our patient could be based on high individual activity of 3A4 enzyme in addition to carbamazepine's inducing effect on CYP3A4 expression (Wittmann *et al.* 2010). In some textbooks of pharmacology, 10-fold interindividual variability in enzyme CYP3A4 activity is described, even if no genetic polymorphisms have been identified for this P450 isozyme (Yellepeddi 2015). The other possible effects enhancing quetiapine metabolic clearance could be: the presence of polymorphism of CYP3A5, which is mentioned in the literature as an overlooked enzyme that can affect the pharmacokinetics of some psychiatric drugs, or hypothetically CYP2D6 genetic polymorphism because the 2D6 enzyme plays a minor role in quetiapine biotransformation in vivo (Ragia *et al.* 2016). An overview of the biotransformation enzymes involved in the metabolism of carbamazepine and quetiapine is shown in Table 2. The patient did not use pomegranate, grapefruit juice or extract of St. John's Wort which are known to interact with CYP3A4 (Awad *et al.* 2016; Hidaka *et al.* 2005; Izzo *et al.* 2016). The patient was rehospitalized one year after carbamazepine withdrawal and her serum concentration on 600 mg of quetiapine was four times higher than after 3 weeks of carbamazepine withdrawal on the same dose of quetiapine (see Table 1). That fact decreases the probability of a major role of genetic variability in CYP3A4, CYP3A5 or CYP2D6 on enzyme activity and increases the influence of induction of the CYP3A4 enzyme by carbamazepine. The clinically significant influence of carbamazepine on CYP3A enzymes lasted at least 3 weeks after carbamazepine withdrawal; however, pharmacokinetic interaction probably lasted longer. Our observation is in accordance with recent findings that de-induction of CYP3A can last 3 weeks (de Leon 2015; Magnusson *et al.* 2008).

CONCLUSION

Our case study shows that carbamazepine interaction with quetiapine lasts at least 3 weeks after carbamazepine withdrawal. This could be new information for psychiatrists to know that in some patients it could be necessary to wait at least 3 weeks after withdrawal of carbamazepine before new treatment with quetiapine is likely to be effective.

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REFERENCES

1 Awad R, Mallah E, Khawaja BA, Dayyih WA, El-Hajji F, Matalka KZ, Arafat T (2016). Pomegranate and licorice juices modulate metformin pharmacokinetics in rats. Neuro Endocrinol Lett. **37**: 202–206.
2 Castberg I, Skogvoll E, Spigset O (2007). Quetiapine and drug interactions: evidence from a routine therapeutic drug monitoring service. The Journal of Clinical Psychiatry. **68**: 1540–1545.
3 De Leon J (2015). The effects of antiepileptic inducers in neuropsychopharmacology, a neglected issue. Part I: a summary of the current state for clinicians. Revista de Psiquiatria y Salud Mental. **8:** 97–115.
4 Djordjevic N, Milovanovic DD, Radovanovic M, Radosavljevic I, Obradovic S, Jakovljevic M, et al (2016). CYP1A2 genotype affects carbamazepine pharmacokinetics in children with epilepsy. European Journal of Clinical Pharmacology. **72**: 439–445.
5 Grimm SW, Richtand NM, Winter HR, Stams KR, Reele SB (2006). Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. British Journal of Clinical Pharmacology. **61**: 58–69.
6 Hasselstrom J, Linnet K (2004). Quetiapine serum concentrations in psychiatric patients: the influence of comedication. Therapeutic Drug Monitoring. **26**: 486–491.
7 Hidaka M, Okumura M, Fujita K, Ogikubo T, Yamasaki K, Iwakiri T, et al (2005). Effects of pomegranate juice on human cytochrome p450 3A (CYP3A) and carbamazepine pharmacokinetics in rats. Drug Metabolism and Disposition. **33**: 644–648.
8 Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K, et al (2011). AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry. **44**: 195–235.
9 Hilal-Dandan R, Brunton LL (2014a). Antiseizure drugs: general considerations. Goodman and Gilman's Manual of Pharmacology and Therapeutics. New York, McGraw-Hill, p. 350.
10 Hilal-Dandan R, Brunton LL (2014b). Drug metabolism. Goodman and Gilman's Manual of Pharmacology and Therapeutics. New York, McGraw-Hill, pp. 81–97.
11 Hubenak J, Tuma I., Bazant J (2015). Association of arterial hypertension and cognitive impairment in euthymic bipolar disorder. Neuro Endocrinology Letters. **36**: 294–300.
12 Izzo AA, Hoon-Kim S, Radhakrishnan R, Williamson EM (2016). A critical approach to evaluating clinical efficacy, adverse events and drug interactions of herbal remedies. Phytotherapy Research. **30**: 691–700.
13 Magnusson MO, Dahl ML, Cederberg J, Karlsson MO, Sandstrom R (2008). Pharmacodynamics of carbamazepine-mediated induction of CYP3A4, CYP1A2, and Pgp as assessed by probe substrates midazolam, caffeine, and digoxin. Clinical Pharmacology and Therapeutics. **84**: 52–62.
14 Muneer A (2015). Pharmacotherapy of bipolar disorder with quetiapine: a recent literature review and an update. Clinical Psychopharmacology and Neuroscience. **13**: 25–35.
15 Nasrallah HA, Ketter TA, Kalali AH (2006). Carbamazepine and valproate for the treatment of bipolar disorder: a review of the literature. Journal of Affective Disorders. **95**: 69–78.
16 Nickl-Jockschat T, Paulzen M, Schneider F, Grozinger M (2009). Drug interaction can lead to undetectable serum concentrations of quetiapine in the presence of carbamazepine. Clinical Neuropharmacology. **32**: 55.
17 Ragia G, Dahl ML, Manolopoulos VG (2016). Influence of CYP3A5 polymorphism on the pharmacokinetics of psychiatric drugs. Current Drug Metabolism. **17**: 227–236.
18 Rybakowski J (2007). Long-term pharmacological treatment of bipolar disorders. Neuro Endocrinol Lett. **28**: (Suppl 1), 71–93.
19 Spina E, Hiemke C, De Leon J (2016a). Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics. Expert Opinion on Drug Metabolism & Toxicology. **12**: 407–422.
20 Spina E, Pisani F, De Leon J (2016b). Clinically significant pharmacokinetic drug interactions of antiepileptic drugs with new antidepressants and new antipsychotics. Pharmacological Research. **106:** 72–86.
21 Thorn CF, Leckband SG, Kelsoe J, Leeder JS, Muller DJ, Klein TE, Altman RB (2011). PharmGKB summary: carbamazepine pathway. Pharmacogenetics and Genomics. **21**: 906–910.
22 Vajda FJ, Eadie MJ (2014). The clinical pharmacology of traditional antiepileptic drugs. Epileptic Disorders. **16**: 395–408.
23 Wittmann M, Hausner H, Kostlbacher A, Hajak G, Haen E (2010). Individual clearance and therapeutic drug monitoring of quetiapine in clinical practice. Neuro Endocrinol Lett. **31**: 203–207.
24 Yellepeddi V (2015). Pharmacokinetics. In: Whalen, K. (ed.) Lippincott illustrated reviews – pharmacology. Philadelphia, PA, Wolters Kluwer, 1–24.