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Concomitant administration of rifampicin and oxcarbazepine results in a significant decrease of the active MHD metabolite of oxcarbazepine

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To the Editors:

The prodrug oxcarbazepine is an antiepileptic agent structurally resembling carbamazepine but differing in its metabolism. Oxcarbazepine inhibits voltage-dependent sodium channels resulting in an interruption of the epileptical discharge [1]. Oxcarbazepine is extensively metabolized by the liver into the active metabolite 10-monohydroxy-carbamazepine (MHD) via cytosolic keto-reductase enzymes. It is further deactivated by uridine diphosphate glucuronosyltransferase (UGT) to the metabolite 10,11-dihydroxy-derivative (DHD) [2]. Oxcarbazepine and MHD inhibit cytochrome P 450 (CYP) 2C19 and induce CYP3A4 and CYP3A5 but lack the ability for autoinduction [3].

Strong enzyme-inducers such as carbamazepine, phenytoin or phenobarbital are known to decrease the serum concentration of MHD by 13% -40% [4-7].

Rifampicin is another potent inducer of CYP isoenzymes, P-glycoprotein and UGT [8]. However, potential effects of rifampicin on the pharmacokinetics of oxcarbazepine are unknown.

Here, we present a 33-year-old female (BMI 27.5 kg/m^2, active smoker) on long-term oxcarbazepine treatment at a daily dose of 1.200 mg for epilepsy. Due to therapy-resistant acne vulgaris rifampicin 600 mg daily and clindamycin 300 mg b.i.d. were initiated. Therapeutic drug monitoring (TDM) of oxcarbazepine and MHD trough concentrations was conducted before, during and after the course of antibiotic therapy on day 0, 3, 7, 14, 21, 35, 59, 83 und 92 days (figure 1). Coadministration with rifampicin resulted in a significant decrease of MHD serum concentrations by 49% on day 7, while oxcarbazepine concentrations remained stable. Oxcarbazepine dosing was adapted to maintain MHD concentrations within the therapeutic range. A 75% increase of the initial oxcarbazepine dose (final daily dose 2.100 mg) was required to achieve similar MHD target concentrations during rifampicin treatment compared to baseline. No other concomitant drugs were

administered during this 10 weeks treatment. Neither the patient's smoking habit nor the patient's weight changed. After discontinuation of rifampicin, MHD serum concentrations increased despite an initial oxcarbazepine dose reduction. Finally the oxcarbazepine dose could be reduced to baseline dosage of 1.200 mg resulting in similar MHD concentrations before rifampicin treatment. The patient did not experience any epileptic seizure and adverse reaction during and after the period of coadministered rifampicin.

In conclusion, this is the first report on coadministration of rifampicin and oxcarbazepine leading to reduced MHD serum concentrations. Since rifampicin is known to induce UGT, this could partially explain the reduced oxcarbazepine exposure. However, only 4% of MHD is supposed to be degraded by UGT in the absence of an UGT inducer. MHD concentrations decreased by 49%, while a dose increase of 75% was necessary for oxcarbazepine during rifampicin therapy. Serum levels between 10-35 mg/L have been suggested for the prevention of epileptic seizures [9]. Although the clinical significance of this drug-drug interaction is not exactly known, decreased MHD concentrations may result in a potential reduction of oxcarbazepine efficacy leading to seizures. If oxcarbazepine and rifampicin are administered concurrently, close monitoring of clinical response to oxcarbazepine and TDM of the active metabolite MHD should be performed. Dose adaptions of oxcarbazepine might be necessary after initiation and discontinuation of the potent CYP inducer rifampicin.

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Disclosure

We have no conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References:

1 Schmutz M, Brugger F, Gentsch C, McLean MJ, Olpe HR (1994) Oxcarbazepine: preclinical anticonvulsant profile and putative mechanisms of action. Epilepsia 35 Suppl 5: S47-50

2 Theisohn M, Heimann G (1982) Disposition of the antiepileptic oxcarbazepine and its metabolites in healthy volunteers. Eur J Clin Pharmacol 22 (6): 545-551

3 Patsalos PN, Zakrzewska JM, Elyas AA (1990) Dose dependent enzyme induction by oxcarbazepine? Eur J Clin Pharmacol 39 (2): 187-188

4 Arnoldussen W HJ, Rentmeester T. (1993) Interaction between oxcarbazepine and phenytoin Epilepsia 34 (Suppl. 6): 37

5 Barcs G, Walker EB, Elger CE, Scaramelli A, Stefan H, Sturm Y, Moore A, Flesch G, Kramer L, D'Souza J (2000) Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. Epilepsia 41 (12): 1597-1607

6 McKee PJ, Blacklaw J, Forrest G, Gillham RA, Walker SM, Connelly D, Brodie MJ (1994) A double-blind, placebo-controlled interaction study between oxcarbazepine and carbamazepine, sodium valproate and phenytoin in epileptic patients. Br J Clin Pharmacol 37 (1): 27-32

7 Tartara A, Galimberti CA, Manni R, Morini R, Limido G, Gatti G, Bartoli A, Strada G, Perucca E (1993) The pharmacokinetics of oxcarbazepine and its active metabolite 10-hydroxy-carbazepine in healthy subjects and in epileptic patients treated with phenobarbitone or valproic acid. Br J Clin Pharmacol 36 (4): 366-368

8 Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT (2003) Pharmacokinetic interactions with rifampicin : clinical relevance. Clin Pharmacokinet 42 (9): 819-850

9 Hiemke C, Baumann P, Bergemann N, Conca A, Dietmaier O, Egberts K, Fric M, Gerlach M, Greiner C, Grunder G, Haen E, Havemann-Reinecke U, Jaquenoud Sirot E, Kirchherr H, Laux G, Lutz UC, Messer T, Muller MJ, Pfuhlmann B, Rambeck B, Riederer P, Schoppek B, Stingl J, Uhr M, Ulrich S, Waschgler R, Zernig G (2011) AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011. Pharmacopsychiatry 44 (6): 195-235

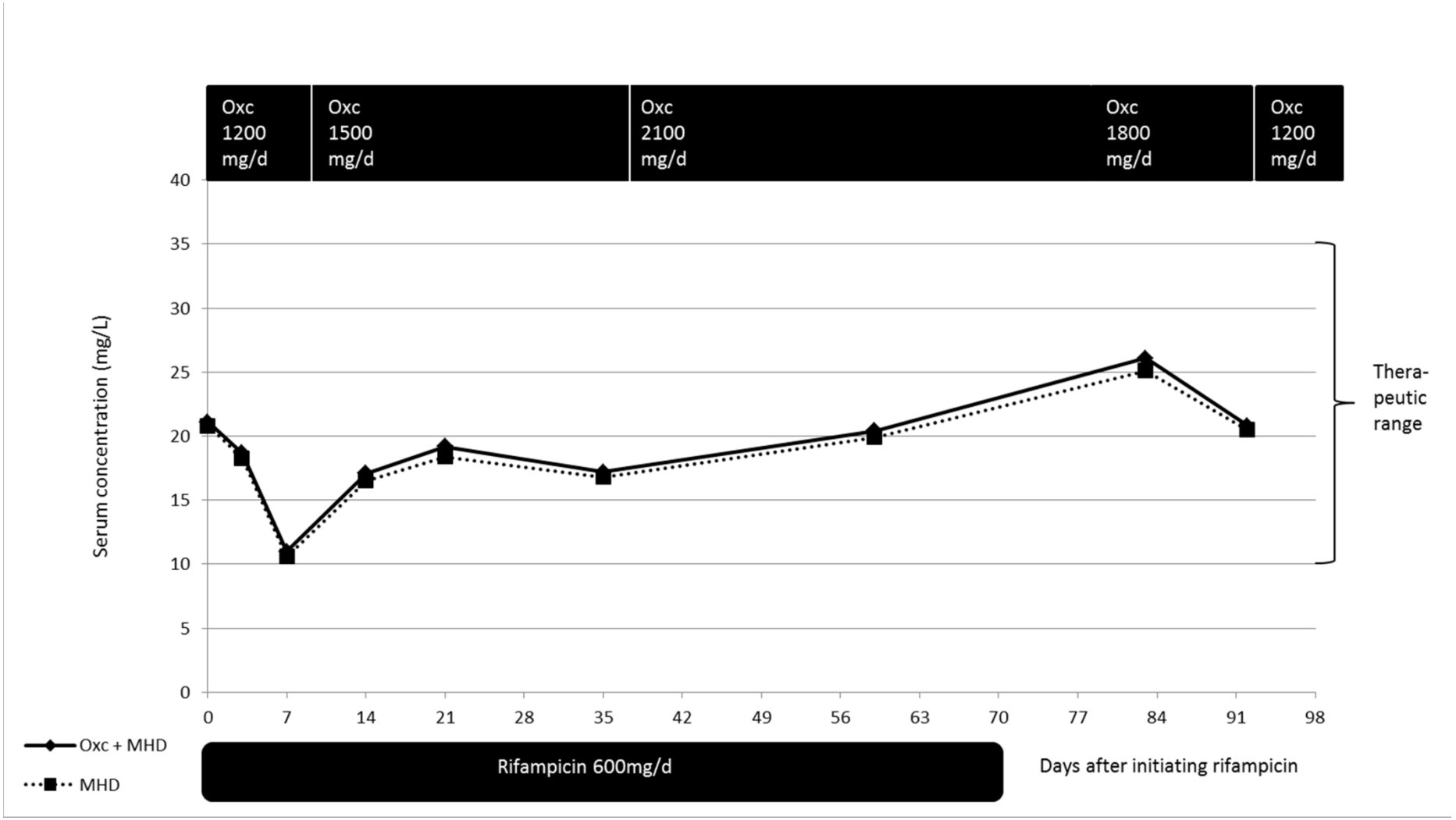

Figure 1: Time course of oxcarbazepine and MHD trough level and oxcarbazepine dose adaptions related to initiation of rifampicin. Therapeutic range (10-35 mg/L) implicates for oxcarbazepine plus MHD [9]; Oxc oxcarbazepine, MHD monohydroxy-derivative