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# Clozapine-associated elevation of plasma cholinesterase

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**Abstract** *Objective* The goal of this study was to identify adverse effects of the atypical neuroleptic clozapine on liver function and lipid metabolism. *Methods* Data which included serum levels of clozapine and its hepatic metabolite N-desmethyl clozapine were collected from medical records of patients treated with clozapine and controls. *Results* We identified a clozapine-associated marked elevation of plasma cholinesterase (ChE) with unchanged levels of AST, ALT or g-GT. ChE was correlated to the serum level of clozapine and even closer to N-desmethyl clozapine. For the total patient group we observed significant correlations of ChE with the body-mass index and body weight. However, clozapine-treated patients and controls did not differ with regard to body-mass index, triglycerides, and cholesterol. *Conclusion* We report for the first time a clozapine-associated and dose-dependent elevation of plasma ChE, which may be related to clozapine-associated effects on hepatic lipid metabolism or ChE enzyme induction.

**Key words** clozapine · liver function · lipid metabolism

## Introduction

Clozapine was the first atypical neuroleptic to be introduced and remains one of the most effective drugs for the treatment of refractory schizophrenia [1]. Clozapine produces fewer extrapyramidal side effects than conventional neuroleptics, but typical adverse reactions include agranulocytosis, seizures, weight gain, constipation, hypersalivation, transient fever and moderate elevation of hepatic transaminases [1, 2]. Recently clozapine has been linked to hypertriglyceridemia, diabetes, and obesity (review in [3, 4]), whereas diabetes mellitus or hyperglycemia were not observed in patients treated with conventional neuroleptics [3]. Olanzapine-associated diabetes mellitus was also reported (cited in [3]). In several cases a clozapine-associated exacerbation of diabetes mellitus or new-onset diabetes mellitus were not attributable to weight gain [3]. Interestingly, two studies reported a link between clozapine-associated weight gain and clinical response to clozapine medication (cited in [3]).

ChE (Acylcholin-acylhydrolyse) is found in the liver, pancreas, heart, plasma and in the white matter of the brain (review in [5]). Elevated plasma ChE usually indicates a fatty liver, which can be due to an increased influx of fatty acids and hepatic accumulation of triglycerides, as associated with diabetic ketoacidosis or obesity. Interestingly, recent reports have linked clozapine to diabetic ketoacidosis (review in [3]). The molecular mechanism underlying the increased hepatic release of ChE due to a fatty liver is not known.

## Methods

In- and outpatients treated in the Department of Psychiatry from October 1999 to June 2000 were entered into this retrospective, open and non-randomized study. Psychiatric diagnosis was established according to DSM-IV criteria. Fifty-one patients predominantly with schizophrenia and schizoaffective disorder were treated with either clozapine (150 to 800 mg) alone or clozapine in addition to other psychopharmaca. The latter group of patients was identified as clozapine group 1 (CLO-1, Table 1). Twenty-five CLO-1 patients were treated with clozapine alone (clozapine group 2, CLO-2). The two clozapine groups (CLO-1, CLO-2) were devised to control for additive effects of clozapine and other psychopharmaca on CHE plasma and clozapine serum levels. Patients with heterogenous psychiatric disorders and treated by psychopharmaca other than clozapine served as

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**Table 1** Descriptive statistics and level of significance of clinical data and selected laboratory test results

| Variables | CLO-1[a] | CON-1[b] | p | CLO-2[c] | CON-2[d] | HCON-2[e] | p |
|---|---|---|---|---|---|---|---|
| Group size (n) | 51 | 41 | – | 25 | 29 | 104 | – |
| Sex male/female | 28/23 | 15/26 | (a) vs. (b): p=n. s. ** | 13/12 | 15/14 | 54/50 | (c) vs. (d): n.s<br>(c) vs. (e): n. s.<br>(d) vs. (e): n. s. |
| Age (years) mean ± SD | 41.9 ± 12.5 | 40.9 ± 12.5 | (a) vs. (b): p=n. s. | 37.2 ± 12.6 | 38.3 ± 11.6 | 29.6 ± 7.8 | (c) vs. (d): n.s<br>(c) vs. (e): $p < 0.0005$, df=1, $t > 2.5$<br>(d) vs. (e): $p < 0.0001$, df=1, $t > 2.7$ |
| Clozapine (nmol/L) mean ± SD) | 887.5 ± 795.0 | – | – | 838.9 ± 898.0 | – | – | (a) vs. (c): p=n. s. |
| N-desmethyl clozapine (nmol/L) mean ± SD | 515.1 ± 472.6 | – | – | 501.3 ± 560.9 | – | – | (a) vs. (c): p=n. s. |
| Plasma cholinesterase (U/L) mean ± SD | 7249 ± 1897 | 5771 ± 1042 | (a) vs. (b): $p < 0.00005$ U=475 | 7154.8 ± 1773 | 5871 ± 1112 | 5212 ± 1108 | (c) vs. (d): p=0.0064, U=197<br>(c) vs. (e): $p < 0.00001$, df=1, $t > 3.37$<br>(d) vs. (e): $p < 0.01$, df=1, $t > 2.36$ |
| Body-mass index (kg/m$^2$) mean ± SD | 26.3 ± 4.4 (n=36; 71 %)* | 25.0 ± 3.7 (n=31; 76 %)* | (a) vs.(b): p=n. s. | 25.6 ± 2.8 (n=17; 68 %)* | 24.9 ± 3.9 (n=24; 83 %)* | – | (c) vs. (d): p=n. s. |
| Triglycerides (mg/dl) mean ± SD | 176.1 ± 117.2 (n=32; 64 %)* | 149.7 ± 73.8 (n=34; 83 %)* | (a) vs.(b): p=n. s. | 167.9 ± 122.1 (n=14; 56 %)* | 150.2 ± 75.2 (n=26; 90 %)* | 127 ± 71 | (c) vs. (d): n.s<br>(c) vs. (e): n. s.<br>(d) vs. (e): n. s. |

[a] total group of clozapine-treated patients, including patients treated with psychopharmaca other than clozapine;
[b] total group of psychiatric disease controls;
[c] patients receiving only clozapine (subgroup of CLO-1);
[d] psychiatric disease controls matched by age and gender to CLO-2 (subgroup of CON-1);
[e] healthy controls, group-matched for gender to CLO-2 and CON-2
* parameter only available for the number and percentage of patients indicated
** p=0.08, df=1, $\chi^2$=3.060

psychiatric disease controls (CON-1, n= 41). Twenty-nine CON-1 patients were group-matched by age and gender to CLO-2 and were summarized as psychiatric disease control group 2 (CON-2). Patients with alcohol addiction and disorders of the liver were excluded.

Data on age, gender, diagnosis and body-mass index were collected from the medical records. Laboratory test results included parameters of liver function, triglycerides, and cholesterol. These parameters were not available for all patients, which is indicated in Table 1. Serum levels of clozapine and its hepatic metabolite N-desmethyl clozapine were obtained for 50/51 CLO-1 patients.

Plama ChE was determined by the S-butylthiocholine assay [6]. The plasma ChE and serum triglyceride values for 104 healthy controls (HCON-2) were group-matched to CLO-2 and CON-2 by gender (Table 1). ChE values did not depend on age in the healthy controls, but we observed a minor increase in triglyceride values with increasing age (data not shown).

Quantification of clozapine and N-desmethyl-clozapine was performed by reversed-phase high performance liquid chromatography with UV detection.

Data were compared using the Mann-Whitney U-Test, and correlations were calculated by Spearman's rank correlation. Group differences of HCON-2 versus CLO-2 or CON-2 were compared using student's t-test, since for HCON-2 only mean, standard deviation, age and gender were available. Group differences for dichotomic variables were compared using the $Chi^2$ test. A two-tailed p-value of less than 0.05 was considered significant. In the case of multiple testing the alpha level was adjusted according to Bonferroni.

## Results

Plasma ChE mean values showed a striking elevation in the total group of clozapine-treated patients, as well as in the subgroup of patients treated with clozapine alone (Table 1). In contrast, we observed only a minor increase of plasma ChE in psychiatric disease controls (Table 1). Serum levels of AST, ALT, γ-GT and cholesterol were not elevated in clozapine-treated patients (data not shown). Body-mass index and serum triglyceride levels did not differ significantly between clozapine-treated patients and controls (Table 1). The significance of this finding is limited by the fact that the latter two parameters were not available for all patients (Table 1). However, if only those patients who had a complete set of data for triglycerides and body-mass index were considered, a significant difference was still observed for plasma ChE ($p=0.004$, $df=1$, $z=2.911$) between CLO-1 and CON-1.

The serum concentrations of clozapine and its metabolite were not significantly influenced by co-medication (Table 1).

For the total patient group we observed significant correlations between plasma ChE and the following parameters: body-mass index ($r=0.40$, $df=2$, $t=3.486$, $p < 0.001$), body weight ($r=0.45$, $df=2$, $t=3.928$, $p < 0.001$). The correlation between plasma ChE and N-desmethyl clozapine ($r=0.45$, $df=2$, $t=3.479$, $p=0.001$) was stronger than that observed between plasma ChE and clozapine ($r=0.33$, $df=2$, $t=2.387$, $p < 0.025$). As expected, we observed a strong correlation between the serum concentrations of clozapine and its hepatic metabolite ($r=0.92$, $df=2$, $t=16.710$, $p < 0.0001$).

## Discussion

Clozapine medication may induce hypertriglyceridemia and weight gain (review in [3]), which in turn may elevate plasma ChE due to a fatty liver. Accordingly, we observed significant correlations between plasma ChE and triglycerides, body weight, body-mass index and γ-GT for the total patient group. However, in the subgroup of clozapine-treated patients the rise in ChE was not paralleled by a significant increase in triglycerides or body-mass index. Thus, additional factors must be responsible for the marked clozapine-associated rise of ChE. Clozapine is predominantly metabolized in the liver by cytochrome P450 [7]. Our finding that the clozapine metabolite N-desmethyl clozapine correlates more closely with ChE than clozapine may indicate that its P450-dependent metabolism is relevant for the clozapine-associated elevation of plasma ChE.

Animal studies may help to identify the molecular mechanisms underlying the clozapine-associated increase of hepatic ChE. These studies could also clarify, whether a clozapine-associated modulation of ChE isoforms is relevant for central nervous effects of the atypical neuroleptic. Future clinical follow-up studies with baseline determinations of ChE will show, whether marked clozapine-induced elevations of the enzyme are indicative for clinical response or late adverse drug reactions, e. g. lipid dysmetabolism and diabetes mellitus. The mechanism underlying the clozapine-associated ChE elevation may also be relevant to other atypical neuroleptics.

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