

PRELIMINARY OBSERVATIONS ON GABAPENTIN AUGMENTATION STRATEGY IN CLOZAPINE-RESISTANT PATIENTS: LACK OF PHARMACOKINETIC INTERACTIONS

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Running title

Clozapine and Gabapentin interaction in clozapine-resistant patients

Abstract

Since Gabapentin, a novel antiepileptic drug with recognised mood stabilising properties, lacks hepatic metabolism, does not induce or inhibit the CYP450 system and has no haematological side effects, it could be a drug of election to adjunct to clozapine in a drug augmentation strategy.

Here we report a small, open-label, not placebo-controlled case series of 11 patients who had failed to respond or had had only a partial response to clozapine and underwent to co-administration with gabapentin at the dose of 300 mg/day in the first week, 600 mg/day in the second week and 900 mg/day from the third week up to the end of the study.

One-way ANOVA with repeated measures showed that during the co-administration of clozapine and gabapentin, total scores of psychopathological scales significantly changed, suggesting that the adjunct of gabapentin to clozapine ameliorated the psychopathology. Moreover, gabapentin did not significantly affect plasma levels of clozapine and its major metabolites.

Our data suggest that gabapentin augmentation strategy may benefit a subgroup of patients with chronic schizophrenia or schizoaffective disorder non responsive to both typical antipsychotics and clozapine. Further studies are necessary to confirm these data.

Key words

Schizophrenia, schizoaffective-disorders, clozapine, gabapentin, drug-interaction

Introduction

Clozapine has a proven efficacy in treatment-resistant schizophrenia (1). However, a substantial minority of patients fail to respond or have only a partial response to this antipsychotic (2). This incomplete success has prompted clinicians to search for potential augmentation strategies to improve outcomes of clozapine-resistant schizophrenic patients. A significant proportion of patients unresponsive to clozapine have a considerable affective component in their psychopathology. In these cases, mood stabilisers such as carbamazepine, sodium valproate and lithium have been used as adjuncts to clozapine treatment (3).

One of the major issue in combining clozapine with other psychotropic drugs relies in the potential adverse pharmacokinetic interactions. Clozapine is metabolised by the hepatic cytochrome P450 (CYP450) system, namely the CYP1A2, CYP2D6, CYP3A4 isoenzymes (4, 5). Hence, the co-administration of drugs affecting the activity of the hepatic microsomal enzymes may profoundly alter clozapine plasma levels with potentially serious adverse effects or with a loss of its therapeutic efficacy.

Gabapentin, a structural analogue of the γ -aminobutyric acid (GABA), is a novel antiepileptic drug with recognised mood stabilising properties (6). Moreover, it lacks hepatic metabolism, does not induce or inhibit the CYP450 system and has no haematological side effects (7). These properties make gabapentin a drug of election to adjunct to clozapine in a drug augmentation strategy. We report here a small, open-label, not placebo-controlled case series of 11 outpatients, who had failed to respond or had had only a partial response to clozapine and underwent a drug augmentation strategy with gabapentin. During the co-administration period, plasma levels of clozapine and its major metabolites were measured to investigate possible pharmacokinetic interactions with gabapentin.

Subjects and methods

The patient sample consisted of 11 outpatients, 7 meeting DSM-IV criteria for schizoaffective disorder (2 for the bipolar subtype, 5 for the depressive subtype) and 4 meeting the criteria for chronic schizophrenia (3 for the paranoid subtype and 1 for the undifferentiated subtype). These patients were part of a larger cohort of subjects that, in the past, had failed to respond to at least 3 different typical antipsychotic at adequate therapeutic doses, given for not less than six weeks each. Therefore, they had started clozapine treatment up to the maximum tolerated dose. After at least 3 months of this maximum clozapine dose regimen, those patients who exhibited a change no greater than 5% on the Brief Psychiatric Rating Scale (BPRS) total score or, although having had a greater reduction in this score, still had a score greater than 4 on the depression subitem of the BPRS were eligible for gabapentin augmentation strategy. Eleven of these patients gave their informed consent to participate in the study. They were 9 men and 2 women, aged 24-26 years (mean \pm SD, 34.9 \pm 11.5 years) with an illness duration ranging from 4 to 33 years (mean \pm SD, 12.6 \pm 9.0 years).

At the time of the study, each patient had been treated with clozapine for more than 1 year and was on stable clozapine dosage for at least 12 weeks. The mean (\pm SD) daily dose of clozapine for the whole patient sample was 463 (\pm 120) mg/day (range: 250-600 mg/day); this dosage remained unchanged for the entire study period. Gabapentin was added at the dose of 300 mg/day (one single morning administration) in the first week, 600 mg/day (two daily administrations) in the second week and 900 mg/day (three daily administrations) in the third week. Psychopathological assessment was performed before the onset of the study and 1, 2 and 6 weeks after the adjunct of gabapentin by means of the following rating scales: 1) BPRS, 2) Scale for the Assessment of Positive Symptoms (SAPS); 3) Scale for the Assessment of Negative Symptoms (SANS).

Blood samples were collected by venipuncture at 8.00 \pm 1.00 h, before the morning administration of the drugs, at baseline (that is before adding gabapentin) and after 1, 2 and 6 weeks

of the co-administration. Plasma was separated by centrifugation and stored at -20°C until assayed for clozapine, N-desmethylclozapine and clozapine-N-oxide, according to the previously described method (8).

Results were expressed as mean \pm SD and statistically analysed by analysis of variance (ANOVA), ANOVA with repeated measures and Student's t-paired test, where appropriate.

Results

As shown in Table 1, mean BPRS, SAPS and SANS total scores slightly, but progressively decreased throughout the study period. One-way ANOVA with repeated measures showed that during the co-administration of clozapine and gabapentin BPRS ($F_{3, 43} = 12.730$, $p < 0.0001$), SAPS ($F_{3, 43} = 18.942$, $p < 0.0001$) and SANS ($F_{3, 43} = 18.543$, $p < 0.0001$) total scores significantly changed, suggesting that the adjunct of gabapentin to clozapine ameliorated the psychopathology. A 57% reduction in the score of the depressed mood subitem of the BPRS was observed at the end of the 6th week of co-administration ($p < 0.0002$).

Gabapentin did not significantly affect plasma levels of clozapine and its major metabolites. Indeed, the mean plasma concentrations of clozapine, N-desmethylclozapine and clozapine-N-oxide did not exhibit significant variations after gabapentin co-administration (Table 1).

After the adjunct of gabapentin, 2 patients complained of mild nausea and 1 of dizziness that spontaneously resolved within a few days. No other side effects was referred or observed.

Table 1: Psychopathological characteristics and plasma levels of clozapine and its major metabolites of clozapine-treated patients before (T-0) and 1 (T-1), 2 (T-2) and 6 (T-3) weeks after the adjunct of gabapentin (300, 600 and 900 mg/day, respectively).

	T-0	T-1	T-2	T-3
BPRS total score	48.6 \pm 9.3	46.4 \pm 10.1 ^a	45.0 \pm 10.3 ^b	43.7 \pm 10.2 ^c
SAPS total score	41.4 \pm 12.6	37.8 \pm 12.6 ^d	37.7 \pm 12.1 ^e	35.9 \pm 12.8 ^e
SANS total score	46.6 \pm 15.7	42.8 \pm 14.6 ^e	41.5 \pm 14.9 ^e	40.3 \pm 14.3 ^f
Clozapine Plasma levels (ng/ml)	485.7 \pm 235.2	484.0 \pm 237.9	477.9 \pm 221.1	493.7 \pm 234.4
N-desmethylclozapine Plasma levels (ng/ml)	337.7 \pm 246.6	356.2 \pm 298.4	338.6 \pm 265.1	328.8 \pm 260.7
Clozapine-N-oxide Plasma levels (ng/ml)	154.8 \pm 53.8	152.1 \pm 56.2	150.1 \pm 54.4	160.5 \pm 45.8

^a $p < 0.01$, ^b $p < 0.001$, ^c $p < 0.0004$, ^d $p < 0.0002$, ^e $p < 0.0001$, ^f $p < 0.0005$

Discussion

To the best of our knowledge, this is the first study exploring the clinical and pharmacokinetic effects of gabapentin addition to clozapine in schizoaffective and schizophrenic patients who were nonresponder or partial responder to clozapine. Two main results emerge from this study: 1) gabapentin, at the dose of 900 mg/day, slightly but significantly ameliorated the symptomatology of clozapine-resistant patients with a robust improvement of the mood symptoms; 2) gabapentin, at the doses of 300, 600 and 900 mg/day, did not affect plasma levels of clozapine, N-desmethylclozapine and clozapine-N-oxide.

Despite the significant limitations of a small sample size and of an open-label non-randomised design, our findings suggest that gabapentin may be an useful strategy to augment clinical response in clozapine unresponsive patients. Because plasma levels of clozapine and its major metabolites did not change throughout the co-administration period, any synergism between clozapine and gabapentin is very likely pharmacodynamic rather than the result of pharmacokinetic interaction. The mechanism of this synergism is not clear. We can only speculate that since gabapentin enhances the release and the action of brain γ -aminobutyric acid (GABA), an increase of central GABAergic transmission would result in an improvement of psychotic symptoms since the GABA system has been reported to be impaired in schizophrenia. Alternatively, because most of our patients had a significant affective component in their psychopathology, the mood stabilising properties of gabapentin may have contributed to their clinical amelioration.

Another important limitation of our study is that the trial duration was for 6 weeks only. Longer duration might be required to accurately estimate the risk/benefit ratio of clozapine and gabapentin co-administration. However, since we did not observe significant clinical side effects after gabapentin addition to clozapine and, as stated above, there was no pharmacokinetic interaction between the two drugs, it seems likely that clozapine + gabapentin is a safe combination strategy. To this regard, it is worth mentioning that the combination of clozapine with other mood stabilising drugs is not devoid of side effects. In fact, carbamazepine, beside the potential risk of inducing neutropenia, is a powerful inducer of the CYP450 system, that may decrease plasma levels of clozapine (9); sodium valproate has been reported either to increase (with severe clinical side effects) or decrease clozapine plasma levels (10), while the combination of lithium with clozapine must be sounded with caution since it has been reported to cause encephalopathy (9).

In conclusion, our data suggest that gabapentin augmentation strategy may benefit a subgroup of patients with chronic schizophrenia or schizoaffective disorder non responsive to both typical antipsychotics and clozapine. We believe that these findings warrant further study to confirm that gabapentin is better than other mood stabilising drugs as adjunct to clozapine in clozapine-resistant patients.

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