Amisulpride Has No Effect on Plasma Clozapine Concentrations

To the Editors:

To date, only a few systematic studies analyzing the use of combinations of antipsychotics have been undertaken.1,2 However, knowing how clozapine and amisulpride interact could be particularly important as patients with schizophrenia might well profit from such a combination treatment; indeed, a few case reports and studies support this notion.3–5 Good efficacy and tolerability of this combination in treating positive and negative symptoms have been reported even when the disease has previously been refractory to treatment. The efficacy of the drug combination can be attributed to the complementary receptor profiles of the two drugs.

The atypical antipsychotic drug amisulpride is a benzamide derivative that selectively blocks the dopamine D2 and D3 receptors with no affinity for any other known receptor. It preferentially blocks mesolimbic, rather than nigrostriatal dopaminergic transmission, and the dopamine D2 autoreceptors, rather than the postsynaptic receptors; the dopamine D3 receptors are antagonized preferentially in the limbic areas.6 The efficacy of amisulpride was confirmed in several studies for both positive and negative symptoms of schizophrenia.7 Amisulpride is rapidly resorbed after oral intake and the plasma concentrations reach a maximum twice, once after 1 hour and again after 3 to 4 hours.8 The first-pass metabolism of amisulpride is low; after oral intake the bioavailability is 48%. Seventeen percent of amisulpride binds to plasma proteins.9 Its elimination half-time is about 12 hours and steady state is achieved after 2 to 3 days.8 Amisulpride is mainly eliminated via the kidneys. After intravenous administration, 75% of the dose can be detected in urine.10 Furthermore, about 90% of amisulpride in the urine was found to be unmetabolized, unbound drug.10,11 After a one-time oral intake of amisulpride, only 24% to 47% of the oral dose was found in urine and, of this, 96% had not been altered metabolically.12 There are no active metabolites; after oral administration, only a minor portion of drug undergoes metabolism by hydroxylation, N-dealkylation, and oxidation of the tetracydropryroll core via the cytochrome P-450 system. However, 2 inactive metabolites have been identified and found in urine; they correspond to about 4% of the administered dose of amisulpride. A far greater percentage of amisulpride is excreted unchanged: about 75% via the kidneys and about 20% via the feces.11 There is a linear relationship between the dose and plasma concentration of amisulpride. As amisulpride is mainly eliminated via the kidneys, the dose of amisulpride has to be corrected if creatinine clearance is restricted. Only little is known about how the interaction with other medications affects the pharmacokinetics of amisulpride.13

The tricyclic dibenzodiazepine clozapine is a strong D4 receptor antagonist. Furthermore, it has a slight antagonistic effect on D1, D2, D3, and D5 receptors and possesses anticholinergic, antihistaminergic, antiserotonergic, and anti-alpha-adrenergic properties. The pharmacokinetics of clozapine is subject to numerous influencing variables. About 95% of orally administered clozapine is absorbed, that is, almost all of it. After about 1 to 4 hours, the maximum plasma concentration is achieved. Clozapine has a low first-pass metabolism, with a bioavailability of about 50% to 60%. About 95% of the substance binds to plasma proteins. The elimination half-time is about 14 hours (6–26 hours) and steady state is not achieved until after about 6 to 10 days. Clozapine is almost completely metabolized in the liver by the cytochrome P-450 isoenzymes CYP 1A2 and CYP 3A4 before it is eliminated. To a minor degree, CYP 2D6 and CYP 2C19 are also involved in clozapine metabolism.14 Four metabolites are known; among these only N-desmethylclozapine is pharmacologically active. About 50% of the orally administered dose are eliminated in metabolized form in the urine and about 30% in the feces.

It is known that plasma concentrations of clozapine are affected by a variety of medications. It is also known, however, that clozapine affects the plasma concentrations of other compounds as well.15 We have demonstrated that clozapine increases the plasma concentration of amisulpride.15,16 Based on the findings that plasma concentrations of amisulpride were higher in patients who were treated with both clozapine and amisulpride than in patients receiving amisulpride monotherapy,13 a longitudinal study was conducted in 5 patients who received comedication with clozapine in addition to amisulpride; in all patients clozapine comedication increased the plasma concentrations of amisulpride, with an average increase of 62%. We assumed that amisulpride is actively secreted via the renal transport system, in particular, via cation-proton-antiporters.17 The effect of clozapine on amisulpride that we observed can most likely be attributed to competitive effects on this transport system. Presumably, both of the main metabolites, clozapine-N-oxide and N-desmethylclozapine, are secreted via the renal tubules by cationic-proton-antiporters, whereby these metabolites are considerably better substrates than the parent compound.18 We thus assumed that the clozapine metabolites in particular compete with amisulpride for binding at the renal transport system. Our assumption that amisulpride is actively secreted and that other organic cations interfere with the transport process is supported by previous data of Kamizono et al,19 who showed in rat studies that renal clearance of sulfotride, a deaminated derivative of amisulpride, is significantly decreased by procainamide.

Because a combined clozapine-amisulpride medication may offer therapeutic advantages, it would be very interesting to learn whether the administration of amisulpride, in addition to
TABLE 1. Patient Characteristics, Overview of Clozapine and Amisulpride Plasma Concentrations at $t_0$ and $t_1$ as well as of Comedications

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Smoker</th>
<th>Clozapine dose (mg/d) at $t_0$</th>
<th>Clozapine plasma level (ng/mL) at $t_0$</th>
<th>Dose-corrected clozapine plasma level (ng/mL:mg) at $t_0$</th>
<th>Days under amisulpride until $t_1$</th>
<th>Amisulpride dose (mg/d) at $t_1$</th>
<th>Clozapine dose (mg/d) at $t_1$</th>
<th>Clozapine plasma level (ng/mL) at $t_1$</th>
<th>Dose-corrected clozapine plasma level (ng/mL:mg) at $t_1$</th>
<th>Dose-corrected clozapine plasma level at $t_1$ [% of $t_0$]</th>
<th>Comedication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pat. 1</td>
<td>38</td>
<td>female</td>
<td>yes</td>
<td>600</td>
<td>335</td>
<td>0.56</td>
<td>10</td>
<td>200</td>
<td>600</td>
<td>296</td>
<td>0.49</td>
<td>88</td>
<td>Venlafaxine, Pirenzepine</td>
</tr>
<tr>
<td>Pat. 2</td>
<td>31</td>
<td>female</td>
<td>no</td>
<td>250</td>
<td>755</td>
<td>3.02</td>
<td>4</td>
<td>100</td>
<td>400</td>
<td>709</td>
<td>2.84</td>
<td>94</td>
<td>Venlafaxine, Pirenzepine</td>
</tr>
<tr>
<td>Pat. 3</td>
<td>41</td>
<td>female</td>
<td>yes</td>
<td>400</td>
<td>303</td>
<td>0.76</td>
<td>5</td>
<td>400</td>
<td>400</td>
<td>348</td>
<td>0.87</td>
<td>115</td>
<td>Venlafaxine, Pirenzepine</td>
</tr>
<tr>
<td>Pat. 4</td>
<td>47</td>
<td>male</td>
<td>no</td>
<td>500</td>
<td>667</td>
<td>1.33</td>
<td>12</td>
<td>400</td>
<td>500</td>
<td>549</td>
<td>1.10</td>
<td>82</td>
<td>Venlafaxine, Pirenzepine</td>
</tr>
<tr>
<td>Pat. 5</td>
<td>19</td>
<td>male</td>
<td>no</td>
<td>125</td>
<td>73</td>
<td>0.58</td>
<td>7</td>
<td>200</td>
<td>125</td>
<td>84</td>
<td>1.10</td>
<td>115</td>
<td>Metixen, Citalopram</td>
</tr>
<tr>
<td>Pat. 6</td>
<td>27</td>
<td>male</td>
<td>yes</td>
<td>700</td>
<td>480</td>
<td>0.69</td>
<td>16</td>
<td>400</td>
<td>700</td>
<td>423</td>
<td>0.67</td>
<td>89</td>
<td>Metixen, Citalopram</td>
</tr>
<tr>
<td>Pat. 7</td>
<td>37</td>
<td>female</td>
<td>yes</td>
<td>400</td>
<td>259</td>
<td>0.65</td>
<td>9</td>
<td>400</td>
<td>400</td>
<td>264</td>
<td>0.60</td>
<td>102</td>
<td>Metixen, Citalopram</td>
</tr>
<tr>
<td>Pat. 8</td>
<td>46</td>
<td>female</td>
<td>no</td>
<td>600</td>
<td>608</td>
<td>2.43</td>
<td>7</td>
<td>400</td>
<td>600</td>
<td>541</td>
<td>0.66</td>
<td>89</td>
<td>Metixen, Citalopram</td>
</tr>
<tr>
<td>Pat. 9</td>
<td>22</td>
<td>female</td>
<td>no</td>
<td>250</td>
<td>221</td>
<td>1.11</td>
<td>7</td>
<td>400</td>
<td>250</td>
<td>193</td>
<td>1.10</td>
<td>100</td>
<td>Metixen, Citalopram</td>
</tr>
<tr>
<td>Pat. 10</td>
<td>35</td>
<td>male</td>
<td>no</td>
<td>600</td>
<td>975</td>
<td>1.63</td>
<td>7</td>
<td>400</td>
<td>600</td>
<td>979</td>
<td>1.36</td>
<td>105</td>
<td>Metixen, Citalopram</td>
</tr>
<tr>
<td>Pat. 11</td>
<td>28</td>
<td>male</td>
<td>yes</td>
<td>350</td>
<td>523</td>
<td>1.49</td>
<td>11</td>
<td>500</td>
<td>350</td>
<td>543</td>
<td>0.58</td>
<td>91</td>
<td>Metixen, Citalopram</td>
</tr>
<tr>
<td>Pat. 12</td>
<td>20</td>
<td>male</td>
<td>no</td>
<td>400</td>
<td>232</td>
<td>0.73</td>
<td>7</td>
<td>450</td>
<td>400</td>
<td>210</td>
<td>0.73</td>
<td>85</td>
<td>Pirenzepine, Propranolol</td>
</tr>
<tr>
<td>Pat. 13</td>
<td>37</td>
<td>male</td>
<td>no</td>
<td>450</td>
<td>327</td>
<td>1.20</td>
<td>5</td>
<td>456</td>
<td>450</td>
<td>479</td>
<td>0.49</td>
<td>110</td>
<td>Doxepin</td>
</tr>
</tbody>
</table>

* $M ± SD = mean ± standard deviation [range].
clozapine, leads to a change in plasma concentrations of the latter. It is assumed that this is not the case as, most likely, only the metabolites but not the parent compound are involved in the renal interaction. Nevertheless, product inhibition of clozapine-metabolizing enzymes by accumulating clozapine metabolites could not be totally excluded because such competitive product inhibition of hepatic biotransformation was already shown for desmethylated or hydroxylated metabolites of various other drugs, including aminopyrine and diazepam.\textsuperscript{20–22} In the following section, we discuss the inhibition of hepatic biotransformation was already shown for desmethylated or hydroxylated metabolites of various other drugs, including aminopyrine and diazepam. In the following section, we discuss the inhibition of hepatic biotransformation was already shown for desmethylated or hydroxylated metabolites of various other drugs, including aminopyrine and diazepam.

In the following section, we report on 13 patients treated with clozapine who received additional treatment with amisulpride because the efficacy of the one drug was unsatisfactory in relieving negative symptoms.

Thirteen inpatients (6 women, 7 men) between 17 and 47 years (mean ± SD: 32.9 ± 8.9), who were being treated with clozapine at the Psychiatric Clinic of the University of Heidelberg for schizophrenia, received amisulpride as comedication. Doses of clozapine and amisulpride were determined for each patient individually. A description of the patients, who were consecutively included in the study, and the individual treatment regimens can be seen in Table 1. Six patients were taking other medications in addition to the antipsychotics.

Plasma concentrations of clozapine were determined before and after the administration of amisulpride. Only those patients were included in the study whose plasma concentrations of clozapine had reached steady state and for whom there was no doubt that the medication was being taken regularly. If the patients were taking other drugs, this was not changed during the study period. Before amisulpride \((t_0)\) was added to the treatment regimen, the patients had been receiving an average daily dose of 433 mg clozapine (SD = 168 mg); after combining this with amisulpride \((t_1)\), the average daily dose of clozapine was 456 mg (SD = 175 mg). The patients had received clozapine in the same dose between 11 and 61 days. The average time span between the two measurements of clozapine plasma concentrations comprised 10.2 days (SD = 4.3). Before \(t_1\), the patients had been receiving amisulpride for at least 4 days and at most for 16 days (mean ± SD: 8.5 ± 3.1 days). At \(t_1\), the mean dose of amisulpride amounted to 415 mg (SD = 199 mg, range: 100–800 mg).

Blood specimens for determining plasma concentrations of clozapine were taken between 8 and 9 AM (ie, 10–12 hours after clozapine had last been taken). Clozapine concentrations were determined by high-performance liquid chromatography analysis with UV detection exactly as described previously.\textsuperscript{23}

After administering amisulpride in addition to the existing clozapine treatment, no significant changes were observed in the clozapine plasma concentrations. The average plasma concentration of clozapine at study point \(t_0\) was 443 ng/mL, at \(t_1\) 456 ng/mL; the dose-corrected plasma concentration was 1.20 ng/mL:mg at \(t_0\) and 1.14 ng/mL:mg at \(t_1\). The difference between the two points in time is not statistically significant \((t\) test for dependent samples) and can be neglected. The individual daily doses of clozapine and amisulpride, the dose-corrected drug plasma concentrations in the 13 patients, and the mean values for the patient group are presented in Table 1.

In a previous study,\textsuperscript{12} an elevated amisulpride plasma concentration under comedication with clozapine as compared with amisulpride monotherapy could be demonstrated. The effect was attributed to a renal interaction. Although the clozapine metabolites clozapine-N-oxide and N-desmethylclozapine compete with amisulpride for binding at the renal transport system, amisulpride comedication does not affect plasma concentrations of clozapine, as could be confirmed by the data presented here.

Polypharmacy is a reality in contemporary psychiatric practice, based upon experience rather than empirical evidence. Only a few data are available on the efficacy of the combination of more than one antipsychotic in the treatment of schizophrenia. Antipsychotic polypharmacy thus clearly requires further trials before clinical recommendations can be made, not only to provide evidence of its efficacy, but also to enhance knowledge of drug-drug interactions.

Niels Bergemann, MD, PhD*
Kai R. Kress, MD*
Alex Frick, MD*
Jürgen Kopitz, PhD†
Departments of Psychiatry and †Molecular Pathology, University of Heidelberg, Germany
Niels_Bergemann@med.uni-heidelberg.de

REFERENCES
7. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry. 2003;60:553–564.
14. Linnet K, Olesen OV. Metabolism of clozapine by cDNA-expressed human cytochrome
Open-label Pilot Study of Ziprasidone for Refractory Generalized Anxiety Disorder

To the Editors:

Although there are several classes of medication indicated for the treatment of adult generalized anxiety disorder (GAD), less than half of treated patients reach remission. For example, benzodiazepine therapy has been shown to result in remission rates of approximately 40%. Similarly, low remission rates are observed for venlafaxine XR (37%) and for paroxetine (36%). The low rates of remission and high rates of nonresponse reported with benzodiazepines and antidepressants indicate treatment resistance for a significant number of GAD patients treated with medication and warrant the investigation of alternative or augmentation strategies to reduce disability and suffering as a result of this chronic disorder.

In the past, Rickels et al have investigated the efficacy of earlier neuroleptics in anxiety with mixed results. Newer atypical neuroleptics with actions on serotonergic and dopaminergic pathways may prove to be more promising agents for the treatment of patients with GAD. These newer agents have also demonstrated an improved side effect profile, with fewer extrapyramidal symptoms such as dystonias and parkinsonism, and a lower incidence of tardive dyskinesia. Treatment with ziprasidone does not appear to result in greater changes in weight and prolactin levels than placebo in double-blind studies.

Although ziprasidone’s efficacy as an antipsychotic agent has been attributed largely to its antagonism at the dopamine D2 receptor, its serotonergic properties may make it a useful agent in the treatment of GAD.

The aim of this study is to provide pilot data on the efficacy and safety of ziprasidone in treatment-resistant GAD. Thirteen adult subjects participated in this open-label study using ziprasidone in a daily dose range of 20 to 80 mg. The study protocol was approved by the institutional review board of the University of Pennsylvania.

To be eligible to participate in the study, subjects had to meet the following inclusion criteria: a score of 4 or greater on the Clinical Global Impression Severity of Illness Scale (CGI-S), a Hamilton Anxiety Rating Scale (HAM-A) score 16 or greater after 8 weeks of treatment with at least 1 first-line antianxiety agent, male or female subjects, aged 18 years or older, and a primary diagnosis of GAD confirmed by the Mini-International Neuropsychiatric Interview.

Exclusion criteria included concomitant use of anticonvulsants and other mood stabilizers, sedative antihistamines, or other antipsychotics; women who are pregnant or breast-feeding; women of childbearing potential who are not practicing a clinically accepted method of contraception; clinically significant abnormalities on electrocardiogram at screening including, but not limited to, a QTc greater than 480 milliseconds; comorbid psychiatric disorders such as a major depressive episode during the previous 6 months; substance dependence or abuse during the previous 12 months; or lifetime bipolar and psychotic disorders.

An Axis I diagnosis other than GAD, such as comorbid dysthymia, panic attacks, or social phobia, was not exclusionary, provided that GAD was the primary diagnosis.

The primary outcome measure was the HAM-A, whereas secondary outcome measures were the CGI-S and the Clinical Global Improvement Scale (CGI-I), the Hamilton Depression Scale (HAM-D), the Sheehan Disability Scale (SDS), and the anxiety subscale of the Hospital Anxiety and Depression Scale (HAD-A). The SDS, HAM-D, and HAD-A were administered at baseline, screen, and weeks 4 and 7, whereas the HAM-A, CGI-I, and CGI-S were assessed at all visits. Side effects were monitored and recorded, and the Abnormal Involuntary Movement Scale was performed at each visit.

During this open-label flexible-dose study, subjects received ziprasidone as monotherapy, for 7 weeks, followed by a 3- to 7-day taper. Patients had the option to continue ziprasidone treatment at the conclusion of the study.

During the first week, all patients received ziprasidone 20 mg daily. Then, depending on clinical response and tolerability, the dose could be increased in 20 mg/wk increments to a maximum of 80 mg/wk. Although the relatively short half-life of ziprasidone (approximately 6–7 hours) would suggest the necessity for bid dosing, the decision to use twice-a-day or once a day dosing was made by the subject and physician based on degree of sedation.

Two-tailed paired t tests were performed to assess significance of change in primary and secondary outcome measures between baseline and treatment.