Increased Clozapine Plasma Concentrations and Side Effects Induced by Smoking Cessation in 2 *CYP1A2* Genotyped Patients

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Abstract: Clozapine, an atypical antipsychotic, depends mainly on cytochrome P4501A2 (CYP1A2) for its metabolic clearance. CYP1A2 is inducible by smoking, and lower plasma concentrations of clozapine are measured in smokers than in nonsmokers. Case reports have been published on the effects of discontinuing smoking in patients receiving clozapine, which might lead to elevated plasma concentrations and severe side effects. We present 2 cases on the consequences of smoking cessation in patients receiving this drug. In the first patient, smoking cessation resulted, within 2 weeks, in severe sedation and fatigue, with an approximately 3-fold increase of plasma clozapine concentrations. In the second patient, a very high plasma concentration of clozapine (3004 ng/mL) was measured 6 days following a 16-day stay in a general hospital, during which smoking was prohibited. In the latter patient, the replacement of omeprazole, a strong CYP1A2 inducer, by pantoprazole, a weaker CYP1A2 inducer, could have contributed, in addition to smoking cessation, to the observed strong increase of plasma clozapine concentrations. Genotyping of the 2 patients revealed that they were carriers of the AA genotype for the −164C>A polymorphism (*CYP1A2*1F*) in intron 1 of *CYP1A2* gene, which has previously been shown to confer a high inducibility of CYP1A2 by smoking. Thus, at the initiation of clozapine treatment, smoking patients should be informed that, if they decide to stop smoking, they are encouraged to do so but must inform their prescriber beforehand. Also, because of the increased use of no-smoking policies in many hospitals, studies examining the consequences of such policies on the pharmacokinetics/pharmacodynamics of drugs metabolized by CYP1A2, taking into account different *CYP1A2* genotypes, are needed.

Key Words: clozapine, CYP1A2, polymorphism, metabolism, smoking, therapeutic drug monitoring

(*Ther Drug Monit* 2005;27:539–543)

Clozapine (CLO) is a highly effective atypical antipsychotic drug for which optimum plasma concentrations of about 350–400 ng/mL have been suggested by several studies (for a review, see Wagstaff and Bryson[1] and Freeman and Oyewumi[2]), while the risks of adverse effects on the central nervous system (confusion, delirium, and generalized seizures) are increased with clozapine concentrations above 1000 ng/mL.[2] Plasma concentrations of clozapine between 4000 and 10,000 ng/mL have been measured in cases of acute clozapine overdose, with side effects such as somnolence, sedation, seizures, unconsciousness, metabolic acidosis, or aspiration pneumonia.[3–5]

Cytochrome P450 1A2 (CYP1A2) is the major enzyme involved in the metabolism of clozapine[6–8] and induction of CYP1A2 by smoking leads to reduced plasma clozapine concentrations,[9] resulting in the need for higher maintenance doses of clozapine in smokers as compared with nonsmokers.[10] A few case reports have been published on the effects of discontinuing smoking in patients receiving clozapine,[11–14] which results in increased plasma concentrations and might lead to confusion,[14] tonic–clonic seizures, stupor and coma,[12,13] or aspiration pneumonia.[11]

Several gene mutations have been identified in the *CYP1A2* gene, in particular in the 5′-flanking region and in intron 1 of *CYP1A2* (see *http://www.imm.ki.se/CYPalleles/cyp1a2.htm*). Some of these polymorphisms may be associated with altered inducibility of gene expression in smokers.[15–17] Of particular interest is the −164C>A polymorphism (*CYP1A2*1F*) in intron 1, which confers a high inducibility of CYP1A2 by smoking, with a 1.6-fold higher metabolic activity in the group of smokers for subjects homozygous for the A allele compared with the other genotypes, whereas no differences were found between genotypes in the group of nonsmokers.[16] Mechanistically, this polymorphism in a noncoding region of *CYP1A2* gene may either result in differential binding of putative regulatory proteins or may be in linkage disequilibrium with other mutations affecting CYP1A2 inducibility.[16] *CYP1A2*1F* genetic polymorphism also influences the induction of CYP1A2 by omeprazole,[18] but it is not known

Received for publication September 9, 2004; accepted March 11, 2005.
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This work was supported in part by the Swiss National Research Foundation (project 3200-065427.01).
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whether the mechanism involved in the induction of CYP1A2 activity by omeprazole is the same as that occurring in cigarette smokers.[18] Case reports suggest that high CYP1A2 activity may lead to low plasma clozapine concentrations and to nonresponse,[19–21] a very rapid CYP1A2 activity in smokers possibly being explained by the presence of the *CYP1A2*1F* allele.[20,21] Such an influence of the *CYP1A2*1F* allele on plasma clozapine concentrations was, however, not found in a recent study, neither in the group of smokers nor in the group of nonsmokers.[10] However, knowing that compliance can be a major issue in patients receiving long-term pharmacotherapy, with a proportion of poor or noncompliance around 50% in patients with schizophrenia,[22,23] the influence of the *CYP1A2*1F* allele on clozapine clearance requires further investigations, in particular with patients whose compliance can be ascertained.

In the present paper, 2 new case reports are presented detailing the consequences of smoking cessation on plasma concentrations of clozapine and on the clinical outcomes in 2 patients receiving clozapine treatment, who were genotyped for *CYP1A2*1F* allele.

METHODS

Subjects and Setting

Patients A and B were included in Geneva and in Yverdon, respectively. Both patients gave their written informed consent to the genetic analysis. This study was carried out in accordance with the Declaration of Helsinki. Blood samplings for trough plasma clozapine concentrations were performed in steady-state conditions approximately 12 hours after the intake of the evening dose, and before the morning dose. Patient A had normal hepatic and renal functions, as assessed by standard clinical laboratory tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, urea, creatinine), whereas patient B had moderately disturbed hepatic functions (less than 4-fold the upper normal limit for ALT and ASP).

Analysis

CLO and NCLO were measured by gas chromatography with the use of a nitrogen phosphorus detector as previously reported.[21] Fluvoxamine was measured by gas chromatography/mass spectrometry as previously described.[24] DNA was isolated using standard methods from blood drawn into 9-mL K-EDTA tubes and stored at −20°C until use. The *CYP1A2*1F* genotype (−164C>A) was determined by real-time PCR with TaqMan (Applied Biosystems, Rotkreuz, Switzerland) according to the manufacturer's instructions. Briefly, the 25 μL PCR mixture contained 12.5 μL TaqMan Universal PCR master mix (×2 solution containing AmpliTaq Gold DNA polymerase, AmpErase UNG, dNTPs, and optimized buffer), 900 nM of each primer, 200 nM of each TaqMan minor groove binder (MGB) probe, and 100 ng of DNA. After the activation step of AmpErase (50°C, 2 minutes) and AmpliTaq Gold enzyme activation (95°C, 10 minutes), 35 PCR cycles were performed with 15 seconds at 92°C and 1 minute at 60°C. The primers were 5′-CTCAGATTCTGTGATGCTCAAAGG-3′ (forward) and 5′-CACTGATGCGTGTTCTGTGCTT-3′ (reverse), and the probes were 5′-CGTCCTGgGCCCA-3′ (FAM, wild-type) and 5′-ATGCGTCCTGtGCC-3′ (VIC, mutated allele).

RESULTS

Patient A, a 51-year-old white male smoker (40 cigarettes/d), had a 16-year history of paranoid schizophrenia (ICD10: F 20.0), which necessitated 5 hospitalizations. He was unsuccessfully treated with several typical antipsychotics (thioridazine 400 mg/d; levomepromazine 150 mg/d; clopenthixol decanoate 200 mg/2 weeks; flupenthixol decanoate 40 mg/2 weeks) with persistence of severe auditory hallucinations, psychomotor agitation, and paranoid delusions. When he was 43 years old, clozapine medication (up to 400 mg/d) was started. The patient improved slightly, becoming less tense and less agitated, but still complained of persistent disturbing delusions and hallucinations. A plasma clozapine concentration measured at this dosage was clozapine 129 ng/mL, norclozapine 64 ng/mL (comedication: lorazepam 1 mg/d). Because the patient was quite reluctant to increase his clozapine dose, fluvoxamine, a potent CYP1A2 inhibitor,[25] was introduced at 50 mg/d (fluvoxamine plasma level 39 ng/mL) even though he did not suffer from any affective comorbid symptoms at that time. This led to a 2.8-fold increase in the plasma clozapine concentration (clozapine 367 ng/mL, norclozapine 160 ng/mL). It is worth noting that the patient was informed by his psychiatrist of the probable elevation of the clozapine plasma concentration caused by the addition of fluvoxamine, but he definitely preferred this solution rather than an increase of the clozapine posology. It must be stressed that, to increase plasma clozapine concentrations, the strategies of increasing clozapine dose or introducing fluvoxamine are not equivalent. The former strategy must be the first choice because of a probable nonlinearity of clozapine kinetics when such a strong CYP1A2 inhibitor is given, requiring close monitoring of plasma clozapine concentrations. Fluvoxamine should be given only to nonresponders when low concentrations of clozapine have been measured, when noncompliance or poor compliance has been excluded, and/or when a very high CYP1A2 activity has been measured.[21]

In the present case, with this combined treatment of clozapine at 400 mg/d plus fluvoxamine at 50 mg/d, the patient's clinical condition improved significantly, although he occasionally complained of some residual auditory hallucinations. This combined treatment was maintained for several years, and a plasma clozapine measurement performed 5 years later yielded the following values: clozapine 230 ng/mL and norclozapine 117 ng/mL. That same year, because of his continuing request to reduce the dose of the medication, the dose of clozapine was decreased to 350 mg/d (150 in the morning, 200 mg at night) while fluvoxamine was maintained at 50 mg/d, with the clinical course remaining stable (comedications were unchanged, except simvastatin, which was introduced at 20 mg/d for the treatment of hypercholesterolemia).

At the age of 50, he abruptly decided to quit smoking without notifying his psychiatrist, and 2 weeks later, he started complaining of severe sedation and fatigue but did not report

such adverse effects until he met again with his physician 8 months later. Plasma concentrations of clozapine and norclozapine measured on this occasion were markedly increased to 667 and 306 ng/mL for clozapine and norclozapine, respectively. To reduce the adverse effects, a progressive dose reduction plan for clozapine, with parallel plasma concentration monitoring, was undertaken. Thus, clozapine dose was slowly decreased to 150 mg/d, with the fluvoxamine dose being kept constant. This resulted in a decrease of clozapine and norclozapine concentrations to 337 ng/mL and 150 ng/mL, respectively (clozapine 150 mg/d; simvastatin 20 mg/d), and in a significant decrease in fatigue and sedation. Subsequently, simvastatin was stopped with no consequences on plasma clozapine concentrations (CLO 336 ng/mL; NCLO 127 ng/mL). A *CYP1A2* genotyping test showed this patient to be homozygous for the −164C>A polymorphism.

Patient B, a 33-year-old white female smoker (about 4 cigarettes/d), had a 1-year history of unspecified nonorganic psychosis (F29), with visual and auditory hallucinations, sudden and intense psychomotor agitation, and disorganized and incoherent speech, which necessitated hospitalization on 3 occasions. During the last hospitalization, she had no response with olanzapine at doses up to 30 mg/d, with persistence of hallucinations and psychomotor agitation. Olanzapine was replaced by clozapine with doses increased up to 250 mg/d in 4 days. After 2 days of treatment with this dose, the patient was transferred to a medical unit for a surgical intervention not related to her psychiatric illness. During her 16-day stay in the surgical unit, she did not smoke because of a no-smoking policy, but her medications were kept constant with the exception of clozapine doses, which were progressively increased to 450 mg/d; lorazepam, which was replaced by clorazepam; omeprazole, which was replaced by pantoprazole; and metronidazole, which was administered for 10 days at 1500 mg/d to treat diarrhea. The day following her transfer to the psychiatric unit (where she could again smoke, about 1 to 2 cigarettes per day), clozapine dose was increased to 550 mg/d because of a sudden, intense, and persistent psychotic episode. Six days following her transfer, because of a slow evolution of her clinical course, therapeutic monitoring of clozapine was requested, which revealed a very high plasma clozapine concentration (CLO 3004 ng/mL; NCLO 1184 ng/mL; comedications: clorazepam 60 mg/d; paracetamol 4 g/d; tramadol 100 mg/d; pantoprazole 40 mg/d; vitamins; enoxaparine 40 mg/d). Clozapine was discontinued for 3 days, although no particular side effects were noted by either the clinical staff or the patient (unfortunately no ECG or EEG were recorded during this period). Clozapine was then reintroduced and increased progressively to 200 mg/d with close monitoring of plasma concentrations (at 125 mg/d, 4 weeks after clozapine reintroduction, CLO 88 ng/jL; NCLO 62 ng/mL; at 200 mg/d, 6 weeks after clozapine reintroduction, CLO 122 ng/mL; NCLO 92 ng/mL; comedications during both blood samplings: clorazepam 60 mg/d; paracetamol 3 g/d; tramadol 100 mg/d; pantoprazol 40 mg/d; ascorbic acid 300 mg/d; iron 275 mg/d). The patient showed a slow improvement, with a decrease of psychiatric symptoms. However, it was not possible to modify the clozapine dose further because after the patient was discharged, 1 of her relatives decided that she should stop clozapine. A *CYP1A2* genotyping test showed this patient also to be homozygous for the −164C>A polymorphism.

DISCUSSION

Clozapine is mainly metabolized by CYP1A2,[6–8] and induction of CYP1A2 by smoking leads to reduced plasma clozapine concentration.[9] A few case reports have been published on the effects of discontinuing smoking in patients receiving clozapine, leading to elevated plasma concentrations and severe side effects.[11–14] In the present report, we present the consequences of smoking cessations in 2 patients treated with clozapine.

In the first patient, smoking cessation, with unchanged doses of clozapine and of comedications, resulted in severe sedation and fatigue within 2 weeks, with an approximately 3-fold increase of CLO plasma concentrations, which necessitated a more than 2-fold decrease of clozapine dose.

In the second patient, a very high plasma clozapine concentration was measured 6 days following a 16-day stay in a general hospital in which smoking was prohibited. It seems unlikely that this very high blood level could be caused by the moderate hepatic impairment observed in this patient (see Methods section), especially in the light of the reduction of plasma clozapine concentrations when the patient smoked again. On the other hand, such a high plasma concentration could have been caused by comedications received by the patient in that hospital that might have inhibited clozapine metabolism. However, the medications received by the patient were essentially kept constant compared with those received in the psychiatric hospital, with the exception of clorazepam, pantoprazole (to replace omeprazole), and metronidazole, which were introduced in the somatic hospital, the latter drug being administered over 10 days. Inhibition of clozapine metabolism by metronidazole appears to be an unlikely mechanism for explaining elevated plasma clozapine concentrations because metronidazole does not affect theophylline disposition, a marker of CYP1A2 activity.[26] Also, although an increase of cyclosporine and tacrolimus blood concentrations has been reported in 2 patients receiving metronidazole,[27] it has been shown that this drug does not affect either midazolam metabolism in vitro and in vivo[28] or the erythromycin breath test[29] or alprazolam clearance,[30] which are all markers of CYP3A4 activity. Furthermore, an inhibition of CYP3A4 by metronidazole is an unlikely mechanism to explain an increase of clozapine concentrations because itraconazole, a potent CYP3A4 inhibitor, does not affect clozapine and norclozapine concentrations,[31] and because nefazodone, another potent CYP3A4 inhibitor, has minimal effects on clozapine metabolism.[32]

Clorazepam treatment could not be the cause of this increase of plasma clozapine concentrations as this drug was still prescribed after the transfer of the patient back to the psychiatric unit, whereas plasma clozapine concentrations had decreased to therapeutic ranges. On the other hand, because pantoprazole is a weaker CYP1A inducer than omeprazole,[33] the replacement of the latter by the former in the general hospital could contribute, in addition to smoking cessation, to

the observed strong increase of plasma clozapine concentrations. However, this can not be the main cause, as therapeutic drug monitoring performed when the patient smoked again, showed a normalization of plasma clozapine concentrations. As the blood sample, which showed very high concentrations of clozapine, was drawn 6 days after the patient started to smoke again, it is not known whether even higher plasma concentrations of clozapine were in fact reached at the end of the nonsmoking period. It should be mentioned that no particular side effects were either reported or noted by the clinical staff, but, unfortunately, no ECG or EEG was performed during this period.

Nonconclusive studies have been published on the consequences of *CYP1A2*1F* allele on clozapine pharmacokinetics.[10,19–21] In the present report, the 2 patients were carriers of the AA genotype for the *CYP1A2*1F* allele. The first patient, a heavy smoker (40 cigarettes/day), had a apparently high CYP1A2 activity as suggested by a low plasma concentrations of clozapine when receiving clozapine at a dosage of 400 mg/d. On the other hand, plasma clozapine concentration determination in the second patient did not suggest a high CYP1A2 activity, but it is not known whether a low consumption of cigarettes (1–2 cigarettes per day) could have contributed to this result.

In summary, we have described the consequences of smoking cessation in 2 patients treated with clozapine, who were carriers of the AA genotype for the *CYP1A2*1F* allele. There is a high frequency of smokers among patients with schizophrenia (more than 80%), and the proportion of carriers of the AA genotype for the *CYP1A2*1F* allele is also important (about 50% in whites).[16] It is interesting to note that, in the present report, smoking cessation was the self-decision of 1 patient but was imposed on the second patient by a no-smoking policy in the hospital. Thus, at the initiation of clozapine treatment, patients who smoke should be informed that, if they decide to stop smoking, they are encouraged to do so but must first inform their prescriber. Also, because of the increased use of no-smoking policies in many hospitals, studies examining the consequences of such policies on the pharmacokinetics/pharmacodynamics of drugs metabolized by CYP1A2 are needed, taking into account different *CYP1A2* genotypes.

ACKNOWLEDGMENTS

The authors thank Mrs. V. Sari for her editorial assistance, and Mrs. J. Rosselet, Mrs. E. Ponce, and Mrs. M. Gobin for their bibliographic help.

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