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Effect of Smoking on the Pharmacokinetics of Inhaled Loxapine

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Background: Loxapine inhalation powder delivered by a hand-held device as a thermally generated aerosol (ADASUVE) was recently approved in the United States and European Union for use in the acute treatment of agitation in patients with bipolar disorder or schizophrenia. As smokers comprise a large subpopulation of these patients, and many antipsychotic drugs require dose adjustments for smokers, the objective of this study was to compare the pharmacokinetics of inhaled loxapine administered to smokers and nonsmokers.

Methods: Pharmacokinetics and sedation pharmacodynamics using a visual analog scale were studied in 35 male and female adult subjects (18 nonsmokers and 17 smokers) following a single dose of 10 mg of inhaled loxapine. Blood samples were drawn at predose, 30 seconds, 1, 2, 3, 10, 30, and 60 minutes, and 2, 6, 12, and 24 hours after dosing. Loxapine and 8-OH-loxapine were analyzed using reverse-phase liquid chromatography coupled with a tandem mass spectrometer. Pharmacokinetic parameters assessed included C_{max}, T_{max}, AUC_{inf}, and $T_{1/2}$ for loxapine and 8-OH-loxapine. Geometric mean ratios (GMRs) were determined for smokers to nonsmokers.

Results: Loxapine C_{max} was similar in smokers and nonsmokers with a GMR of 99.0%. The median loxapine T_{max} was 1.88 and 1.01 minutes for nonsmokers and smokers, respectively. Loxapine AUC_{inf} and AUC_{last} values in nonsmokers were comparable with smokers (GMRs of 85.3% and 86.7%, respectively). A slight decrease in the observed mean terminal half-life values was observed for smokers (6.52 hours for smokers and 7.30 hours for nonsmokers).

Conclusions: Sedation profiles and visual analog scale scores at each time point were similar for nonsmokers and smokers. It was concluded that inhaled loxapine does not require dosage adjustment based on smoking behavior.

Key Words: inhaled loxapine, 8-OH-loxapine, smoking, pharmacokinetics, cytochrome P450 1A2

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INTRODUCTION

Loxapine is a dibenzoxazepine antipsychotic that has dopamine D2 blocking activity and binding affinity for the serotonin 5-HT_2 receptor.[1] It was first introduced in the United States in 1975 and is currently marketed as an oral form in the United States and an intramuscular form in Europe. Loxapine inhalation powder delivered by a hand-held device as a thermally generated aerosol was recently approved in the United States and European Union (ADASUVE; Alexza Pharmaceuticals, Inc, Mt.View, CA) for use in the acute treatment of agitation in patients with bipolar disorder or schizophrenia.[2]

The prevalence of smoking in patients with schizophrenia is 64% and in bipolar disorder is 44%.[3] About half of the individuals diagnosed with schizophrenia and bipolar affective disorder reported smoking more than 20 cigarettes per day.[4] The high frequency for both smoking prevalence and heavy smoking in psychotic patients may reflect smoking-stimulated dopaminergic activity in the brain, and there is evidence that cigarette smoking can mitigate dopamine hypofunction in the prefrontal cortex.[5]

Cigarette smoking can affect the pharmacokinetics and pharmacodynamics of many antipsychotic drugs[6,7] by increasing the metabolic activity of cytochrome P450 (CYP) enzymes, especially CYP1A2.[8,9] Olanzapine is metabolized by CYP1A2, and plasma concentration-to-dose ratios were reported to be 5-fold lower in smokers than in nonsmokers, with nonsmokers more frequently reporting side effects.[10] The major metabolite of clozapine is also formed via CYP1A2,[11] and smoking has been associated with lower plasma levels.[12–17] Therapeutic drug monitoring of clozapine was recommended to minimize dose-dependent toxic adverse events, and a 50% lower starting dose has been recommended for both clozapine and olanzapine in nonsmokers.[14] Likewise, smokers may require a dose reduction for antipsychotic drugs upon smoking cessation.

The metabolism of loxapine is similar to that of clozapine because it is a close structural analog where the oxazepine ring of loxapine is replaced by a diazepine ring. Because of this substitution, loxapine cannot form the nitrenium intermediate that has been associated with agranulocytosis. However, like clozapine and olanzapine, loxapine's

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major metabolite, 8-hydroxy-loxapine, is formed mainly through CYP1A2,[18,19] and therefore, loxapine's pharmacokinetics and pharmacodynamics could be influenced by smoking.

The lung contains several enzymatic pathways capable of xenobiotic metabolism, and it is generally agreed that the CYPs are the main system catalyzing the oxidative metabolism and/or metabolic activation of most drugs.[20] CYP enzyme expressions in the lung are not as well characterized as those in the liver because of their low abundance.[21,22] The total lung CYP content is only 1% that in the liver.[23] Although pulmonary metabolic capacity is far lower than that in the liver, the pulmonary veins have very large vascular surface areas, and the concentrations of a drug being exposed to the lung can be much higher than the concentrations in the liver. Smoking has been associated with increased permeability of the pulmonary capillary epithelium, resulting in faster absorption.[24]

As the induction of CYP1A2 in smokers could influence the exposure of loxapine after inhalation delivery, and the increased alveolar permeability in smokers could affect the rate and extent of loxapine absorption after inhalation, the objective of this study was to assess the pharmacokinetics and sedation pharmacodynamics of a single dose of inhaled loxapine administered to smokers compared with nonsmokers.

MATERIALS AND METHODS

The study was conducted between April 2009 and July 2009 at the Covance Clinical Research Unit in Evansville, Indiana. Independent Investigational Review Board, Inc (Plantation, FL) reviewed and approved the consent form and study protocol, and the study was carried out in accordance with the Declaration of Helsinki. Written informed consents were obtained from each participant before any study-related procedures.

Subjects

Healthy male and female subjects, 20–50 years old (inclusive), with a body mass index of 18–30 kg/m^2 (inclusive), were enrolled. Female subjects were not pregnant and not lactating. Health status was assessed by a complete medical history, physical examination, 12-lead electrocardiogram, blood chemistry profile, hematology, and urinalysis. Smokers had to have a history of smoking more than 15 cigarettes per day for at least the past 2 years and had to have a urine cotinine level of ≥500 ng/mL. Nonsmokers had to have a history of never smoking more than 5 cigarettes per day, not smoked for at least the past 2 years, and a urine cotinine level of ≤40 ng/mL.

Exclusion Criteria

We recruited 2 groups of subjects—nonsmokers (never smoked more than 5 cigarettes per day and not smoked for at least the past 2 years, with a urine cotinine level of ≤40 ng/mL) and smokers (smoked more than 15 cigarettes per day for at least the past 2 years, with a urine cotinine level of ≥500 ng/mL). At recruitment, subjects in both groups met the following criteria: 20–50 years old (inclusive), body mass index of 18–30 kg/m^2 (inclusive), female subjects were not pregnant and not lactating, healthy based on a complete medical history, physical examination, 12-lead electrocardiogram, blood chemistry profile, hematology, and urinalysis, forced expiratory volume in 1 second ≥80% of predicted and forced vital capacity ≥80% of predicted. Subjects were excluded for any acute illness in the prior 5 days; upper respiratory tract infection in the prior 6 weeks or bronchitis/pneumonia in the prior 6 months; use of a bronchodilator for the treatment of wheezing within 12 months; lung resection or other pulmonary surgery within 12 months; treatment with an investigational drug within 30 days; taking drugs other than acetaminophen, ibuprofen, oral contraceptives, or vitamins within 5 days before study drug administration. Study subjects were informed that they were free to discontinue the study at any time.

Study Treatments

In this single-center, single-dose, single-treatment, open-label study, 35 male and female adult subjects (18 nonsmokers and 17 smokers) received a single dose of loxapine. A 10-mg dose of loxapine was selected for evaluation because it was the highest dose evaluated in clinical studies.[25] Subjects were administered inhaled loxapine and confined to the clinical research unit under medical observation from the time of check-in procedures until the completion or discharge procedures (approximately 14 hours before the dose of study medication and until at least 24 hours after receiving the study treatment).

Plasma Collection and Analysis

Blood samples were drawn at predose, 30 seconds, 1, 2, 3, 10, 30, and 60 minutes, and 2, 6, 12, and 24 hours after dosing. Plasma samples were assayed for loxapine and 8-OH-loxapine concentrations at Alturas Analytics (Moscow, ID) using a validated method.[26] Plasma samples all utilized K_2EDTA as the anticoagulant. Loxapine and 8-OH-loxapine were extracted from plasma using solid phase extraction and were analyzed using reverse-phase liquid chromatography coupled with a tandem mass spectrometer operating in the positive ionization mode. Quantitation was performed using similarly extracted plasma calibration samples ranging from 0.050 to 50 ng/mL for loxapine and 8-OH-loxapine. For the standard curves analyzed, weighted ($1/x^2$) linear regression analysis gave average correlation coefficients greater than 0.990 for all analytes evaluated. On all occasions, peak area ratios were generated by taking the peak area of the product ion of the analyte of interest and measuring it against the peak area of the product ion of the corresponding stable label internal standard. Intraassay precision, defined by the percent coefficient of variation of the quality controls in each validation run, was within 14.4% in all instances. Interassay precision, defined by the percent coefficient of variation of the quality controls in all validation runs, was within 9.4% in all instances; and accuracy, as defined as the percent difference between the nominal and mean measured quality control standard concentration and represented as percentage bias, was never more than 13%.

Pharmacokinetic Analysis

It has been shown that after inhalation of loxapine as a thermally generated aerosol, the drug is rapidly absorbed

systemically, with high bioavailability and intravenous-like pharmacokinetics.[25] Because the intravenous-like post-peak pharmacokinetic (PK) profile falls much more rapidly than suggested by the terminal half-life, $T_{half\text{-}max}$ (time from T_{max} to time when concentration falls to half peak level, ie, $C_{max}/2$) was calculated to provide a simple, direct measure of the rapid fall after T_{max}. For each subject, noncompartmental PK parameters were estimated: C_{max}, T_{max}, $T_{half\text{-}max}$, area under the concentration curve (AUC) from 0 to the last measurable value (AUC_{last}), and from 0 to infinity (AUC_{inf}), k_e, and $T_{1/2}$ were estimated for loxapine and 8-OH-loxapine. Clearance uncorrected for bioavailability (CL/F) was estimated for loxapine.

Summaries [descriptive statistics including 90% confidence interval (CI)] by group (smokers and nonsmokers) and across groups (overall) included: C_{max}, T_{max}, $T_{half\text{-}max}$, AUC_{inf}, AUC_{last}, k_e, and $T_{1/2}$ for loxapine and 8-OH-loxapine, as well as CL/F for loxapine.

Analysis of variance (ANOVA) on smoking status was carried out on the log-transformed PK parameters dependent on dose (ie, C_{max}, AUC_{inf}, and AUC_{last},) using smoking status as a fixed effect. Geometric mean ratios (GMRs) with 90% CIs were calculated to compare each of the dose-dependent PK parameters for loxapine and metabolite between smokers and nonsmokers based on these ANOVA models. Nontransformed PK parameters (ie, T_{max}, $T_{half\text{-}max}$, k_e, and $T_{1/2}$) for loxapine and each metabolite (and CL/F for loxapine) were analyzed by ANOVA with smoking status as a fixed effect, and the difference of the least squares means (LSmeans) for smokers versus nonsmokers (ie, smokers − nonsmokers) and its 90% CI was calculated. A subgroup analysis of pharmacokinetics by gender was also conducted.

Pharmacodynamic Data Analysis

As sedation is a consistent effect of antipsychotic agents, it served as the primary pharmacodynamics measure in the study. Subject sedation was measured using a 100-mm visual analog scale (VAS) at predose, 2, 5, 10, 30, and 60 minutes, 2 and 6 hours after dosing. Descriptive statistics were calculated for the sedation VAS results. LSmeans, difference in LSmeans, and 90% CIs for the differences between smoking and nonsmoking populations (ie, smoker − nonsmoker) were calculated for the change from baseline for each post-baseline time point by ANOVA with a fixed-effect term for smoking status.

Safety Data Analysis

All treatment-emergent adverse events were summarized by system organ class/preferred term for each group using the Medical Dictionary for Regulatory Activities. Descriptive statistics were calculated for all quantitative safety measures (systolic and diastolic blood pressure, heart rate, and respiration rate). LSmeans and 90% CIs for the differences between smoking and nonsmoking populations (ie, smoker − nonsmoker) were calculated for the change from baseline for each vital sign for each post-baseline time point by ANOVA with a fixed-effect term for smoking status.

Data Analysis

A sample size of 18 smokers and 18 nonsmokers was considered adequate to detect clinically important differences in the major PK parameters. The safety population comprised every subject who received a dose of study medication. The PK population comprised every subject who received a dose of study medication and provided at least 1 measurable plasma concentration of loxapine.

RESULTS

Of the 99 subjects who were screened for the study, 35 subjects completed the study and no subject discontinued prematurely.

Participants

The patient demographics and baseline characteristics for enrolled subjects are shown in Table 1.

Pharmacokinetics

The pharmacokinetics of loxapine and its main metabolite, 8-OH-loxapine, in smokers and nonsmokers after administration of a 10 mg dose of inhaled loxapine is shown in Figure 1 and the PK parameters for loxapine and 8-OH-loxapine are listed in Tables 2 and 3, respectively.

After administration of inhaled loxapine, plasma loxapine concentrations increased rapidly in both smokers and nonsmokers. The mean plasma concentration–time profiles were similar in the smoker and nonsmoker groups. Loxapine C_{max} was similar for smokers and nonsmokers with a GMR of 99.0%. Median loxapine T_{max} was similar for the groups (1.88 and 1.01 minutes for nonsmokers and smokers, respectively). The $T_{half\text{-}max}$, k_e, and terminal half-life of loxapine were also similar for smokers and nonsmokers.

Loxapine AUC_{inf} and AUC_{last} values were comparable for smokers and nonsmokers (GMRs of 85.3% and 86.7%, respectively). The observed AUC_{inf} and AUC_{last} values are consistent with the increased clearance in smokers and the

TABLE 1. Patient Demographics

	Nonsmoker (N = 18)	Smoker (N = 17)
Gender, n (%)		
Female	9	7
Male	9	10
Age (yr)		
Mean ± SD (min–max)	26 ± 7 (20–45)	32 ± 8 (20–45)
Race		
Caucasian	13	14
Black	3	3
Hispanic	1	0
Other*	1	0
Weight (kg)		
Mean ± SD (min–max)	75 ± 11 (56–96)	75 ± 9 (56–90)

*"Other" race: Native Hawaiian or other Pacific Islander, white/European heritage.
SD, standard deviation.

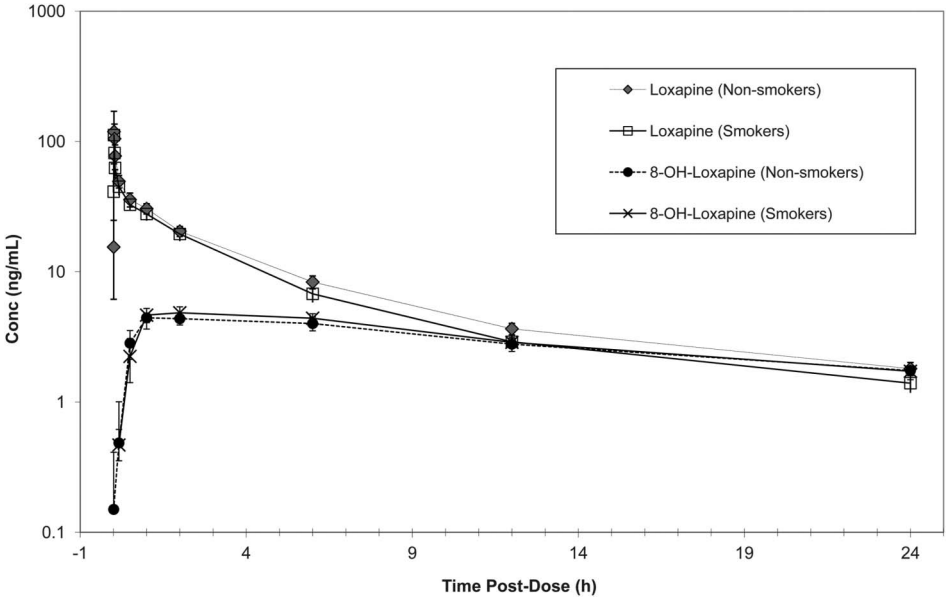

FIGURE 1. Mean loxapine and 8-OH-loxapine plasma concentration (in nanogram per milliliter) (90% CI) versus time postdose (in hours) by smoking status; log scale (PK population).

observed mean terminal half-life values (6.52 hours for smokers and 7.30 hours for nonsmokers).

The exposure ratios of 8-OH-loxapine to loxapine in smokers and nonsmokers were similar for male smokers and nonsmokers but were slightly higher in female smokers.

Sedation Pharmacodynamics

All 35 subjects were included in the pharmacodynamics analysis. Sedation profiles and VAS scores at each time point were similar for nonsmokers and smokers. The largest sedation effects were observed at 30 minutes. At that time point, the mean change from baseline for sedation (100-mm VAS) was −62.1 mm for nonsmokers and −58.9 mm for smokers. By 6 hours, the change from baseline was approximately half of maximum.

Safety and Tolerability

Inhaled loxapine was well tolerated. The most common adverse event was somnolence (present in 91.4% of subjects) and dizziness (in 51.4%), both of which are known adverse effects of loxapine administered through other routes. Somnolence was reported in 94.4% of subjects in the nonsmoker group compared with 88.2% in the smoker group, with the severity of events similar in the groups. Dizziness was reported in 50.0% of the nonsmokers and 52.9% of smokers, and most dizziness resolved quickly.

TABLE 2. PK Parameters for Loxapine in Smokers and Nonsmokers After Inhaled Loxapine Administration

Parameter	Loxapine 10 mg Nonsmoker (N = 18)	Loxapine 10 mg Smoker (N = 17)	Total (N = 35)	Ratio (Smoker to Nonsmoker) (90% CI); Ratio (CI Difference)*
T_{max} (min)†	1.88 (0.864, 30.0)	1.01 (0.636, 9.95)	1.57 (0.636, 30.0)	70.3% (−4.41 to 1.95)
$T_{half\text{-}max}$ (min)†	6.05 (0.852, 108)	4.85 (0.960, 79.5)	5.80 (0.852, 108)	95.4% (−21.3 to 18.6)
k_e (1/h)‡	0.101 (0.0268)	0.116 (0.0340)	0.108 (0.0310)	115% (−0.00250 to 0.0324)
$T_{½}$ (h)‡	7.30 (1.78)	6.52 (2.01)	6.92 (1.91)	89.3% (−1.86 to 0.305)
CL/F (L/h)‡	48.4 (8.28)	57.1 (11.1)	52.6 (10.5)	118% (3.08 to 14.2)§
Parameter	**Loxapine 10 mg Nonsmoker (N = 18)**	**Loxapine 10 mg Smoker (N = 17)**	**Total (N = 35)**	**Ratio (Smoker to Nonsmoker) (90% CI); GMR (90% CI Ratio)¶**
C_{max} (ng/mL)‡	136 (109)	132 (91.0)	134 (99.3)	99.0% (64.8% to 151%)
AUC_{inf} (ng·h/mL)‡	213 (39.0)	183 (42.9)	198 (43.1)	85.3% (76.4% to 95.3%)§
AUC_{last} (ng·h/mL)‡	194 (37.0)	169 (39.7)	182 (39.8)	86.7% (77.5% to 97.1%)§

*Disposition parameters (T_{max}, $T_{half\text{-}max}$, k_e, $T_{½}$, and CL/F) were not transformed. The LSmean was equivalent to the arithmetic mean for this model. The ratio and the difference of LSmeans and the 90% CI for the difference were calculated.

†T_{max} and $T_{half\text{-}max}$ presented as median (min–max).

‡Data presented as mean (standard deviation).

§CI does not include zero (nonexponentiated) or 100% (exponentiated).

¶Exposure parameters (C_{max}, $AUC_{0\text{–}2h}$, AUC_{inf}, and AUC_{last}) were natural log transformed. The LSmean was equivalent to the geometric mean for this model. GMR and 90% CI were calculated (exponentiated).

TABLE 3. PK Parameters for 8-OH-Loxapine in Smokers and Nonsmokers After Inhaled Loxapine Administration

Parameter	Loxapine 10 mg Nonsmoker (N = 18)	Loxapine 10 mg Smoker (N = 17)	Total (N = 35)	Ratio (Smoker to Nonsmoker) (90% CI); Ratio (CI Difference)*
T_{max} (min)†	120 (59.9, 366)	120 (59.7, 360)	120 (59.7, 366)	142% (−11.9 to 102)
k_e (1/h)‡	0.0459 (0.00893)	0.0530 (0.00932)	0.0494 (0.00968)	115% (0.0019 to 0.0123)§
$T_{½}$ (h)‡	15.7 (3.35)	13.6 (3.09)	14.7 (3.36)	86.4% (−3.98 to −0.289)§
Parameter	**Loxapine 10 mg Nonsmoker (N = 18)**	**Loxapine 10 mg Smoker (N = 17)**	**Total (N = 35)**	**Ratio (Smoker to Nonsmoker) (90% CI); GMR (CI Ratio)¶**
C_{max} (ng/mL)‡	4.90 (1.59)	5.38 (1.66)	5.14 (1.62)	111% (91.2 to 135)
AUC_{inf} (ng·h/mL)‡	112 (41.9)	110 (31.1)	111 (36.5)	99.3% (82.9 to 119)
AUC_{last} (ng·h/mL)‡	71.1 (20.7)	74.9 (20.3)	73.0 (20.3)	106% (89.8 to 125)

*Disposition parameters (T_{max}, k_e, and $T_{½}$) were not transformed. The LSmean was equivalent to the arithmetic mean for this model. The ratio and the difference of LSmeans and the 90% CI for the difference were calculated.

†T_{max} presented as median (min, max).

‡Data presented as mean (standard deviation).

§CI does not include zero (nonexponentiated) or 100% (exponentiated).

¶Exposure parameters (C_{max}, $AUC_{0–2h}$, AUC_{inf}, and AUC_{last}) were natural log transformed. The LSmean was equivalent to the geometric mean for this model. GMR and 90% CI were calculated (exponentiated).

DISCUSSION

As loxapine exposure was similar in smokers and nonsmokers, it was not surprising that loxapine sedation profiles and VAS scores were similar for nonsmokers and smokers.

Loxapine AUC_{last} concentrations were only 13.3% higher in nonsmokers versus smokers after inhalation. In contrast, exposures of orally administered clozapine and olanzapine have been reported to be substantially higher in nonsmokers compared with smokers: 50% for clozapine and 67% for olanzapine.[14] 8-OH-loxapine, mainly formed by CYP1A2, which is induced in smokers, was only slightly higher (6%) in nonsmokers compared with smokers. Desmethylclozapine, the CYP1A2 metabolite for clozapine, was 57% higher in nonsmokers compared with smokers.[15]

Loxapine exposure (AUC_{last}) after the 10 mg inhalation dose was 182 ng·h/mL. Exposure after a 50 mg oral dose of loxapine was reported to be 153 ng·h/mL,[27] demonstrating inhalation provided more than a 5-fold reduction in the oral dose to achieve effective levels. As CYP1A2 is found primarily in the liver,[22] the low pulmonary metabolism observed in inhalation as opposed to hepatic metabolism after oral delivery (8-OH-loxapine to loxapine AUC ratios were 3.5 after oral administration and 0.48 after inhalation administration) may have decreased the effect of CYP1A2 induction in smokers. This contributed to the small differences in exposure between smokers and nonsmokers through the inhalation route compared with the larger differences typically observed after oral delivery.

It has been estimated that CYP1A2 in nonsmokers is approximately 60% that of subjects smoking greater than 11 cigarettes per day, and this increase in CYP1A2 was reported to result in an approximate 30% increase in clearance after an oral dose.[28] Smokers were reported to clear olanzapine 55% faster than nonsmokers or ex-smokers after administration of an oral dose.[29] An 18% increase in the clearance of loxapine was observed for smokers compared with nonsmokers, and there was a corresponding increase of 15% in the elimination rate of 8-OH-loxapine in smokers.

Smoking has been shown to increase pulmonary absorption.[30,31] After inhalation of a nebulized formulation of terbutaline, the T_{max} was 17 minutes for smokers and 50 minutes in nonsmokers, with corresponding C_{max} values of 23 and 14 nM, respectively.[24] Similarly, smokers had a 3-5 fold increase in C_{max} and a shorter T_{max} compared with nonsmokers after inhaled administration of insulin.[32,33] After loxapine inhalation, there was only a slight change in T_{max} (1.01 and 1.88 minutes) but no marked change in C_{max} (136 and 132 ng/mL) for smokers and nonsmokers, respectively. This may be due to loxapine having moderate-to-high permeability[34] compared with terbutaline, which has low permeability.[35] Most likely, the rapid delivery of the small particle size loxapine condensation aerosol provides a high concentration to the lung that accelerates the passive, diffusive permeability of loxapine; and therefore, the increased alveolar permeability resulting from smoking had little or no effect.

A nonsignificant trend toward lower (78%) clozapine concentrations in male smokers was reported, and a significant decrease (45%) in clozapine levels in smoking and nonsmoking females (n = 13) was also observed.[15] The statistical power of our study was too low to analyze for gender subset differences, but we observed a slight trend toward lower (3.6%) loxapine concentrations in male smokers, and a trend toward lower levels (25.7%) in female smokers. CYP1A2 activity has been reported to be higher in males than in females,[36,37] thus extent of induction of CYP1A2 may be more significant in females smokers than in male smokers.

A daily consumption of 7–12 cigarettes was concluded to be sufficient for maximum induction of clozapine and olanzapine absorption and/or metabolism,[13] and a 50% lower starting dose of both drugs in nonsmokers was recommended. In contrast, when subjects who had a daily consumption of at least 15 cigarettes were administered loxapine through inhalation delivery, no substantial change in absorption or metabolism was observed.

CONCLUSIONS

Smokers constitute a large and critical subpopulation of patients with schizophrenia and bipolar disorder. Like other antipsychotics, loxapine is primarily metabolized by CYP1A2, an enzyme that is induced in smokers. However, unlike similarly metabolized drugs, such as clozapine and olanzapine, there was no substantial reduction in exposure or large increase in clearance in smokers. This reflects the high bioavailability of the inhaled form, which allowed a lower dose than is normally delivered orally. In addition, inhalation delivery bypasses first pass hepatic metabolism because metabolizing enzymes are more prevalent in the liver than in the lung. Unlike the other antipsychotics, the inhalation delivery of loxapine does not require dosage adjustment based on smoking behavior.

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