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Interactions between Alcohol and the HIV Entry Inhibitor Maraviroc

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Abstract

Background—Alcohol use is common among people with HIV, and beliefs about alcohol interactions with medications predict decreased medication adherence, risking drug-resistant mutations. Maraviroc is an HIV entry inhibitor approved for treatment of both drug-sensitive and drug-resistant HIV strains. The present study evaluated the effects of alcohol on maraviroc pharmacokinetics, and of maraviroc on alcohol pharmacokinetics.

Methods—Ten healthy adults completed alcohol (1 g/kg) and placebo alcohol pharmacokinetics sessions before and after 7 days of maraviroc administration.

Results—Alcohol concentrations increased 12% following maraviroc. Maraviroc pharmacokinetics were unaffected by alcohol.

Conclusions—Maraviroc treatment should not be interrupted if alcohol is consumed.

Keywords

alcohol; maraviroc; drug interactions; HIV/AIDS

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INTRODUCTION

Alcohol use is common among people with HIV, and unhealthy alcohol use is a risk factor for both HIV seroconversion and disease progression [1]. Many people with HIV believe they should not take their antiretroviral therapy (ART) medication when they drink alcohol [2]. Frequent missed HIV medication doses allow HIV to mutate and develop ART resistance [3]. One of the medications approved for the treatment of drug-resistant HIV strains is the entry inhibitor maraviroc, which inhibits entry of some strains of HIV into CD4 cells [4]. If patients with drug-resistant HIV were to miss doses of maraviroc and develop resistance to this medication as well, fewer HIV treatment options would remain. As a result, there is a need to know if alcohol affects maraviroc metabolism or side effects, or if maraviroc affects alcohol metabolism, and thus whether patients can be advised to continue maraviroc doses when consuming alcohol.

Alcohol and maraviroc taken together might produce drug-drug interactions. Maraviroc is is a substrate of cytochrome P 450 3A4 (CYP 3A4) [5]. Alcohol is metabolized in part by CYP 3A4 [6], and thus might compete with maraviroc for metabolism by CYP 3A4, which could increase concentrations and toxicities of either alcohol or maraviroc when consumed together. This study evaluated both the effects of alcohol on maraviroc pharmacokinetics and of maraviroc on alcohol pharmacokinetics in HIV-negative, healthy volunteers.

METHODS

Participant recruitment and selection

The study was approved by the University of California San Francisco (UCSF) Institutional Review Board and registered at ClinicalTrials.gov (NCT00879047). Participants gave voluntary, written, informed consent to participate and received monetary compensation for their time.

Eligible individuals were 21 years or older, were in good health without current serious medical or psychiatric illnesses or substance use disorders, were not pregnant, had no evidence of HIV infection (by HIV antibody and HIV viral load tests), and were not being treated with medications known to be strong inducers or inhibitors of CYP 3A4 or CYP 2E1 metabolic enzyme function, as determined by medical history, physical examination, electrocardiogram, and clinical laboratory testing.

Urine was tested prior to study sessions and randomly (at least once weekly) during maraviroc administration for ethyl glucuronide (immunoassay with cutoff of 500 ng/mL to identify recent drinking), opioids (including morphine, codeine, methadone, buprenorphine, and oxycodone), cocaine, amphetamines, marijuana and benzodiazepines.

Study Procedures

This was a randomized, double-blind, placebo-controlled within-subjects trial in which participants were randomly assigned to either oral alcohol (1 g/kg) (to produce moderate intoxication) or alcohol placebo, followed by maraviroc administration at standard clinical

doses (150 mg twice daily) for seven days. Participants then underwent two study sessions in which alcohol or alcohol placebo was administered with maraviroc.

Study Sessions

Participants were admitted to the Clinical Research Center for pharmacokinetic studies where they were oriented to study procedures one day prior to study sessions. On the day of the study, a standardized breakfast was consumed 1.25 hours prior to alcohol administration. Baseline cardiovascular measures (heart rate and blood pressure) and blood alcohol concentration (BAC) were collected just prior to alcohol administration. Alcohol (1 g/kg dissolved in a total volume of 16 ounces of an orange-flavored drink) or placebo (16 ounce orange flavored drink with alcohol sprayed on the surface of the drink only) was then administered. On days that included maraviroc administration, maraviroc 150 mg was administered immediately upon completion of alcohol ingestion. Blood sampling occurred over the next 8 hours at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours (in sessions where maraviroc was administered additional blood samples were collected at 10 and 12 hours). Cardiovascular measurements were obtained prior to collection of each blood sample. The Adverse Symptoms Checklist [7] was administered at the beginning (-60 minutes) and end (at 8 hours in the pre-maraviroc conditions, 12 hours in the maraviroc conditions) of each session. Electrocardiograms were performed 1 hour before and 2 hours after alcohol administration. Plasma was separated after collection and stored at −80°C until analysis.

Maraviroc dosing

Upon completion of the first set of study sessions, maraviroc 150 mg was administered once daily for seven days by clinic staff at the Addiction Medicine Research Clinic. The second daily maraviroc 150 mg dose (and any weekend doses) was encapsulated with riboflavin 25 mg, which produces urine fluorescence, allowing research staff to assess medication adherence at research clinic visits.

Biochemical Assays

Alcohol concentrations in plasma samples were measured using gas chromatography with flame ionization detection, using isopropanol as the internal standard. Maraviroc was quantified using a validated liquid chromatography tandem mass spectrometry assay with methyl indinavir as an internal standard.

Pharmacokinetics Analyses

Alcohol and maraviroc pharmacokinetics were calculated following administration of each alone, and following co-administration. Area under the concentration-time curve (AUC) was calculated using the trapezoidal rule. Maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), and minimum plasma concentration (C_{min}), were determined by inspection of the concentration-time curve. The elimination rate was determined from the slope of the linear portion of the descending arm of the concentration-time curve. Bioavailability-adjusted clearance (CL/F) was determined using the noncompartmental analysis module of WinNonLin Professional Version 3.2 (Pharsight Corp., Mountain View, CA).

Pharmacokinetic parameters were compared within subjects using the paired *t*-test, except for the nonparametric T_{max} for which the Wilcoxon test was used.

RESULTS

Participants included 8 men and 2 women, 9 Caucasians and 1 African-American, with a mean age of 29 (3.1) years (mean (standard error) [SE]). Current alcohol use was 4.4 (0.9) standard drinks/week, and none used tobacco. Medical conditions (1 tension headaches, 1 irritable bowel syndrome, 1 strabismus) did not require current treatment and were not expected to affect study findings. Clinical laboratory findings, including liver function tests, renal function tests, and complete blood count, were within normal range prior to and following all study procedures. Adverse symptoms were mild and included increased reports of drowsiness and nausea during sessions that included alcohol administration.

Alcohol administration had no significant effect on maraviroc pharmacokinetics (Table 1). Maraviroc administration at standard clinical doses was associated with increased alcohol concentrations as shown by a significant increase in AUC (p=0.01) representing an increase in blood alcohol concentrations over time of 12% relative to alcohol alone administration (Table 1). A trend for increased maximum alcohol plasma concentration was observed (p=0.06). There was also a trend observed for decreased alcohol elimination with maraviroc administration (p=0.08) (Table 1).

DISCUSSION

This study shows that acute alcohol ingestion has no significant effect on the pharmacokinetics of maraviroc. Maraviroc co-administration with alcohol, however, was associated with a significant increase in BAC over the 8 hour study interval of 12%. These findings indicate that alcohol consumption in those maraviroc could be subject to some elevation in risk for greater intoxication. Those with HIV disease who are chronic, heavy consumers of alcohol might be at somewhat greater risk for alcohol-associated toxicities if receiving ART containing maraviroc.

The basis for the increase in BAC with maraviroc administration is unclear. At clinically relevant doses, maraviroc has no significant effect on CYP 3A4, 1A2, 2B6, 2D6, 2C8, 2C9 or 2C19 [5]. The main mechanism for alcohol metabolism is via conversion to acetaldehyde via alcohol dehydrogenase [8]. There have been no studies of the potential effect of maraviroc on alcohol dehydrogenase, but the trend for slower elimination observed in this study indicates that such an effect may occur.

We recently reported on an observed decline in BAC after alcohol administration in individuals with HIV infection who had started expert-recommended antiretroviral therapy [9] relative to BAC prior to starting HIV therapy [10]. In no case was maraviroc a component of the recommended therapies. We postulated that the lower alcohol bioavailability observed after treatment of HIV infection was a result of decreased inflammation in gut-associated lymphoid tissue which has been linked to intestinal epithelial damage [11]. In contrast, the findings of the present study conducted in non-HIV infected

volunteers indicate that treatment of HIV infection with maraviroc-containing regimens may not show a diminution in BAC.

These findings underscore the need to encourage ART adherence even if the treated individual chooses to drink alcohol, while also providing treatment for any alcohol use disorders to reduce the risk of alcohol-related toxicities among people with HIV.

Limitations

Maraviroc was used infrequently in our clinical population at the time of this study, necessitating that we employ a single drug-drug interaction paradigm in healthy subjects. While not an ideal design, the information gained can be used by clinicians in providing effective HIV ART.

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Table 1

Pharmacokinetic Parameters

Maraviroc	**Placebo**	**Alcohol**	**p value**
AUC_{0-12}(ng-h/mL)	500 (79)	474 (87)	0.78
C_{max} (ng/mL)	103 (22)	137 (36)	0.35
T_{max} (h)	2 (1.5–6)	2 (1–4)	n.s.
C_{12}(ng/mL)	.02 (.004)	.02 (.004)	0.80
Cl/F (L/h)	442 (101)	520 (142)	0.38
Alcohol	Pre-Maraviroc	Post-Maraviroc	p value
AUC_{0-8}(mg-h/dL)	559 (40)	627 (48)	0.011
C_{max} (ng/mL)	125 (10)	137 (11)	0.06
T_{max} (h)	1.5 (0.25–3.0)	1.0 (0.5–2.0)	n.s.
C_8 (ng/mL)	3.8 (2.0)	8.4 (3.1)	0.33
Elimination rate (mg/dL-h)	22.1 (1.2)	20.5 (0.9)	0.08

Note: Values are the mean (standard error of the mean), except that T_{max} is given as median (range). The paired t-test was used to determine p-values for all parameters except T_{max}, where the Wilcoxon test was used.