

## Effect of opioid substitution therapy on alcohol metabolism

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### Abstract

Forty opioid substitution patients (methadone,  $n = 14$ ; LAAM,  $n = 14$ ; and buprenorphine,  $n = 12$ ) who were participating in a study on the impact of opiate substitution treatment on driving ability and 22 non-opiate-using control subjects were administered 14.7 g/70 kg of alcohol in two separate sessions, one 2–3 hours before opioid pharmacotherapy dosing and the other 1–2 hours after dosing. The mean blood alcohol concentration (BAC) in the post-opioid dose session was significantly lower than that in the pre-opioid dose session ( $p < .05$ ). There was a significant effect of experimental group (LAAM, methadone, buprenorphine, or control) on BAC in sessions conducted 1–2 hours after the opioid substitution dose ( $p < .01$ ). There was a trend for a reduced effect of experimental group on BAC in the pre-opioid substitution dose session ( $p = .06$ ). The BAC of non-opioid substitution control subjects was significantly higher than that of the LAAM (before and after LAAM dosing) and methadone (after methadone dosing;  $p < .05$ ) patients. These findings provide evidence for the first time of an interaction between opiates and alcohol in humans that is strongest at the time of peak opiate plasma levels in the hours after opioid dosing. © 2006 Elsevier Inc. All rights reserved.

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### 1. Introduction

Alcohol abuse is common in people in opioid substitution treatment (Anglin, Almg, Fisher, & Peters, 1989). Although there is certainly a pharmacodynamic interaction occurring in this situation, there are also some evidence of a pharmacokinetic interaction. Human research is lacking on this topic; however, in animal studies, ethanol has repeatedly been shown to influence the metabolism of methadone and vice versa.

In the rat model, ethanol consumption can either increase or decrease methadone plasma levels, depending on the circumstances. Acute ethanol consumption increases the

peak methadone concentration (Donnelly et al., 1983; Tommasello & Adir, 1984). Chronic alcohol consumption, on the other hand, reduces peak methadone levels (Borowsky & Lieber, 1978; Kreek, 1978, 1981; Tommasello & Adir, 1984; Wendell & Thurman, 1979; Whitehouse, Templeton, & Paul, 1979). Immediately following the abrupt cessation of alcohol consumption, methadone peak plasma levels remain reduced (Kreek, 1978, 1981). These findings are consistent with a common metabolic pathway for alcohol and methadone in the rat, which becomes saturated in acute alcohol administration and induced by chronic alcohol administration.

Similarly, methadone administration has been found to influence ethanol metabolism in the rat. Acute methadone administration results in a reduced rate of elimination of ethanol (Donnelly et al., 1983). Chronic methadone administration reduces blood alcohol levels following acute

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administration of alcohol (Umans, Kreek, Rodriguez, & Raghunath, 1982; Wendell & Thurman, 1979) to a greater extent than is seen with chronic alcohol administration alone.

In humans, almost no research has been conducted on this issue. One study on five participants found no consistent increase in methadone levels 2 and 4 hours after dosing in five methadone-maintained participants given a single dose of 90 ml of 50% ethanol solution taken 1 hour after consumption of methadone (Cushman, Kreek, & Gordis, 1978). On the other hand, it has been observed clinically that methadone-maintained patients appear to get less effect from alcohol than other patients (Kreek, 1981, 1984). It is also a perception by clinical staff that alcohol-abusing opioid substitution patients report more opiate/sedative effects at the time of peak methadone levels but that the effects of methadone dissipate more rapidly over the next 24 hours, with a resulting increase in opiate withdrawal symptoms reported (Kreek, 1981).

Lenné, Dietze, Rumbold, Redman, and Triggs (2003) noted differential effects of alcohol administration as part of their wider study on the effects of opioid substitution therapies on simulated driving. Their findings showed small but significant differences in blood alcohol concentrations (BACs) between patients stabilized on LAAM, buprenorphine, and methadone and non-drug-using control subjects, with the highest BACs being for non-drug-using control subjects, despite the doses of alcohol being calibrated to patient body weight. The aim of this current study was to explore the findings of Lenné et al. further by determining (1) if there is a dose-dependent effect of opioid substitution therapy on BAC by comparing BAC resulting from a standard dose of alcohol before with that after pharmacotherapy dose administration and (2) whether Lenné et al.'s finding that regular consumption of methadone, LAAM, or buprenorphine results in differential effects on BAC after dosing in opioid substitution therapy also holds before dosing.

## 2. Materials and methods

### 2.1. Participants

As described by Lenné et al. (2003), 14 methadone, 14 LAAM, and 12 buprenorphine patients who were enrolled in randomized controlled trials of LAAM versus methadone (Clark, Ritter, Lintzeris, Kutin, & Bammer, 2001; Ritter, Lintzeris, Clark, Kutin, Bammer, & Panjari, 2003) and buprenorphine versus methadone (Ritter, Lintzeris, Clark, Kutin, & Bammer, 2001) volunteered to participate in this study. All participants gave written informed consent. The study was approved by the Monash University Standing Committee on Ethics in Research in Humans. Eligible opioid substitution participants were required to (1) have been stable on their opiate substitution medication for at least 3 months, (2) have no concurrent serious medical or

psychiatric illness, and (3) have consumed some alcohol in the previous month. Non-drug-using participants who had been unemployed for at least 3 months and had consumed some alcohol in the previous month were included as control subjects, forming a fourth group. The main characteristics of the participants are detailed in Table 1.

### 2.2. Procedures

Each participant in opioid substitution therapy attended two testing sessions (before dosing and after dosing) that involved alcohol administration, with the order of these sessions counterbalanced. Non-drug-using control subjects attended one session involving alcohol administration. At each session, participants were required to perform driving simulation tasks (the results of these tasks were reported by Lenné et al., 2003). For participants in opioid substitution therapy, sessions were conducted either immediately before (before dosing) or approximately 1–2 hours after (after dosing) a dose of their pharmacotherapy. Participants were asked not to eat for 2 hours before each session and to abstain from alcohol for at least 24 hours before each session. Participants were also asked how many standard drinks they had consumed per week in the month prior to participation to control for recent alcohol consumption history.

Participants received 14.7 g/70 kg of alcohol. Alcohol was administered to participants as 37.5% (vol/vol) vodka (0.70 ml/kg body weight) mixed with 200 ml of orange juice, with the aim of increasing BAC to approximately 0.05% wt/vol (gm alcohol/100 ml volume; cf. Lenné, Triggs, & Redman, 1999). Participants were allowed 15 minutes in which to consume the alcohol. To remove residual alcohol from the mouth and thereby reduce the chance of erroneous breath alcohol readings, the participants drank a mouthful of water before the first alcohol reading.

Blood alcohol concentration was measured using a LION SD-2 breathalyzer (Lion Laboratories, Vale of Glamorgan, UK) at 30, 55, and 80 minutes after commencing the

Table 1  
Sample characteristics

Group	Age (years; <i>M</i> )	Male sex (%)	Pharmacotherapy dose (mg; <i>M</i> ± <i>SD</i> )	Weekly alcohol consumption <1 standard drink (%)
Non-drug-using control subjects	34	41	Not applicable	65
LAAM				
Before dosing	31	48	32.6 ± 4.0	50
After dosing				
Methadone				
Before dosing	33	67	48.1 ± 2.8	7
After dosing				
Buprenorphine				
Before dosing	31	73	14.4 ± 1.8	27
After dosing				

consumption of alcohol (referred to as alcohol measurement Times 1, 2, and 3 respectively).

### 2.3. Data analysis

Three separate analyses of variance (ANOVAs) were conducted.

A four-way ANOVA was conducted with the between-subject factors of pharmacotherapy group (methadone, LAAM, and buprenorphine) and past month alcohol consumption (<1 standard drink per week, >1 per week) as well as the within-subject factors of pharmacotherapy testing time (before or after pharmacotherapy dosing) and alcohol measurement time (Times 1, 2, and 3) to examine the effects of alcohol at different times of plasma pharmacotherapy curves among opioid substitution clients. A three-way ANOVA was then conducted with the BAC measurements taken before the opioid substitution clients received their pharmacotherapy dose along with the non-opioid-using control subjects to examine the effects of opioid substitution on BAC. In this analysis, the three factors were the between-subjects factors of experimental group (methadone, LAAM, buprenorphine, control) and past month alcohol consumption as well as the within-subjects factor of alcohol measurement time (Times 1, 2, and 3). This analysis was repeated using the BAC measurements taken after the opioid substitution clients received their pharmacotherapy dose—an analysis almost identical to that reported by Lenné et al. (2003). In cases where significant departures from sphericity were noted, the Huynh–Feldt adjustment was used to adjust the degrees of freedom to provide a more conservative test of any observed main effect

or interaction. Planned pairwise comparisons were undertaken to examine the effects of alcohol measurement time where it was expected that BAC levels would decline across the three measurement times. Post hoc tests of main effects of subject group were computed using Dunnett's *t*. All analyses were conducted using SPSS V12.0.1. Initial analysis including participants' sex as an independent variable revealed neither significant effects of participants' sex nor any interaction between participants' sex and any of the other independent variables of interest. For this reason, participants' sex was not included in the analysis reported in this study.

### 3. Results

The unadjusted means for the four experimental groups (including both before-dosing and after-dosing sessions for the opioid substitution clients) at the three testing times are shown in Fig. 1.

#### 3.1. Effect of pharmacotherapy testing time for pharmacotherapy clients

The mean BAC in the session after the opioid substitution clients received their dose ( $M = 0.039$ ) was significantly lower than that measured in the session before they received their dose,  $M = .049$ ,  $F(1, 29) = 6.75$ ,  $p < .05$ . There was also an effect of alcohol measurement time,  $F(1.52, 44.19) = 3.75$ ,  $p < .05$ . Planned pairwise comparisons showed that mean BAC was significantly higher at Time 1 (30 min,  $M = 0.047$ ) than at Time 3 (80 min,

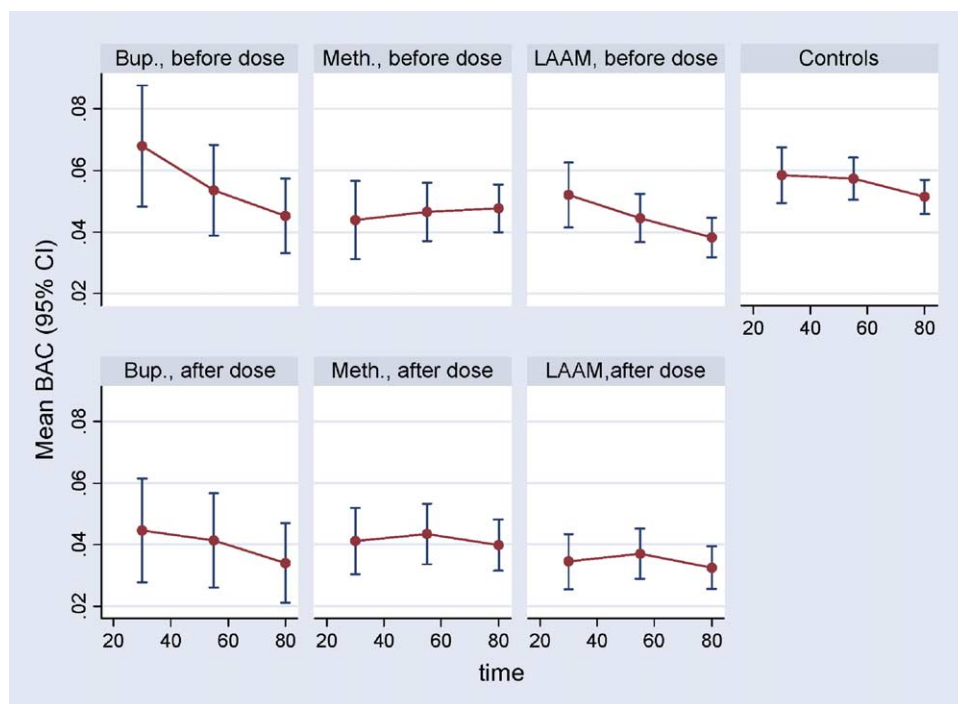


Fig. 1. Mean BAC following alcohol challenge in patients taking buprenorphine, methadone, and LAAM (before and after their daily dosing) and in non-opioid-dependent control subjects.

$M = 0.040$ ). Mean BAC at Time 2 (55 min,  $M = 0.044$ ) was lower than that at Time 1 and higher than that at Time 3, but these differences failed to reach significance. There was no other significant main effect or interaction among the independent variables (all  $F \leq 2.01$ , all  $p \geq .14$ ).

### 3.2. Effects of experimental group and alcohol measurement time

#### 3.2.1. Before pharmacotherapy dosing for opioid substitution clients

There was a significant main effect of alcohol measurement time,  $F(1.70, 85.03) = 6.68$ ,  $p < .01$ . Planned pairwise comparisons showed that mean BAC was significantly higher at Times 1 (30 min,  $M = 0.055$ ) and 2 (55 min,  $M = 0.050$ ) than at Time 3 (80 min,  $M = 0.045$ ), but the difference between Times 1 and 2 failed to reach significance. Although the main effect of experimental group on the BAC measurements taken for the non-drug-using control subjects and before the opioid substitution groups received their dose failed to reach significance,  $F(3, 50) = 2.63$ ,  $p = .06$ , the pattern was similar to that described subsequently in that the LAAM ( $M = 0.045$ ) and methadone ( $M = 0.045$ ) groups had lower BACs than either the buprenorphine ( $M = 0.056$ ) or the non-drug-using control ( $M = 0.056$ ) group. There was no other significant main effect or interaction among the independent variables (all  $F \leq 1.95$ , all  $p \geq .09$ ).

#### 3.2.2. After pharmacotherapy dosing for opioid substitution clients

As detailed by Lenné et al. (2003), there was a significant main effect of experimental group on the BAC measurements taken for the non-drug-using control subjects and after the opioid substitution groups received their dose,  $F(3, 50) = 8.34$ ,  $p < .01$ . Post hoc tests revealed that the mean BAC was significantly higher for the control group ( $M = 0.056$ ) than for both the LAAM and methadone groups ( $M = 0.035$  and  $0.040$ , respectively). Although the mean BAC for the buprenorphine group ( $M = 0.040$ ) was identical to that for the methadone group and therefore lower than that for the control group and higher than that for the LAAM group, these differences failed to reach significance. Furthermore, although the pattern of the effect of alcohol measurement time was similar to that abovementioned ( $M$  for Times 1, 2, and 3 =  $0.044$ ,  $0.044$ , and  $0.039$ , respectively), these differences failed to reach significance,  $F(1.7, 85) = 2.53$ ,  $p > .05$ . Again, there was no other significant main effect or interaction among the independent variables (all  $F \leq 1.83$ , all  $p \geq .18$ ).

## 4. Discussion

These findings expand those initially reported by Lenné et al. (2003), showing a significant effect of opiates in

reducing the BAC in response to the consumption of alcohol administered in a body weight-controlled dose. This effect has been reported in animal studies but has not previously been demonstrated in humans. The pharmacokinetic interaction between opiates and alcohol was initially evident 1–2 hours after the opiate dose, at a time close to the peak effects of methadone and buprenorphine. The findings reported here provide evidence of a dose–response relationship in that the reduction in BAC in the opiate users was less in the pre-opioid dose sessions (when the levels of opiates are lowest) than in the post-opioid dose sessions. Although the BAC in opiate substitution patients was still lower than that in control subjects in the before-dosing testing, the reductions were of a smaller magnitude than in the after-dosing testing and were only statistically different from those of control subjects for the patients treated with LAAM, which has the longest half-life (including active metabolites) and the smallest ratio of peak-to-trough levels (Fudala, 1996; Kaiko & Inturrisi, 1975). The converse applies to buprenorphine, which, although a long-acting opioid, has low blood levels 24 hours after dosing (Elkader & Sproule, 2005). Although buprenorphine had a lesser effect than methadone and LAAM in the after-dosing session, there was virtually no effect on BAC in the before-dosing session. By demonstrating a difference in the magnitude of the interaction between sessions at times of expected peak and trough levels of opioid substitution doses, these new findings strengthen the case for a true pharmacokinetic interaction between opiates and alcohol.

Two possible sites of interaction between methadone and alcohol have been proposed in the literature. Cushman (1987) raised the possibility that hepatic microsomal enzymes may be involved in both opiate and alcohol metabolism and thus a site of potential interaction. Kreek (1984) suggested that there may be a hormonal mechanism of interaction.

Chronic ethanol consumption induces the liver enzyme cytochrome P450 isoenzyme 2E1, thought to be the main enzyme responsible for the microsomal ethanol oxidizing system (Oneta et al., 2002). When activated, this pathway can increase the metabolism of ethanol by up to 50%, and this is thought to be the main way in which tolerance is induced (Matsumoto & Fukui, 2002). Cytochrome P450 2E1 can increase the metabolism of several drugs, although methadone has not been shown to be one of them (Oneta et al., 2002). The participants in this study were not high consumers of alcohol (mean weekly intake = 1–2 standard drinks), so induction of this enzyme pathway would have been unlikely.

Recently, ethanol has also been shown to induce CYP3A4 activity in the rat (Shinderman et al., 2003). Methadone, LAAM, and buprenorphine are mainly metabolized by CYP3A4, although CYP2C8 and CYP2D6 may also be involved (Shinderman et al., 2003; Wang & DeVane, 2003). The findings in rat studies are consistent with ethanol

and methadone competition for the CYP3A4 enzyme in the acute setting, leading to increased ethanol and methadone levels, and induction of the enzyme in the chronic setting, leading to reduced ethanol and methadone levels.

Kreek (1984), on the other hand, suggested that the interaction between opiates and alcohol observed in animals may be mediated by hormonal mechanisms (in particular, estrogen and testosterone). Testosterone levels are frequently low in opioid substitution patients (Cicero et al., 1975; Mendelson, Inturrisi, Renault, & Senay, 1976). Both low testosterone and high estrogen have been associated with increased alcohol metabolism in the rat model (Cicero, Bernard, & Newman, 1980; Umans et al., 1982). Although the effects on BAC may be hormonally mediated, circulating estrogens may also be higher in the drug-using population due to liver disease and not due to opioid consumption. The lack of sex differences observed in this study, however, suggests that this has not been the mechanism of interaction in this study.

An alternative mechanism by which opiates may reduce peak BAC is by delayed gastric emptying. Published clinical trials demonstrated that buprenorphine delays gastric emptying in humans (Adelhof, Petring, Ibsen, Brynnum, & Poulsen, 1985; Trotter, Rowbotham, Windram, & Mushambi, 1991). Product information on methadone and LAAM indicate the same (Prod Info Methadone HCL, 1996; Prod Info Orlaam, 2000). Delayed gastric emptying has in turn been shown to slow absorption of alcohol and reduce peak BAC (Kechagias, Jonsson, & Jones, 1999). Although the results of this study lend weight to the theory of a pharmacokinetic interaction between alcohol and methadone in humans, it does not provide sufficient evidence in its own right. Nicotine consumption is a potential confounder, as smoking is high in patients in opioid substitution therapy (Asnafi-Farhang, Hatchuel, Bourhis, Divine, & Lagrue, 2001) and nicotine has been associated with reduced BAC in rats (Chen, Parnell, & West, 2001). Unfortunately, nicotine consumption data were not collected in this study.

What would be the clinical significance of the pharmacokinetic interaction observed here? The magnitude of the reduction in BAC with opiate substitution therapy observed in this study is small and is unlikely to be clinically noticeable. Even if opioid substitution patients have lower BACs in response to alcohol than non-opioid-consuming control subjects, they will still experience a greater opioid effect due to the combined sedative effect of the opioid and the alcohol. An issue of greater concern, although not directly tested here, is that the interaction between opiates and alcohol may mean that opioid metabolism may be induced by alcohol, leading to a reduction in trough opioid levels and less-effective opioid substitution. As mentioned, at least one of the ways in which opiates and alcohol interact in chronic alcohol consumers may be due to CYP3A4 enzyme induction, with resulting increased metabolism of both opioids and alcohol. The resulting decrease in levels of

opiates could potentially be an issue for the many patients who find that methadone does not really remain effective for 24 hours (Dyer & White, 1997). Further research should be conducted to confirm and extend these findings and, in particular, to investigate the role of CYP3A4. In the meantime, the potential for opioids and alcohol to interact should urge caution in the use of alcohol for opioid substitution patients.

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