Lactational State Modifies Alcohol Pharmacokinetics in Women

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Abstract

Background—Given the physiological adaptations of the digestive system during lactation, the present study tested the hypothesis that lactation alters alcohol pharmacokinetics.

Methods—Lactating women who were exclusively breastfeeding a 2- to 5-month-old infant and 2 control groups of nonlactating women were studied. The first control group consisted of women who were exclusively formula-feeding similarly aged infants, whereas the other consisted of women who had never given birth. A within-subjects design study was conducted such that women drank a 0.4 g/kg dose of alcohol following a 12-hour overnight fast during one test session (fasted condition) or 60 minutes after consuming a standard breakfast during the other (fed condition). Blood alcohol concentration (BAC) levels and mood states were obtained at fixed intervals before and after alcohol consumption.

Results—Under both conditions, the resultant BAC levels at each time point were significantly lower and the area under the blood alcohol time curve were significantly smaller in lactating women when compared with the 2 groups of nonlactating women. That such changes were due to lactation per se and not due to recent parturient events was suggested by the finding that alcohol pharmacokinetics of nonlactating mothers, who were tested at a similar time postpartum, were no different from women who had never given birth. Despite lower BAC levels in lactating mothers, there were no significant differences among the 3 groups of women in the stimulant effects of alcohol. However, lactating women did differ in the sedative effects of alcohol when compared with nulliparous but not formula-feeding mothers. That is, both groups of parous women felt sedated for shorter periods of time when compared with nulliparous women.

Conclusions—The systemic availability of alcohol was diminished during lactation. However, the reduced availability of alcohol in lactating women did not result in corresponding changes in the subjective effects of alcohol.

Keywords

Alcohol; Pharmacokinetics; Women's Health; Lactation; Mood

A wide variety of drugs, including alcohol (da-Silva et al., 1993; Kesaniemi, 1974; Lawton, 1985; Mennella and Beauchamp, 1991), enter breastmilk and affect the lactational processes of milk production and the behavior and physiology of the recipient infant (Dorman et al., 2001; Hale et al., 2004; Little et al., 1989; Mennella and Beauchamp, 1991; Mennella et al., 2005). Much less is known about how the dynamic physiological processes that occur during lactation influence the absorption, distribution, and elimination of drugs and how such changes in drug pharmacokinetics impact the health of lactating women (Dan et al., 1993; Mitani et al., 1987; Nahum et al., 2006).

Several lines of evidence from human and animal models support the hypothesis that lactational state could alter drug pharmacokinetics. First, the growth of the mammary glands during lactation provides a new compartment of drug distribution, excretion (Clewell and Gearhart, 2002), and possibly metabolism as alcohol dehydrogenase (ADH) is expressed in breast tissue (Saleem et al., 1984; Triano et al., 2003). Second, the high nutritional demands associated with milk production coincide with remarkable changes in the gastrointestinal tract (Hammond, 1997; Hunt and Murray, 1958; Uvnas-Moberg et al., 1987). In rodents, lactation is associated with dramatic intestinal growth (e.g., increased height of the villi) and a generalized hypertrophy and hyperplasia of the mucosal epithelium (Hammond, 1997). Such lactation-induced changes in the gastrointestinal tract significantly extend the surface area of the intestines, which, in turn, may modulate nutrient as well as drug absorption. Third, the act of nursing results in a surge of hormones (e.g., oxytocin) and gastrointestinal regulatory peptides that modifies the rate of gastric emptying (Franceschini et al., 1990; Holst et al., 1986; Ohlsson et al., 2004; Uvnas-Moberg et al., 1987; Widstrom et al., 1984; Winberg, 2005) and, in turn, may modify the pharmacokinetics of a variety of orally administered drugs including alcohol (Oneta et al., 1998; Pang, 2003). Fourth, the hypertrophy of the liver (da-Silva et al., 1996; DeSantiago et al., 1998; Gordon et al., 1985), and altered liver enzyme levels and liver functioning during lactation (David et al., 2000; Tigas et al., 2002) may affect the liver's oxidative capacity and, in turn, alter drug metabolism. For example, it has been suggested that the lactation-induced liver hypertrophy contributes to the significantly faster rate at which alcohol is eliminated in lactating when compared with nonlactating rats (Abel et al., 1979; Gordon et al., 1985). Similarly, reproductive state may alter the activity of enzymes (e.g., ADH, microsomal ethanol oxidizing system) responsible for the metabolism of alcohol in the liver as well as other sites (Badger et al., 2005; Gordon et al., 1985).

Information on alcohol pharmacokinetics during lactation in humans is limited to one study of 5 lactating women and 8 nonlactating control women. Three of the women in the control group were tested within months of stopping breastfeeding and the parity of the other 5 was not reported. Nevertheless, the data revealed that blood alcohol levels peaked later and the mean area under the blood alcohol time curve (AUC), an indicator of systemic availability of the drug, was significantly smaller in lactating women (da-Silva et al., 1993). However, unlike that observed in rodents (Abel et al., 1979), there were no significant differences in alcohol elimination rates. The lack of differences in alcohol disappearance rates may be due to the lack of appropriate control groups or statistical power because of the limited sample size or both. Therefore, the hypothesis that alcohol is eliminated at a faster rate during lactation cannot be rejected.

Given the physiological adaptations of the digestive system during lactation (Hammond, 1997; Hunt and Murray, 1958; Uvnas-Moberg et al., 1987), the present study tested the hypotheses that lactation alters alcohol pharmacokinetics and that the metabolic differences between lactating and nonlactating women would be more striking when analyzing alcohol pharmacokinetics when alcohol was consumed with a meal. To this end, we studied lactating women who were exclusively breast feeding a 2- to 5-month-old infant and 2 control groups of nonlactating women under 2 conditions: when alcohol was consumed following a meal or on an empty stomach. The first control group consisted of women who were exclusively formula-feeding similarly aged infants, whereas the other consisted of women who had never given birth. These 2 control groups were included to determine whether differences, if any, observed between the groups were due to lactation per se and not a consequence of the physiological changes that occur during pregnancy and parturition. Subjective ratings of mood and drug effects during the rising and falling portions of the blood alcohol concentration (BAC) time curve were also obtained to determine whether reproductive state was associated with changes in the biphasic effects of alcohol.

MATERIAL AND METHODS

Subjects

Subjects were recruited from advertisements in local newspapers, breastfeeding support groups, and the Women, Infants and Children Centers throughout the Philadelphia area. During the initial screening, women were excluded if they were pregnant, lifetime alcohol abstainers, or diabetic. In addition, women whose carbon monoxide (CO) levels, as measured by a CO monitor (Vitalograph Inc., Lenexa, KS), were > 10 ppm, or whose body mass index (BMI) was >30 kg/m^2 were excluded as smoking (Desai et al., 2001) and obesity (Casati and Putzu, 2005) can induce physiological modifications that affect the pharmacokinetic parameters of a variety of drugs, including alcohol (Niemela et al., 2000; Zevin and Benowitz, 1999).

Three groups of healthy, nonsmoking women, who were matched for a variety of variables including age, weight, height, and drinking habits, were studied (see Table 1). The lactating group consisted of women who were exclusively breastfeeding 2- to 5-month-old infants; none had resumed menses by the time of the study. The formula-feeding group consisted of women who were exclusively formula feeding a similarly aged infant and were tested at a similar time postpartum; all had resumed menses. The nulliparous group consisted of women who had never given birth. Although research revealed that there were no significant effects of menstrual cycle phase on alcohol pharmacokinetics (Mumenthaler et al., 1999) or alcohol-induced subjective effects (Holdstock and de Wit, 2000), cycle phase was controlled for in the 2 control groups of women. The first day of testing occurred 7.6 (± 0.9) days after their first day of menses, which, for the vast majority (88%) of women, coincided with the follicular phase of the menstrual cycle. Three of the participants (2 formula-feeding mothers and 1 nulliparous woman) were taking oral contraceptives at the time of the study. Five additional women began testing but were excluded because of lack of compliance (*N* = 4) or procedural difficulties (*N* = 1). All procedures were approved by the Office of Regulatory Affairs at the University of Pennsylvania, and each subject gave informed written consent before testing.

Procedures

A within-subjects design study that controlled for time of day was conducted. Subjects were tested on 2 days separated by approximately 1 week (± 1 day). On each testing day, women arrived at the Monell Chemical Senses Center at approximately 8:00 AM, having been instructed to abstain from alcohol for 36 hours and food for 12 hours. As shown in Fig. 1, at approximately 8:30 AM, capillary blood glucose was measured from a finger-prick sample (OneTouch®, LifeScan, Milpitas, CA) to ensure that the women had indeed fasted. Only those whose blood glucose level was <99 mg/dL participated in the study. At the beginning of each test session, a pregnancy test was also administered to confirm that the subjects were not pregnant (First Response®, Church & Dwight Co. Inc., Princeton, NJ). Because the act of suckling can release gastric hormones (Franceschini et al., 1990;Holst et al., 1986;Uvnas-Moberg et al., 1987;Widstrom et al., 1984;Winberg, 2005), which, in turn, decreases gastric motility, we controlled for the amount of breast stimulation women received during the experimental period so that any changes observed between the groups were not due to the immediate effects of breast stimulation per se. To this end, each of the women in the lactating group emptied their breasts via an electronic breast pump (Medela, Crystal Lake, IL) before the start of the study and did not use the breast pump again throughout each of the testing sessions.

At approximately 9:00 AM, subjects consumed a standard breakfast during one day (fed condition) or remain fasted during the other (fasted condition). The order of testing was randomized among subjects. The breakfast, which consisted of 1 bagel (150 cal), 1 packet of jelly (35 cal), 5 g of margarine (25 cal), 6 oz of orange juice (110 cal), 6 oz of lactose-lowfat milk (110 cal), and 52 g of cereal (100 cal), was consumed within a 20-minute period

(Ramchandani et al., 2001). One hour later (hereafter referred to as time 0), subjects drank a 0.4 g/kg dose of alcohol. The beverage, a 15% v/v solution of 100% alcohol mixed with a noncaloric Strawberry-Kiwi flavored drink (Crystal Lite, Kraft Food Inc., Northfield, IL), was aliquoted into 2 equal volumes, and each aliquot was consumed within consecutive 5-minute periods.

Blood alcohol concentration levels were estimated by having subjects breathe into a fuel-cell sensor analyzer (Alco-Sensor III, St. Louis, MO) at fixed intervals before and after the consumption of the alcoholic beverage: −1, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 175, and 205 minutes. The rationale for estimating BACs from "breath alcohol" measurements was based on the noninvasive nature, simplicity, accuracy, and reliability of the method, which has become a standard procedure in alcohol pharmacokinetic studies (Mumenthaler et al., 2000; O'Connor et al., 1998). However, we acknowledge its limitation as there is a paucity of research on the effects of lactation on the alveolar membranes involved in gas exchange.

Subjects also completed the Addiction Research Center Inventory (ARCI) and the Biphasic Alcohol Effect Scales (BAES) to assess alcohol's subjective effects (Holdstock and de Wit, 1998, 2000; Holdstock et al., 2000; King et al., 1997; Martin et al., 1993; Morzorati et al., 2002) before (−30 min) and after (25, 55, 85, and 175 minutes) they consumed the alcoholic beverage. The ARCI questionnaire consists of a number of scales including the Morphine Benzedrine Group (MBG) scale that measures drug-induced euphoria; the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) scale that measures sedation; the Lysgeric (LSD) scale that measures dysphoric and somatic effects; the Benzedrine Group (BG) and Amphetamine (A) scales that measure stimulant-like effects; and the Drunk Scale that measures drunkenness. The BAES, a self-report rating scale, was used to measure both the stimulant and sedative effects of alcohol (Martin et al., 1993).

Classical Pharmacokinetic Measures

Following the methods of Mumenthaler et al. (1999), we determined time-to-peak BAC, peak BAC, disappearance rate (β_{60}), total amount of alcohol eliminated per hour (b_{60}), elimination rate (R), and AUC. In brief, linear least-squares regression lines were calculated for each subject, under each condition (fed and fasted), within the apparent linear portion of the descending limb of the BAC versus time curve. The slope of these regression lines represented the alcohol disappearance rate (β_{60}). To exclude the upper distribution phase and lower first-order elimination phase of the apparent lineal portion of the curve, we used the first value taken 0.5 hours after the peak BAC and all subsequent readings ≥0.20 g/L. The total amount of alcohol eliminated from the body per hour, b_{60}, was calculated as $b_{60}=\beta_{60}\times TBW/B_w$, taking total body water (TBW) into account with TBW = [0.1069×height (cm)]+[0.2466×weight (kg)]−2.097 and B_W=0.80. This standardized anthropometric equation estimates TBW for women with a precision of ±9 to 11% (Watson et al., 1980) and has been used extensively (Brick, 2006; Khaole et al., 2004; Mumenthaler et al., 1999). Although there are no studies to date that validate the Watson anthropometric equation for use in lactating women, previous research that estimated TBW by deuterium-dilution methods revealed that TBW in women before pregnancy was no different from that observed at 6 months postpartum (Solstrom and Forsum, 1997). Moreover, TBW did not change significantly at 3, 6, and 12 months postpartum in lactating women (Butte et al., 1997).

The alcohol elimination rate (R), expressed as the amount of alcohol eliminated per kilogram of the body per hour, was calculated as $R=\beta_{60}$/body weight. Only those subjects whose linear least-squares regression lines (β_{60}) were statistically significant were included in the calculation of b_{60} and R. Area under the blood alcohol time curve were calculated from data collected from the beginning of alcohol administration (time 0) to the last time point (time 205)

by using software program (OriginLab® Corporation, Northampton, MA) based on the trapezoidal rule.

Data Analyses

Blood alcohol concentration levels and mood states were analyzed by using separate 3-way mixed ANOVA with reproductive state (lactating, formula feeding, and nulliparous) as the between-subjects factor and condition (fed and fasted) and time since alcohol postconsumption sampling time as the within-subjects factors. The classical pharmacokinetic parameters (time-to-peak, peak BAC, β_{60}, b_{60}, R, and AUC) were also analyzed with separate mixed ANOVAs with reproductive state as the between-subjects factor and condition as the within-subject factor. When the ANOVAs revealed significant effects or interactions, post hoc Fisher least significant difference analyses were conducted. The critical value for significance was $p<0.05$.

RESULTS

BAC Time Curves and Classical Pharmacokinetic Measures

Blood alcohol concentration time curves in lactating, formula feeding, and nulliparous women under the fed and fasted conditions are shown in Fig. 2. There were significant main effects of reproductive state on BAC levels [$F(2, 41)=4.98$; $p<0.025$], peak BAC [$F(2, 41)=4.8$; $p<0.025$], and alcohol AUCs [$F(2, 41)=5.3$; $p<0.01$]. Although there were no significant differences between the groups in time to reach peak alcohol levels ($p=0.25$), BAC levels and peak BAC levels were significantly lower and AUCs were significantly smaller in lactating women when compared with both groups of nonlactating women (Table 2). There were no significant differences in any of these measures between nulliparous women and parous women who were formula-feeding their infants.

In alcohol elimination measures, we were able to obtain these measures for data collected during the fasted condition (1 lactating woman and 1 formula-feeding woman were excluded because their regression lines were not significant). There were no significant differences in β_{60}, b_{60}, or R among the groups (all p's>0.50). A different picture emerged when we tried to calculate these measures for data obtained during the fed condition. That is, β_{60} values for the fed condition were obtained for 78% of the formula-feeding mothers and 87% of the nulliparous women but only 45% of the lactating women; this difference among the groups was significant [$\chi^2(df=2)=7.33$; $p=0.026$]. The β_{60} for 6 of the lactating women could not be calculated because there were not enough values 0.5 hours after the peak BAC that were above 0.20 g/L alcohol, a requisite for the calculation. Five additional lactating women were excluded because their regression lines were not significant.

Table 3 depicts the alcohol elimination data from the subset of subjects for whom we have data for both the fed and fasted conditions (i.e., 29 women: 9 lactating, 7 formula feeding, and 13 nulliparous). The correlation coefficient for the slope of the regression lines representing the alcohol disappearance rate (β_{60}) was, on average, -0.96 ± 0.05 for the fed and -0.96 ± 0.01 for the fasted condition. Analyses of this dataset revealed no significant main effect of reproductive state nor interaction between reproductive state and condition ($p>0.10$).

Regardless of reproductive state, there were significant effects of condition on BAC levels and alcohol elimination measures. Alcohol disappearance rates [$F(1, 26)=8.1$; $p=0.009$], b_{60} [$F(1, 26)=6.5$; $p=0.017$], and R [$F(1, 26)=7.4$; $p=0.011$] were significantly faster when alcohol was consumed after a meal compared with when it was consumed on an empty stomach. On average, there was a 17% ($\pm 7\%$) increase in the total amount of alcohol eliminated per hour (b_{60}; g/h) when alcohol was consumed following the intake of food compared with that following an overnight fast. Similarly, BAC levels [$F(1, 41)= 245.4$; $p<0.0001$] were significantly lower

and alcohol AUCs were significantly smaller [$F(1, 41) = 275.9$; $p<0.0001$] on the day women consumed the alcoholic beverage after eating a meal when compared with the day they consumed alcohol on an empty stomach. In addition, it took longer to reach peak BAC levels [$F(1, 41)=13.6$; $p<0.001$] and the height of the peak was significantly diminished [$F(1, 41) =153.2$; $p<0.0001$] during the fed when compared with the fasted condition in the 3 groups of women.

Subjective Effects of Alcohol

Alcohol consumption produced both stimulant-like and sedative-like effects, as determined by the ARCI and BAES (Fig. 3). In sedative-like effects, there was a significant interaction between reproductive state and time since alcohol consumption on the Sedation scale of the BAES [$F(8, 164)=3.27$; $p<0.0025$]. Post hoc analysis revealed that although there were no significant differences among the groups on feelings of sedation at baseline, the sedative effects of alcohol exhibited a different time course in parous women (lactating, formula-feeding groups) when compared with the nulliparous women. Regardless of condition, nulliparous women continued to exhibit sedative effects at 175 minutes postalcohol consumption, whereas lactating and formula-feeding women were back to baseline levels by 175 and 55 minutes postalcohol consumption, respectively (see Fig. 3). Similar findings were observed for the sedative subscale (PCPG), as measured by the ARCI, but the effect did not reach statistical significance ($p = 0.08$).

In stimulant-like effects, there were no significant main effects of reproductive state (ARCI-A subscale: $p>0.80$; BAES Stimulation scale: $p>0.78$) nor was there an interaction between reproductive state and condition (ARCI-A subscale: $p=0.65$; BAES Stimulation scale $p=0.21$). However, there were significant main effects of time and condition. Alcohol consumption significantly increased subjective ratings of stimulation, as measured by the ARCI-A scale [$F(4, 164)=6.65$; $p=0.0001$] and the BAES Stimulation scale [$F(4, 164)=4.69$, $p<0.0025$] during the immediate hour following consumption of the alcoholic beverage. Stimulant-like effects [ARCI-A: $F(1, 41)=5.44$; $p=0.024$, BAES $F(1, 41)=4.74$, $p<0.025$; and feelings of drunkenness $F(4, 164)=7.5$; $p<0.0001$] were significantly higher when alcohol was consumed on an empty stomach when compared with the day alcohol was consumed after a meal (data not shown).

DISCUSSION

The systemic availability of alcohol is diminished during lactation, a finding that extends the previous work of da-Silva et al. (1993). Regardless of whether alcohol was consumed following a meal or on an empty stomach, the resultant BAC levels were significantly lower and AUC were significantly smaller in lactating women when compared with the 2 groups of nonlactating women. As expected, these differences were most apparent when alcohol was consumed with food. Blood alcohol concentration levels were so low at approximately 1 hour postalcohol consumption (specifically at 0.5 hours after peak BAC) that we could not calculate several of the alcohol elimination measures for the majority of lactating subjects. That such changes were due to lactation per se and not due to recent parturient events was suggested by the finding that alcohol pharmacokinetics of nonlactating mothers, who were tested at a similar time postpartum, were no different from women who had never given birth.

The lactation-associated changes in alcohol pharmacokinetics could be due to changes in absorption, distribution, and/or elimination. Because we could not calculate several of the alcohol elimination measures for the majority of lactating subjects on the day they consumed alcohol after a meal, we focused here on data obtained during the fasted condition to see whether there was an effect of lactational state on alcohol elimination. Such analyses revealed no significant differences in alcohol elimination measures or the time to reach peak BAC levels as a function of reproductive state. Notably, alcohol elimination parameters calculated for the

women in the present study are in strong agreement with the values reported previously by other researchers (Mumenthaler et al., 1999; Ramchandani et al., 2001).

Nevertheless, because alcohol was orally administered, we could not determine the effects of lactation on alcohol absorption separately from its effects on alcohol elimination. Therefore, the possibility that physiological and metabolic adaptations of the digestive system during lactation result in different patterns of alcohol elimination cannot be discounted, and future studies using breath alcohol concentration clamps (O'Connor et al., 1998; Ramchandani et al., 2001) are warranted to elucidate the mechanisms underlying lactation-associated changes in the bioavailability of alcohol. However, we emphasize here that the mathematical models that estimate BAC based on breath alcohol contents (BrAC) are complex (Jones et al., 1997). Research is needed to determine whether lactation alters functioning of the alveolar membranes involved in gas exchange and, in turn, modifies the BrAC/BAC conversion ratio before breath alcohol clamping studies are conducted.

In breath alcohol clamping studies, alcohol is intravenously administered until a steady state of BAC levels is achieved for a prolonged period of time. Under such a steady-state condition, the amount of alcohol infused in the vein is a direct measure of the amount of alcohol being eliminated. Furthermore, physiologically based pharmacokinetic programs (Levitt, 2002) can then be applied to the IV input ethanol data to determine whether lactation alters the time course of intestinal absorption and first-pass metabolism (FPM), the fraction of a given dose of a drug that is metabolized in its passage through the gut and liver before reaching the systemic circulation (Baraona, 2000; Levitt, 2002). That the FPM of alcohol may be increased during lactation is suggested by the present findings that peak BAC levels and AUC were reduced in lactating women and alcohol elimination measures were unaltered, at least under fasted conditions. Although the site (i.e., liver and/or stomach) where alcohol FPM occurs is still a matter of controversy, it is clear that FPM increases under circumstances in which the alcohol-absorption phase is prolonged (Crabb, 1997; Gentry, 2000; Jones, 2000; Levitt, 2002).

One such circumstance is when alcohol consumption is accompanied by a meal. That is, it took significantly longer for ethanol to be absorbed when administered with a standard breakfast; the rate of ethanol absorption was primarily limited by the rate of gastric emptying (Gentry, 2000; Jones, 2000; Levitt, 2002). In addition, the presence of food in the stomach significantly increases alcohol elimination rates, probably via an increase in hepatic blood flow and/or an increase in the activity of alcohol-metabolizing enzymes (Hahn et al., 1994; Ramchandani et al., 2001). Consistent with previous research (Gentry, 2000; Jones, 2000), the present study revealed that it took a longer time to reach peak BAC levels and consequently the height of the peak BAC and the AUC were significantly diminished and alcohol was eliminated faster when it was consumed after eating a meal when compared with when it was consumed on an empty stomach.

We hypothesize that lactation modifies the pharmacokinetics of alcohol, in part, through the release of gastrointestinal regulatory peptides, which in turn alter gastric emptying rates (see also Pepino et al., 2002). When gastric emptying is slower, the passage of alcohol from the stomach to the duodenum and the liver is delayed and so the extent of the FPM increases (Crabb, 1997; Gentry, 2000; Jones, 2000; Oneta et al., 1998). Although the lactating women did not receive any breast stimulation during the test session, each woman used an electronic breast pump to empty their breasts approximately 1 to 1.5 hours before drinking the alcoholic beverage on both days of testing and immediately before eating the breakfast during the fed condition day. Therefore, we cannot disregard the possibility of some gastric effects triggered by breast stimulation. Future studies are currently underway in our laboratory to determine the short-term and long-term effects of breast-pumping stimulation on alcohol pharmacokinetics.

We would argue that if there are alterations in the pharmacokinetics of alcohol during lactation, then one would expect that the pharmacokinetics of other drugs would also be affected. Indeed, there is some evidence, albeit limited. The time it took Fleroxacin, a broad-spectrum antimicrobial fluoroquinolone, to reach maximum plasma concentrations was twice as long and its total clearance was reduced by 25% in lactating women (Dan et al., 1993). Clearly, more research is needed to determine how the dynamic physiological processes that occur during lactation influence the absorption, distribution, and elimination of alcohol as well as other drugs, and if so, the mechanisms underlying such changes.

As expected, alcohol consumption induced both sedative and stimulant effects in women, and the biphasic effects of alcohol were more pronounced during the test session in which they drank alcohol on an empty stomach. Parous women felt sedated for significantly shorter periods of time postalcohol consumption when compared with nulliparous women. One explanation for the observed attenuation in feelings of sedation could be a consequence of the lower BAC levels in the lactating women. However, the formula-feeding mothers, who had BAC levels similar to nulliparous women, were also less sensitive to alcohol's sedative effects. Moreover, despite lower BAC levels, we found no lessening of the stimulant effects of alcohol during lactation. Perhaps sleep deprivation, which is common among mothers of young infants, contributed to these findings. To this point, we found that despite different BAC levels, there was no difference in the biphasic effects of alcohol between formula-feeding and lactating mothers.

Epidemiological studies have shown that women have a greater sensitivity to alcohol toxicity and develop an accelerated progression to physiological and psychological problems from alcohol use when compared with men (Bradley et al., 1998; Brienza and Stein, 2002; Mann et al., 2005). The findings reported herein highlight the need for additional research to determine how lactational state modifies alcohol pharmacokinetics and metabolism and whether drinking during lactation increases a woman's enhanced vulnerability to develop alcohol-related diseases (see Baraona et al., 2001). Although the data are equivocal for humans (Gordon et al., 1985), studies in rats revealed that blood levels of acetaldehyde, a reactive and toxic metabolite of alcohol, reached a 15-fold increase at the peak of lactation (Gordon et al., 1985). If there is an increase in alcohol oxidation that is not matched with increased acetaldehyde metabolism, then lactating women who drink cannot only potentially expose their infants to alcohol in milk (Mennella and Beauchamp, 1991), but they and their infants may be exposed to higher levels of acetaldehyde and therefore subjected to a greater susceptibility to alcohol toxicity. Providing insights into some of the aspects of how the metabolism of alcohol is modified during lactation will aid in the development of sound guidelines for alcohol consumption during lactation.

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Time of Day: 8:30, 9:00, 9:30, 10:00, 10:10, 10:25, 10:35-12:25, 12:55, 13:25

Time of Day	8:30	9:00	9:30	10:00	10:10	10:25	10:35-12:25	12:55	13:25
Time Relative to Drinking Beverage	−90	−60	−30	0	10	25	35-145	175	205
Events	-Glucose test -Pregnancy test -Breast-Pumping for lactating group only	Breakfast (Fed Day) *or* No Breakfast (Fasted Day)		Start drinking alcoholic beverage	End drinking alcoholic beverage				
BAC	x		x (−1 min)			x	xxxxxxxxxxxx (every 10 min)	x	x
ARCI BAES			x x			x x	x x x x	x x	

Fig. 1.

Schedule of events. Each subject arrived at the Center at 8:30 AM following a 12-hour overnight fast. Capillary blood glucose was measured to ensure that the women had fasted and a pregnancy test was administered to confirm they were not pregnant. For those who were lactating, the women emptied their breasts via an electronic breast pump. At 9:00 AM, women consumed a standard breakfast during one test day (fed condition) or remained fasted during the other (fasted condition). One hour later (hereafter referred to as time 0), subjects drank a 0.4 g/kg alcoholic beverage. The symbol X denotes determination of blood alcohol concentrations (BAC) and completion of Addiction Research Center Inventory (ARCI) and Biphasic Alcohol Effect Scales (BAES) questionnaires to evaluate various mood states.
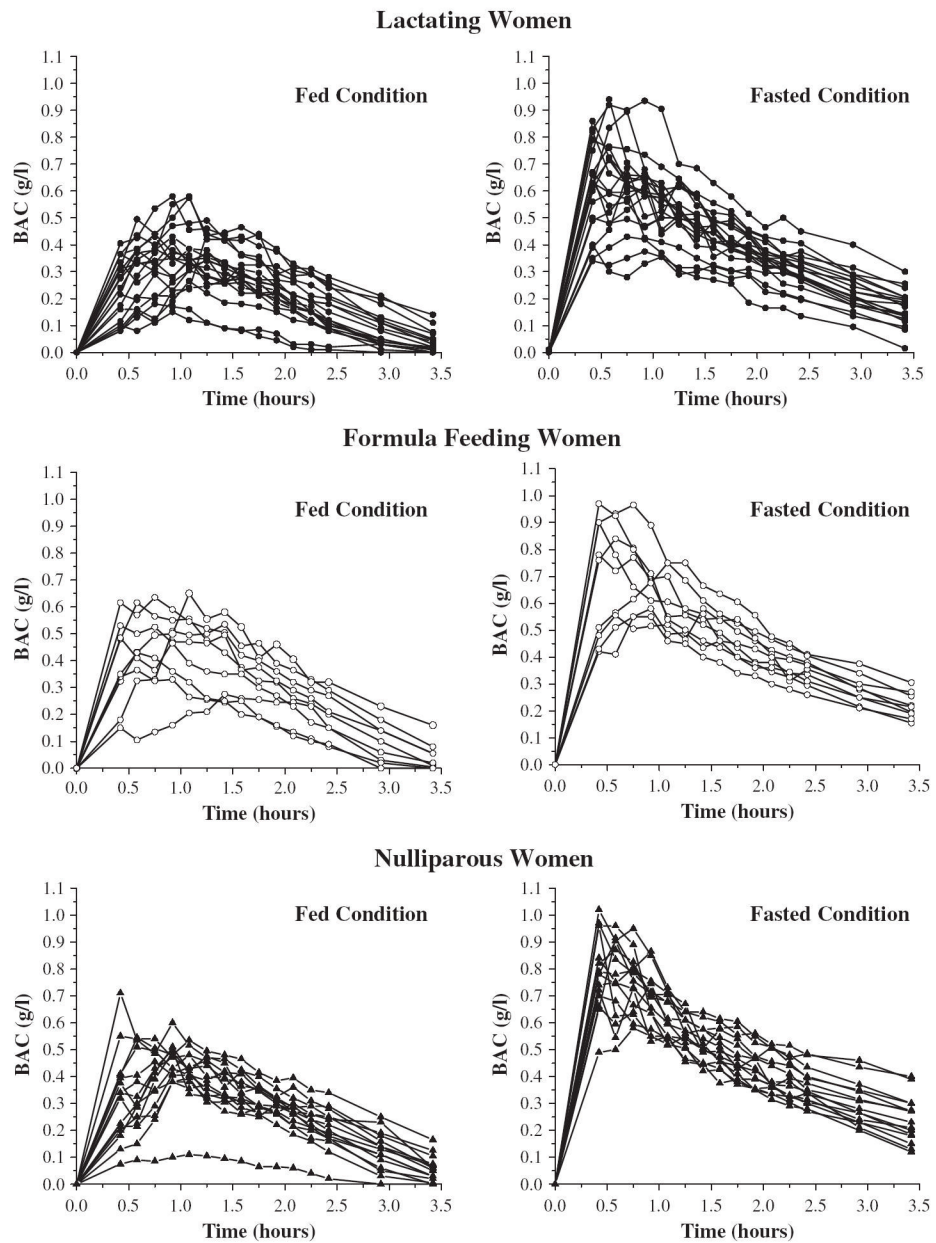
Fig. 2.
Blood alcohol concentrations (BACs) (g/L) for lactating (*N*=20; **top panel**, ●), formula feeding (*N*=9; **middle panel**, ○), and nulliparous (*N*=15; **bottom panel**, ▲) women after drinking a dose of 0.4 g/kg body weight. Each line represents an individual subject. Panels on the left depict data obtained during the fed condition and panels on the right depict data obtained during the fasted condition.
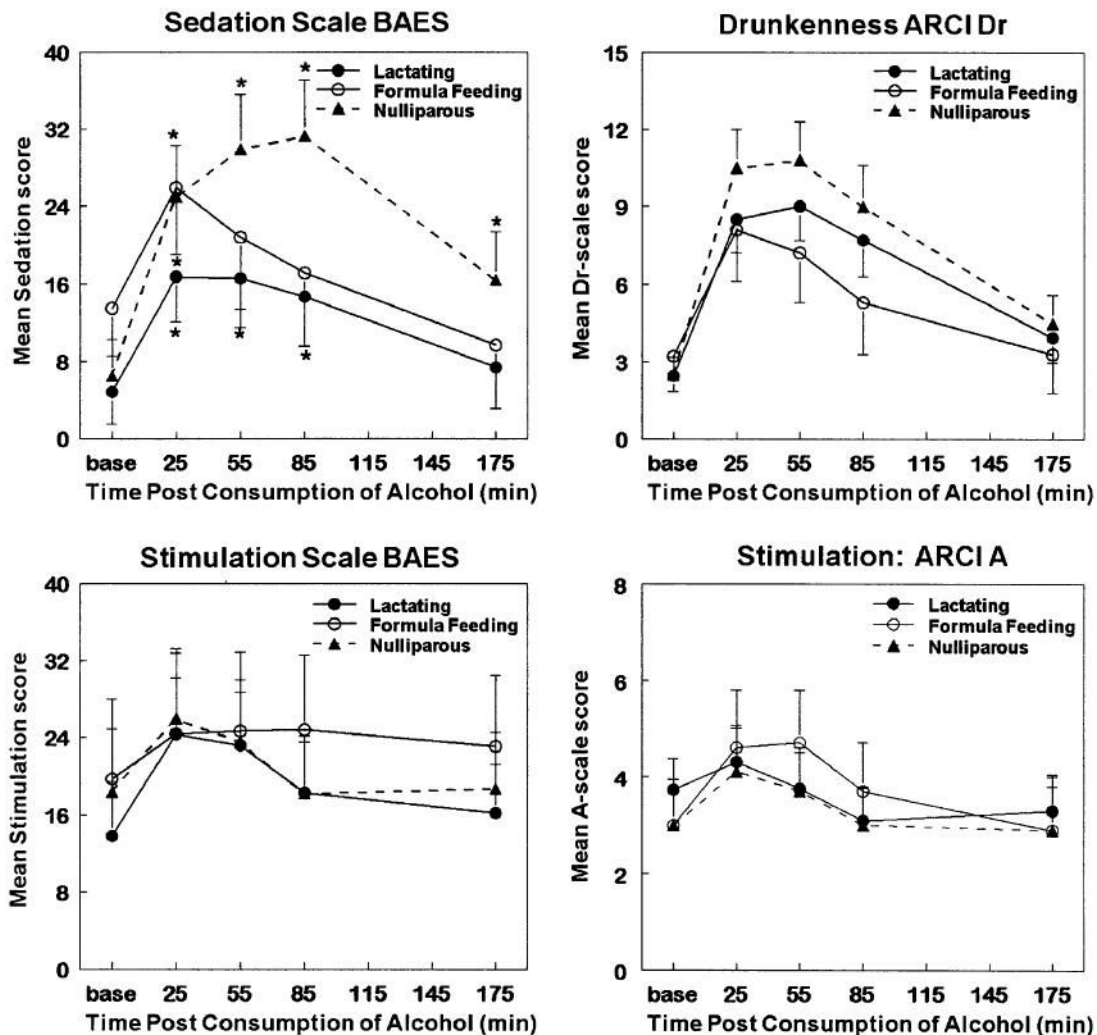
Fig. 3.
Subjective effects of alcohol consumption in lactating (●), formula feeding (○), and nulliparous (▲) women. Panels on the **left** depict data obtained from the Biphasic Alcohol Effect Scales (Sedation scale on the **top panel**; Stimulation scale on the **bottom panel**) and those on the **right** depict data obtained from the Addiction Research Center Inventory (ARCI) scales (Drunkenness on the ARCI-Dr scale on the top panel, and stimulant-like effects on the ARCI-A on the bottom panel). Values represent mean ± SEM. Data collapsed across fed and fasted conditions. *Values within the test session that are significantly different from their respective baseline values ($p<0.05$).

Table 1

Subject Demographics

	Lactating women	Formula-feeding women	Nulliparous women
Number of subjects	20	9	15
Height (m)	1.65 ± 0.01	1.67 ± 0.01	1.66 ± 0.02
Weight (kg)	65.0 ± 1.5	69.0 ± 4.9	67.2 ± 3.2
BMI (kg/m^2)	24.1 ± 0.7	24.8 ± 1.8	24.4 ± 0.9
TBW	31.5 ± 0.4	32.8 ± 1.2	32.2 ± 0.9
Parity (number)	1.7 ± 0.1	1.7 ± 0.2	NA
Race/ethnicity (%)			
Caucasian	40.0	44.4	40.0
African American	35.0	33.3	26.7
Hispanic	10.0	0.0	6.7
Asian	10.0	0.0	13.3
Other	5.0	22.3	13.3
Alcohol consumption during past 3 wk			
Number of standard drinks	4.0 ± 1.5	4.0 ± 1.9	9.5 ± 2.7
Number of drinking occasions	2.5 ± 0.9	1.6 ± 0.6	2.8 ± 0.7

TBW, total body water; BMI, body mass index; NA, not applicable.

Table 2

Pharmacokinetic Measures (Mean ± SEM) Obtained From 3 Groups of Women (Lactating, Formula Feeding, and Nulliparous) Following the Consumption of a 0.4 g/kg Dose of Alcohol Under Fed and Fasted Conditions and the Average of Both Conditions

Measures	Lactating women			Formula-feeding women			Nulliparous women		
	Fed	**Fasted**	**Both**	**Fed**	**Fasted**	**Both**	**Fed**	**Fasted**	**Both**
Time-to-peak BAC (h)[c]	0.93 ± 0.07	0.65 ± 0.05	0.79 ± 0.04	0.92 ± 0.10	0.73 ± 0.08	0.83 ± 0.06	0.84 ± 0.08	0.58 ± 0.06	0.71 ± 0.05
Peak BAC(g/L)[cd]	0.39 ± 0.03	0.69 ± 0.03	0.54 ± 0.03[a]	0.50 ± 0.04	0.76 ± 0.05	0.63 ± 0.04[b]	0.46 ± 0.03	0.84 ± 0.04	0.65 ± 0.03[b]
AUC (g/L/h)[cd]	0.68 ± 0.06	1.30 ± 0.06	0.99 ± 0.05[a]	0.90 ± 0.09	1.49 ± 0.09	1.20 ± 0.08[b]	0.86 ± 0.07	1.58 ± 0.07	1.22 ± 0.06[b]
Number of subjects		20/20			9/9			15/15	

[a] is significantly different than [b].

[c] Depicts significant effect of condition.

[d] Depicts significant effect of group.

BAC, blood alcohol concentration; AUC, area under the blood alcohol time curve.

Table 3

Alcohol Elimination Measures (Mean ± SEM) Obtained From 3 Groups of Women (Lactating, Formula Feeding, and Nulliparous) Following the Consumption of a 0.4g/kg Dose of Alcohol Under Fed or Fasted Conditions

Measures	Lactating women		Formulafeeding women		Nulliparous women	
	Fed	**Fasted**	**Fed**	**Fasted**	**Fed**	**Fasted**
Disappearance rate, β_{60} (g/L/h)[a]	0.18 ± 0.02	0.15 ± 0.02	0.22 ± 0.02	0.17 ± 0.02	0.17 ± 0.01	0.16 ± 0.01
Elimination rate, R (g/kg body weight/h)[a]	0.11 ± 0.01	0.09 ± 0.01	0.13 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.10 ± 0.01
Total eliminated, b_{60} (g/h)[a]	7.27 ± 0.70	6.58 ± 0.50	9.14 ± 0.79	7.18 ± 0.69	6.90 ± 0.58	6.38 ± 0.50
Number of subjects[b]	9/20		7/9		13/15	

Values represent a subset of the women in each of the groups for whom we could calculate these measures.

[a]Significant effect of condition.

[b]Significant effect of group.