Published in final edited form as:

Am J Obstet Gynecol. 2016 October ; 215(4): 497.e1–497.e7. doi:10.1016/j.ajog.2016.05.016.

Bupropion therapy during pregnancy: the drug and its major metabolites in umbilical cord plasma and amniotic fluid

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Abstract

Background—Bupropion is used for treatment of depression during pregnancy. However, its use as a smoking cessation aid for pregnant women is currently under evaluation.

Objectives—The aim of this opportunistic study was to investigate the transfer of bupropion and its major pharmacologically active metabolites, hydroxybupropion and threohydrobupropion, across the placenta *in vivo*. In addition, the concentrations of the drug and its metabolites were determined in the amniotic fluid.

Methods—The following samples were collected at deliveries from twenty-two women taking bupropion: maternal blood (n=22), umbilical cord venous blood (n=22), and amniotic fluid (n=9). The concentrations of the drug and its metabolites in blood plasma and amniotic fluid were determined by means of liquid chromatography-mass spectrometry. Placental passage was calculated as a ratio of umbilical cord venous plasma to maternal plasma concentrations.

Results—The levels of hydroxybupropion and threohydrobupropion in umbilical cord venous plasma were invariably lower than their corresponding concentrations in maternal plasma. The concentrations of bupropion in umbilical cord plasma were lower than in maternal plasma in the majority of the maternal-cord blood pairs. The median values of the umbilical cord venous plasma to maternal plasma ratios were: bupropion, 0.53 (interquartile range 0.35, n=18), hydroxybupropion, 0.21 (interquartile range 0.12, n=18), and threohydrobupropion, 0.61 (interquartile range 0.11, n=21). In umbilical cord venous plasma, the median concentration of bupropion was 5.3 ng/ml; hydroxybupropion, 103.6 ng/ml and threohydrobupropion, 59.6 ng/ml. Bupropion and its metabolites were detectable in the amniotic fluid but the concentrations of threohydrobupropion were higher than those in the corresponding umbilical cord venous plasma.

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The study was conducted at: Department of Obstetrics & Gynecology, University of Texas Medical Branch (UTMB), Galveston, TX; UTMB Regional Maternal Child Health program (RMCHP) clinics at Pearland, TX and Pasadena, TX.

Conflict of interest: The authors report no conflict of interest

Conclusion—Bupropion and its active metabolites cross the placenta to the fetal circulation. The concentrations of hydroxybupropion and threohydrobupropion in umbilical cord venous plasma were higher than bupropion concentrations suggesting a higher fetal exposure to the metabolites than the parent drug. The higher levels of threohydrobupropion in the amniotic fluid than those in umbilical cord venous plasma suggest that enzymes involved in the metabolism of bupropion to threohydrobupropion are most likely active in the fetus. The biological consequences of fetal exposure to maternally administered bupropion and/or its active metabolites via placental transfer and recirculation of the amniotic fluid are yet to be determined.

Keywords

amniotic fluid; bupropion; hydroxybupropion; placental passage; pregnancy; threohydrobupropion; umbilical cord plasma

Introduction

A substantial number of women of childbearing age experience clinical depression.¹ Consequently, it is often necessary to start or continue treatment of depression during pregnancy.^{2,3} Bupropion hydrochloride is one of the most frequently prescribed antidepressant in the US, and is used to treat depression in pregnant women.^{4,5}

Despite the known risks of adverse effects of prenatal smoking on the fetus, 10.7% of pregnant women continue smoking throughout pregnancy.⁶ Bupropion, under the brand name Zyban, has been successfully used to aid in smoking cessation in males and non-pregnant females.⁷ However, to date, bupropion has not been approved, by the U.S. Food and Drug Administration, for smoking cessation during pregnancy due to insufficient data on its safety and efficacy.

The exact mechanism of action of bupropion is not well understood. Nevertheless, it appears that bupropion exerts its antidepressant effect by inducing the release of norepinephrine and dopamine, as well as decreasing the reuptake of these two neurotransmitters.⁸ Moreover, bupropion noncompetitively inhibits several nicotinic acetylcholine receptors, which is thought to contribute to bupropion efficacy as a smoking cessation aid.⁸

The human liver biotransforms bupropion to three major metabolites, namely: hydroxybupropion (OHBUP), threohydrobupropion (TB), and erythrohydrobupropion (EB).⁹ OHBUP, the major hepatic metabolite of bupropion, is half as potent as the parent drug, while TB and EB have very low activity.^{9,10} At steady state, the plasma level of OHBUP exceeds that of the parent compound by 10 folds or more. Therefore OHBUP is thought to be the major contributor to the pharmacologic activity of bupropion.^{10,11,12}

Ex vivo studies utilizing dual perfusion of placental lobule demonstrated that bupropion and OHBUP cross the human placenta.^{13,14} Moreover, *in vitro* experiments showed that bupropion is metabolized by placental tissue, with TB being the major placental metabolite of bupropion.¹⁵ These data, obtained *ex vivo* and *in vitro*, suggest that *in vivo* fetal exposure to bupropion and its pharmacologically active metabolites is plausible. To the best of our

knowledge, the extent of maternal/fetal exchange of bupropion and its metabolites *in vivo* has not been reported.

Amniotic fluid represents another potential pathway of fetal exposure to maternally administered medications.¹⁶ During early gestation, the amniotic fluid consists primarily of ultrafiltrate of maternal serum.¹⁷ However, later in pregnancy, fetal urine contributes significantly to the amniotic fluid content.¹⁷ Amniotic fluid reaches the fetus via several routes, particularly via swallowing into the gastrointestinal tract and possibly via inhalation into the respiratory system.¹⁶ Moreover, prior to fetal skin keratinization, which begins at 19–20 weeks of gestation and is usually complete by 25 weeks of gestation, the amniotic fluid is accessible to the fetus by transcutaneous absorption.¹⁷ If amniotic fluid contains significant quantities of bupropion and its active metabolites, then continuous fetal exposure to the maternally administered drug is plausible.

The primary objective of this work was to examine the extent of *in vivo* placental passage of bupropion and its major pharmacologically active metabolites. The secondary objective was to determine the concentrations of bupropion and its metabolites in the amniotic fluid.

Methods

Study overview

The participants in this study were from the cohort of subjects enrolled in the opportunistic study to determine the pharmacokinetics (PK) of bupropion during pregnancy. Women with a prior history or current medical examination consistent with the presence of clinically significant alterations in hepatic, renal or gastrointestinal function were excluded from participation. The eligible participants in the current investigation were pregnant women taking bupropion within the last 7 days prior to delivery. As an opportunistic study, the subjects were prescribed bupropion previously by their health provider for treatment of depression. The subjects were recruited at the University of Texas Medical Branch (UTMB), Galveston, TX and affiliated clinics in Pasadena and Pearland, TX. Written informed consent was obtained prior to data collection. The study was conducted following the protocol approved by the UTMB Institutional Review Board. Due to the opportunistic design of the study, the obstetrical and neonatal outcomes have not been gathered.

Aliquots of maternal venous blood were obtained and placed in BD Vacutainer heparinized tubes less than 4 hours prior to delivery or immediately after delivery. The blood was centrifuged for 15 min at room temperature, and the supernatant (plasma) transferred to cryovials. Aliquots of umbilical cord venous and arterial blood were obtained after the delivery of the placenta and processed as described above. When feasible (and if the collection did not interfere with patient care), amniotic fluid samples were collected as part of the planned Cesarean section, using a sterile 30cc needleless syringe after rupture of membranes. All samples were stored at –80°C until analysis of their content.

Quantification of bupropion, OHBUP and TB

The concentrations of bupropion, OHBUP and TB in maternal plasma, umbilical cord venous and arterial plasma, and amniotic fluid were determined by liquid chromatography-

concentrations in matched maternal and cord venous plasma ($r=0.87$), however there was no correlation observed for maternal plasma concentrations below 10 ng/ml (Figure 2A).

The concentrations of bupropion, OHBUP and TB in the amniotic fluid (n=9) and corresponding maternal plasma and umbilical cord venous plasma are shown in Table 2. The drug and its metabolite OHBUP were below their respective LOD and LLOQ in one sample of the amniotic fluid (subject C), but similar to levels in the corresponding umbilical cord venous plasma. The concentrations of OHBUP in the amniotic fluid (n=9) were either lower or similar to those in corresponding umbilical cord venous plasma, but invariably lower than in the maternal plasma. The concentrations of bupropion in the amniotic fluid of subjects D, J, L, and O were higher than those in umbilical cord venous plasma. However, with the exception of subject D, the levels of bupropion in amniotic fluid were lower than in the maternal plasma. On the other hand, the ratio of TB concentrations in amniotic fluid to that in cord venous plasma ranged from 1.2 to 4.7 (n=9) with the median value being 2.2 and IQR=1.6 (Table 2). Moreover, with the exception of subjects E and Q, TB levels in the amniotic fluid were higher than corresponding maternal plasma concentrations.

Comments

Currently, bupropion is indicated for treatment of depression and as an aid for smoking cessation.¹⁹ The recommended daily dose of bupropion for treatment of major depressive disorders ranges between 75 and 450 mg.^{6,7} The use of antidepressants, and bupropion in particular, in treatment of pregnant patients is consistent with several practice guidelines.^{2,20} The use of bupropion (Zyban) as an aid for smoking cessation is available for males and non-pregnant females and typically lasts 7 or 12 weeks and the recommended dose is 150 mg twice a day.⁵

Pregnant women who participated in the current study were receiving various daily doses of bupropion for treatment of depression. Accordingly, there is a wide range for concentrations of bupropion and its major metabolites, OHBUP and TB, in the maternal plasma at delivery. On the other hand, the inter-individual variability in the concentrations of bupropion, OHBUP and TB in maternal plasma of subjects who have been taking the same dose of the drug (Table 1) could be explained by one or more of the following: time of the last dose before delivery, bupropion formulation, or inter-individual variability in bupropion biodisposition.⁹ The availability of data regarding the time of the last dose before delivery was limited to fourteen subjects out of twenty-two (Table 1). However, the substantial differences in steady state plasma concentrations of bupropion and its metabolites among individuals are attributed to variability in bupropion metabolism.²¹ Bupropion is extensively biotransformed by the liver via oxidative and reductive pathways.¹² The formation of the primary active hepatic metabolite, OHBUP, is predominantly catalyzed by CYP2B6.⁹ The formation of TB and EB is catalyzed by hepatic 11 β -hydroxysteroid dehydrogenase 1 (11 β HSD1) and carbonyl reductases.²² In addition, CYP2C19 contributes to the metabolism of bupropion, and possibly TB and EB also.²³ Both CYP2B6 and CYP2C19 are highly polymorphic and gene variants in *CYP2B6* and *CYP2C19* have been associated with altered plasma concentrations of bupropion and its metabolites.^{21,23} Allelic frequencies of *CYP2B6* and *CYP2C19* differ by race and ethnicity.²⁴ The subjects in our study were predominantly

of white/non-Hispanic origin, which precluded stratification of our cohort of subjects by race/ethnicity. Furthermore, data from *in vitro* and *ex vivo* placental perfusion experiments suggested that human placenta metabolizes bupropion and that the major placental metabolite TB could be released into the maternal and fetal circulations.^{13,15} The active role of placenta in bupropion biodisposition could also play role in the extent of fetal exposure to the drug and its metabolites.

In the current investigation, the fetal-to-maternal (F:M) ratio for bupropion was determined for 18 subjects and ranged from 0.30 to 4.94, with the median F:M value being 0.53 (Table 1). For OHBUP, the F:M ratio ranged from 0.07 to 0.41 (median value was 0.21, n=18); and for TB, the F:M ratio ranged from 0.41 to 0.80 (median value was 0.61, n=21 subjects). The concentrations of OHBUP and TB in the umbilical cord venous plasma at delivery were invariably lower than in the corresponding maternal plasma. However, in four subjects (K, M, N, and V), the umbilical cord venous plasma concentrations of bupropion were higher than their corresponding concentrations in maternal plasma. This could be attributed in part to bupropion retention/accumulation by placenta and the following release of the drug from the placental tissue into the fetal circulation. Moreover, due to extensive hepatic biotransformation of bupropion, maternal clearance of bupropion is most likely higher than placental and fetal clearance of the drug, therefore, in instances when sufficient time from the last dose has passed, the concentrations of the drug in the fetal circuit could be higher than in maternal.²⁵

We observed correlations between the levels of bupropion, OHBUP and TB in matched umbilical cord venous and maternal plasma pairs (Figure 2). However, the concentrations of bupropion in 13 out of 18 maternal plasma samples were below 10 ng/ml, and for these subjects, no correlation was observed in the levels of bupropion in the matching cord-maternal plasma. Accordingly, it appears that the concentrations of bupropion metabolites, and to a lesser extent, the parent drug, in the fetal circulation could be predicted from their concentrations in maternal plasma. This conclusion is valid for term pregnancies and should not be extrapolated to earlier stages of pregnancy. Nevertheless, it should be noted that the median concentrations of OHBUP (103.6 ng/ml) and TB (59.6 ng/ml) in the umbilical cord venous plasma at delivery were higher than the concentrations of bupropion (5.3 ng/ml). Taken together, these data indicate that, in utero, the fetus could be primarily exposed to bupropion metabolites, which are pharmacologically less active than the parent drug.

The levels of bupropion, OHBUP and TB in umbilical cord arterial plasma were similar to those of their corresponding concentrations in umbilical cord venous plasma. Since we cannot exclude cross contamination of umbilical cord arterial blood with venous blood for some samples, no conclusions will be made at this time.

The amniotic fluid was collected from nine deliveries; this relatively small sample size was a limitation of our study that could potentially impact the interpretation of the results. Nevertheless, the levels of OHBUP in amniotic fluid (n=9) were similar to those in the umbilical cord venous plasma and were significantly lower than in maternal plasma (Table 2). However, this pattern was not observed between the concentrations of bupropion in the amniotic fluid, umbilical cord venous plasma and maternal plasma. Alternatively, the

concentrations of TB in the amniotic fluid were consistently higher than those in the umbilical cord and were either similar, or higher, than their levels in the corresponding maternal plasma.

At late gestation, fetal urine is produced at a rate of up to 1000 ml/day thus contributing to most of the volume and composition of the amniotic fluid.²⁶ The elimination of amniotic fluid occurs primarily by fetal swallowing at an estimated rate between 210 and 760 ml/day.²⁶ The swallowed amniotic fluid is either recycled through the fetal kidneys or is transferred to the maternal compartment via the umbilical cord artery and the placenta. Approximately 70% of the blood carried by the umbilical vein from the placenta enters the fetal hepatic circulation.²⁷ The expression of CYP2B6 and 11 β HSD1 has been detected in fetal liver, although at low levels.^{27,28,29} This suggests that bupropion ingested by the fetus with the amniotic fluid as well as that reaching the fetus via the umbilical blood supply, could undergo fetal hepatic clearance by its metabolic oxidative and reductive pathways. Furthermore, the observed higher concentrations of TB in the amniotic fluid than in the umbilical cord plasma could be explained by fetal reductive metabolism of bupropion.

In summary, data from our *in vivo* study demonstrated that maternally administered bupropion and its pharmacologically active metabolites cross term human placenta and appear in the fetal circulation. The concentrations of OHBUP and TB in umbilical cord venous plasma exceed those of bupropion suggesting a higher fetal exposure to bupropion metabolites, which are pharmacologically less active than the parent drug. Nevertheless, the levels of OHBUP, TB and bupropion (except for the above mentioned 4 subjects) in the umbilical cord plasma are lower than those in the maternal plasma. However, higher permeability of fetal blood brain barrier and the lower affinity of fetal plasma proteins to the drugs, could increase fetal exposure to the circulating drug and its metabolites.³⁰ Furthermore, our data suggest that continuous fetal exposure to bupropion and its active metabolites via recirculation of the amniotic fluid could occur. Further studies are needed to evaluate the effect(s) of bupropion, TB and OHBUP on the neonatal outcome of infants exposed to the drug and its metabolites *in utero*.

Acknowledgments

Financial support: The study was supported by R01 DA030998 to G.H. and T.N., and NICHD U10-HD47891 to G.H.

The authors appreciate the support of the physicians and nurses of the Labor & Delivery Ward of the UTMB, Galveston, TX and affiliated clinics in Pasadena, TX and Pearland, TX. We also appreciate the help of Erik Rytting who has contributed to revising the manuscript.

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Figure 1.
The individual umbilical cord venous plasma/maternal plasma ratios for bupropion and its metabolites. The lines connect the ratios obtained from a single subject. The dotted line at the ratio of 1.0 is provided for reference. BUP, bupropion; OHBUP, hydroxybupropion; TB, threohydrobupropion.¹ BUP and OHBUP not available.

Figure 2. The concentrations of bupropion (A), OHBUP (B) and TB (C) in the umbilical cord venous plasma against those in the maternal plasma. BUP, bupropion; OHBUP, hydroxybupropion; TB, threohydrobupropion; r , Pearson's correlation coefficient

Table 1

The concentrations of bupropion, OHBUP and TB in the corresponding umbilical cord venous plasma and maternal plasma

Subject ID	Age, years	Race/ethnicity	GA, weeks ^{days}	Bupropion dose,		Time between the last dose and delivery, hrs	Umbilical cord venous plasma (ng/ml)			Maternal venous plasma (ng/ml)			Umbilical cord venous plasma to maternal plasmaratio		
				mg	Frequency		BUP	OHBUP	TB	BUP	OHBUP	TB	BUP (n=18)	OHBUP (n=18)	TB (n=21)
A	32	White/non-Hispanic	37 ⁴	150	BID	12	4.5	204.6	168.3	8.0	497.2	289.9	0.56	0.41	0.58
B	23	White/non-Hispanic	37 ¹	150	BID	16	<LOD	<LLOQ	3.1	0.13	1.4	4.4	ND	ND	0.70
C	33	White/Hispanic	39 ⁰	150	BID	NA	<LOD	<LLOQ	6.4	0.22	1.5	9.8	ND	ND	0.65
D	38	White/non-Hispanic	36 ⁶	150	BID	10	15.9	205.8	111.9	29.0	687.4	190.9	0.55	0.30	0.59
E	38	White/non-Hispanic	39 ⁰	150	BID	29	2.5	125.5	45.0	5.9	565.6	77.0	0.42	0.22	0.59
F	25	White/non-Hispanic	39 ¹	150	BID	NA	<LOD	<LOD	<LOD	<LOD	<LOD	<LLOQ	ND	ND	ND
G	30	White/Hispanic	38 ²	150	BID	NA	0.24	0.83	6.6	0.4	4.4	10.4	0.53	0.19	0.63
H	30	Black/non-Hispanic	34 ⁵	150	BID	2	2.2	17.4	59.6	5.4	138.1	125.8	0.41	0.13	0.47
I	42	White/non-Hispanic	37 ⁵	300	QD	21	12.2	103.1	88.6	26.5	912.4	198.8	0.46	0.11	0.45
J	24	White/non-Hispanic	37 ³	300	QD	NA	20.4	150.5	198.0	36.4	716.6	323.8	0.56	0.21	0.61
K	25	White/non-Hispanic	40 ¹	300	QD	NA	6.2	249.1	244.5	1.8	780.7	359.5	3.48	0.32	0.68
L	42	White/Hispanic	38 ²	75	BID	25	0.91	44.7	18.6	1.8	172.5	28.7	0.50	0.26	0.65
M	31	White/Hispanic	36 ⁵	75	BID	45	6.1	108.9	219.5	1.2	536.7	360.6	4.94	0.20	0.61
N	29	White/non-Hispanic	37 ⁴	75	BID	NA	18.1	84.3	58.7	4.7	542.5	124.9	3.86	0.16	0.47
O	24	White/non-Hispanic	39 ²	150	QD	20	2.9	32.9	24.0	9.7	279.6	58.9	0.30	0.12	0.41
P	21	White/non-Hispanic	39 ⁰	150	QD	48	0.7	2.3	21.1	1.9	11.8	39.4	0.36	0.20	0.54
Q	25	White/non-Hispanic	39 ⁰	150	QD	48	14.3	282.6	239.7	28.6	1,180.9	378.2	0.50	0.24	0.63
R	28	White/non-Hispanic	39 ⁰	150	QD	4	28.5	104.2	66.2	53.7	366.7	90.4	0.53	0.28	0.73
S	39	White/non-Hispanic	39 ⁴	150	QD	30	3.8	115.2	90.7	4.4	362.3	143.9	0.86	0.32	0.63
T	22	White/Hispanic	37 ⁰	150	QD	NA	0.22	0.70	12.4	0.68	9.7	29.6	0.33	0.07	0.42
U	25	White/Hispanic	41 ²	100	QD	NA	<LOD	<LOD	0.4	<LOD	<LLOQ	0.5	ND	ND	0.80
V	23	White/non-Hispanic	38 ²	75	QD	43	6.8	84.3	72.8	5.3	482.7	97.3	1.29	0.17	0.75
Median	28.5		38 ⁴				5.3	103.6	59.6	5.0	424.7	97.3	0.53	0.21	0.61
IQR	42		41 ²				11.5	108.3	93.3	12.3	489.5	169.2	0.35	0.12	0.11

QD, once daily; BID, twice per day; GA, gestational age; NA, not available; ND, not determined; BUP, bupropion; OHBUP, hydroxybupropion; TB, threohydrobupropion; LLOQ, lower limit of quantification; LOD, lower limit of detection; IQR, interquartile range

Table 2

The concentrations of bupropion, OHBUP, and TB in the amniotic fluid and corresponding umbilical cord venous plasma and maternal plasma

Subject ID	Bupropion dose,		Bupropion, ng/ml			OHBUP, ng/ml			TB, ng/ml		
	mg	Frequency	Umbilical cord venous plasma	Amniotic fluid	Maternal plasma	Umbilical cord venous plasma	Amniotic fluid	Maternal plasma	Umbilical cord venous plasma	Amniotic fluid	Maternal plasma
C	150	BID	<LOD	<LOD	0.2	<LLOQ	<LLOQ	1.5	6.4	13.9	9.8
D	150	BID	15.9	48.0	29.0	205.8	185.2	687.4	111.9	399.4	190.9
E	150	BID	2.5	3.0	5.9	125.5	72.0	565.6	45.0	101.2	77.0
I	300	QD	12.2	13.3	26.5	103.1	123.2	912.4	88.6	157.1	198.8
J	300	QD	20.4	27.6	36.4	150.5	104.6	716.6	198.0	339.5	323.8
L	75	BID	0.9	1.9	1.8	44.7	38.8	172.5	18.6	63.6	28.7
O	150	QD	2.9	8.6	9.7	32.9	40.0	279.6	24.0	112.5	58.9
P	150	QD	0.7	0.7	1.9	2.3	1.2	11.8	21.1	52.7	39.4
Q	150	QD	14.3	14.1	28.6	282.6	77.3	1,180.9	239.7	291.0	378.2
Median			7.6	10.9	9.7	114.3	74.6	565.6	45.0	112.5	77.0
IQR			12.6	14.8	26.8	122.5	69.5	544.1	90.8	227.4	159.3

QD, once daily; BID, twice per day; OHBUP, hydroxybupropion, TB, threohydrobupropion; LLOQ, lower limit of quantification; LOD, lower limit of detection; IQR, interquartile range