

Analyzing the Association Between Single Nucleotide Polymorphisms and Combinations of Buprenorphine and Associated Metabolite Concentrations

Amelia Monfared¹, Melissa Hoang¹, Derek E. Murrell², Darshan S. Shah³, Stacy D. Brown⁴, Cara L. Carter⁴, Lauren E. Dickerson⁴, and Sam Harirforoosh¹

¹School of Pharmacy, Chapman University, Irvine, CA

²Crown Laboratories, Johnson City, TN

³Quillen College of Medicine, East Tennessee State University, Johnson City, TN

⁴Gatton College of Pharmacy, East Tennessee State University, Johnson City, TN



Statement of Purpose

As the opioid crisis continues to be a problem among pregnant women in the United States, the prevalence of neonatal abstinence syndrome (NAS) consequently continues to cause troublesome effects. To reduce the incidence of NAS, pregnant women receive medicated-assisted treatments, preferably buprenorphine (BUP). However, BUP has risks of fetal toxicity [1]. When metabolized, BUP produces several biologically active metabolites, including norbuprenorphine (NBUP), buprenorphine-3-glucuronide (BUP-Gluc), and norbuprenorphine-3-glucuronide (NBUP-Gluc) [2]. Previously, we reported significant associations of several single nucleotide polymorphisms (SNPs) with individual concentrations of BUP or its metabolites. However, there is currently limited data on the association between particular SNPs with BUP in combination with its metabolites or a combination of metabolites. In this subsection study, BUP and its metabolites were tested to determine the association between observed SNPs and various concentration combinations.

Description of Methods

The prospective observational cohort study investigated the utilization of BUP in pregnant women and its impact on newborns. Neonates were closely monitored for NAS, with appropriate measures taken to ensure their well-being. With maternal consent, fetal umbilical cord blood samples were collected and analyzed for BUP and its metabolites via LC-MS. In this study, an iPLEX ADME PGx, Pro V1.0 panel was used to genotype 15 samples. Relationships between SNPs and concentrations were assessed using the PLINK v1.7 software program, with statistical significance set at $p < 0.05$. Concentration values are reported as mean \pm standard deviation.

Data & Results

Fourteen unique SNPs were identified to be significant ($p < 0.05$) across the concentration combinations tested (Table 1). Of these, six were associated with BUP + BUP-Gluc (22.24 \pm 11.29 ng/mL): rs1801265, rs4124874, rs2273697, rs4149117, rs7311358, and rs7294. Four SNPs (rs55785340, rs4244285, rs762551, and rs35742686) were found to be associated with BUP + NBUP (22.08 \pm 8.28 ng/mL).

Table 1. SNPs that are significantly associated with drug and metabolite concentration

Drug	Gene	SNP	BP ^a	A1 ^b	MAF ^c	HWE ^d	Beta (95% CI) ^e	P-value
BUP + BUP-Gluc	UGT1A1	rs4124874	234665659	C	0.467	0.503	12.32 (5.50 to 19.15)	0.005
	VKORC1	rs7294	31102321	A	0.433	0.843	-13.52 (-21.25 to -5.79)	0.006
	CYP2B6	rs3745274	41512841	G	0.467	0.503	11.46 (4.14 to 18.78)	0.011
	ABCC2	rs2273697	101563815	A	0.233	1.000	10.54 (3.25 to 17.84)	0.016
	SLCO1B3	rs4149117	21011480	T	0.167	1.000	14.59 (4.53 to 24.66)	0.016
	SLCO1B3	rs7311358	21015760	G	0.167	1.000	14.59 (4.53 to 24.66)	0.016
	VKORC1	rs9934438	31104878	A	0.267	0.563	-17.27 (-31.79 to -2.76)	0.040
	VKORC1	rs9923231	31107689	T	0.267	0.563	-17.27 (-31.79 to -2.76)	0.040
	BUP + NBUP	CYP3A4	rs55785340	99365983	G	0.036	1.000	21.24 (8.37 to 34.10)
CYP2C19		rs4244285	96541616	A	0.143	1.000	11.01 (2.79 to 19.23)	0.025
BUP-Gluc + NBUP-Gluc	UGT1A1	rs4124874	234665659	C	0.467	0.503	19.00 (6.03 to 31.97)	0.015
	SLCO1B3	rs4149117	21011480	T	0.167	1.000	24.73 (7.27 to 42.20)	0.018
	SLCO1B3	rs7311358	21015760	G	0.167	1.000	24.73 (7.27 to 42.20)	0.018
	ABCC2	rs2273697	101563815	A	0.233	1.000	17.64 (4.87 to 30.42)	0.020
	VKORC1	rs7294	31102321	A	0.433	0.843	-18.91 (-34.41 to -3.41)	0.036
	ABCC2	rs3740066	101604207	A	0.300	0.721	-13.34 (-24.57 to -2.10)	0.040
	VKORC1	rs9934438	31104878	A	0.267	0.563	-28.80 (-54.10 to -3.49)	0.048
NBUP + NBUP-Glu	CYP2C19	rs4244285	96541616	A	0.143	1.000	21.35 (7.65 to 35.05)	0.012
	CYP2C8	rs1058930	96818119	G	0.100	1.000	21.95 (3.27 to 40.64)	0.042
BUP-Gluc + NBUP + NBUP-Gluc	UGT1A1	rs4124874	234665659	C	0.467	0.503	22.39 (5.94 to 38.84)	0.022
	VKORC1	rs7294	31102321	A	0.433	0.843	-22.68 (-42.00 to -3.35)	0.042
	CYP2C19	rs4244285	96541616	A	0.143	1.000	25.72 (3.89 to 47.56)	0.044
BUP + BUP-Gluc + NBUP + NBUP-Gluc	UGT1A1	rs4124874	234665659	C	0.467	0.503	22.39 (5.94 to 38.84)	0.022
	VKORC1	rs7294	31102321	A	0.433	0.843	-22.68 (-42.00 to -3.35)	0.042
	CYP2C19	rs4244285	96541616	A	0.143	1.000	25.72 (3.89 to 47.56)	0.044

BUP: buprenorphine; BUP-Gluc: buprenorphine-glucuronide; NBUP: norbuprenorphine; NBUP-Gluc: norbuprenorphine-glucuronide. ^aPhysical position (bp); ^bMinor allele; ^cMinor allele frequency overall; ^dp-value for Hardy-Weinberg equilibrium test; ^eBeta adjusted for covariates (birth weight and maternal drug dose)

Data & Results – Continued

Cumulative BUP-Gluc + NBUP-Gluc (41.80 \pm 24.32 ng/mL) was associated with rs1801265, rs4124874, rs1143672, rs2273697, rs3740066, rs4149117, rs7311358, and rs3745274. The NBUP + NBUP-Glu combination (41.62 \pm 19.16 ng/mL) was associated with rs4244285 and rs1058930. The combination of BUP-Gluc + NBUP + NBUP-Gluc (57.59 \pm 25.21 ng/mL) was found to be associated with rs1143672. Finally, the combination of BUP + BUP-Gluc + NBUP + NBUP-Gluc (60.94 \pm 28.08 ng/mL) was associated with rs1801265, rs4124874, rs1143672, rs2273697, rs3740066, rs4149117, rs7311358, rs3745274.

Conclusion

Our study revealed relationships between polymorphism and detected drug and metabolite concentration combinations. This highlights the importance of pharmacogenetics in assessing the correlation between combined drug and metabolite concentrations, SNPs, and overall usage of BUP during pregnancy. More research is needed to investigate the clinical influence of certain SNPs which might be linked to NAS.

References

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Conflict of Interest

The author declares no conflict of interest.