Null Results in Brief

CYP2B6 Genotype Does Not Alter Nicotine Metabolism, Plasma Levels, or Abstinence with Nicotine Replacement Therapy

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Introduction

CYP2A6 metabolically inactivates nicotine to cotinine and further metabolizes cotinine to 3-hydroxycotinine (1, 2). Genetically slow CYP2A6 activity reduces the rate of nicotine metabolism (3), reduces the 3’-trans-hydroxycotinine/cotinine (3HCOT/COT) ratio (a phenotypic measure of CYP2A6 activity ref. 4), decreases cigarettes smoked per day (4-6), increases the likelihood of quitting smoking (7), and results in higher plasma nicotine levels and abstinence among individuals receiving nicotine patch therapy (4, 8).

CYP2B6 can also metabolize nicotine but with lower affinity (9, 10); it may contribute to nicotine metabolism that is not mediated by CYP2A6 (1). Recently, the CYP2B6*6 allele was found to be associated with increased rates of nicotine and cotinine metabolism among CYP2A6 reduced metabolizers (ref. 11; defined as <75% of normal activity; ref. 3) and the CYP2B6*4 allele was associated with higher 3HCOT/COT ratios (12), suggesting that CYP2B6 may contribute to nicotine metabolism, at least where CYP2A6 activity is slower. We investigated whether the CYP2B6*6 and CYP2B6*4 alleles alter the baseline 3HCOT/COT ratio, plasma nicotine levels from nicotine patch and nasal spray, and quit rates following treatment with nicotine patch and nasal spray among smokers with CYP2A6 gene variants known to be associated with normal or reduced nicotine-metabolizing activity.

Materials and Methods

This analysis includes 369 participants of European ancestry (patch, 176; nasal spray, 193); details were previously published (4, 8). Baseline variables included plasma nicotine, cotinine and 3-hydroxycotinine, smoking history, demographics, and the Fagerström Test for Nicotine Dependence (13). Plasma nicotine and cotinine were assessed at baseline for all participants and at 1 week after the quit date for all participants verified by breath CO to be abstinent (136 patch, 127 spray). Abstinence was measured as 7-day point prevalence (biochemically verified by CO < 10) at the end of treatment and the 6-month follow-up. All P values are two tailed. We had 80% power to detect a difference of 0.08 in the 3HCOT/COT ratio in all smokers and a difference of 18% in abstinence rate at end of treatment within each treatment arm at P = 0.05.

CYP2B6 haplotyping methods have previously been reported (14). CYP2A6 genotypes were previously assessed (4). Seven participants with a CYP2B6*4/*6 genotype and two participants with the CYP2A6*1XN duplication allele were omitted. Participants were classified into CYP2B6*1 (CYP2B6*1/*1), CYP2B6*4 (CYP2B6*1/*4 and CYP2B6*4/*4), and CYP2B6*6 (CYP2B6*1/*6 and CYP2B6*6/*6) groups. Participants were classified into two predicted CYP2A6 activity groups (3): CYP2A6 normal metabolizers (CYP2A6 NM; 100% activity, no variants) and CYP2A6 reduced metabolizers (CYP2A6 RM; <75% activity; ref. 11). Linkage disequilibrium between CYP2A6 and CYP2B6 alleles was assessed with Haploview 3.32.

Results

The CYP2A6 NM and CYP2A6 RM groups consisted of 77% and 23% of the population, respectively. The CYP2B6*1, CYP2B6*4, and CYP2B6*6 groups consisted of 50%, 4%, and 46% of the population, respectively. The allele frequencies for CYP2B6*4 and CYP2B6*6 were 0.02 and 0.28, respectively, and both were in Hardy-Weinberg equilibrium (P = 0.99 and P = 0.27, respectively). There was no significant linkage disequilibrium between the CYP2A6*2, CYP2A6*4, CYP2A6*9, and CYP2A6*12 alleles with CYP2B6*6 or CYP2B6*4 (D’ = 0.00-1.00; logarithm of odds = 0.01-1.38; r² = 0.00-0.06).

Consistent with previous data on CYP2A6 slow metabolizers (defined as <50% of normal activity; ref. 4), the CYP2A6 RM group had significantly higher values than the CYP2A6 NM group on baseline 3HCOT/COT ratio [t(289) df = 2.43, P = 0.016] and plasma nicotine during patch treatment [t(134) df = 3.39, P = 0.001] but not during nasal spray treatment [t(125) df = 0.50, P = 0.62].
There were no differences in baseline 3HCOT/COT by CYP2B6 genotype among all participants [F(2, 288) = 1.87, P = 0.16], the CYP2A6 NM group [F(2, 227) = 0.78, P = 0.46], or the CYP2A6 RM group [F(2, 58) = 1.80, P = 0.18; Fig. 1A]. There were no significant differences by CYP2B6 genotype in baseline Fagerström nicotine dependence, cigarettes per day, CO levels, and plasma nicotine and cotinine levels.

Among nicotine patch participants who were abstinent 1 week after the quit date (n = 136), there were no differences in steady-state plasma nicotine or cotinine levels by CYP2B6 genotype among all participants [F(2, 133) = 0.54 and 0.68, P = 0.71 and P = 0.51], the CYP2A6 NM group [F(2, 103) = 0.15 and 0.24, P = 0.86 and P = 0.79], or the CYP2A6 RM group [F(2, 27) = 0.07 and 0.49, P = 0.94 and P = 0.62; Fig. 1B]. Similar results were seen in the nicotine nasal spray arm (n = 127), with no differences in plasma nicotine and cotinine levels by CYP2B6 genotype among all participants [F(2, 124) = 1.01 and 0.13, P = 0.37 and P = 0.89], the CYP2A6 NM group [F(2, 98) = 1.30 and 0.17, P = 0.28 and P = 0.85], or the CYP2A6 RM group [F(2, 23) = 0.24 and 0.47, P = 0.79 and P = 0.63]. The CYP2B6*4 group was omitted from abstinence analyses due to low numbers (n = 15). In the nicotine patch arm, there were no differences in abstinence rates at end of treatment or at 6-month follow-up between CYP2B6*1 and CYP2B6*6 groups among all participants [χ²(1 df) = 0.00 and 0.37, P = 0.99 and P = 0.54], the CYP2A6 NM group [χ²(1 df) = 0.00 and 0.33, P = 0.99 and P = 0.56], or the CYP2A6 RM group [χ²(1 df) = 0.00 and 0.03, P = 0.97 and P = 0.86; Fig. 2]. In the nicotine nasal spray arm, no differences in abstinence rates were seen between the CYP2B6*1 and CYP2B6*6 groups at end of treatment or at 6-month follow-up among all participants [χ²(1 df) = 0.07 and 0.34, P = 0.79 and P = 0.56], the CYP2A6 NM group [χ²(1 df) = 0.41 and 0.01, P = 0.52 and P = 0.91], or the CYP2A6 RM group [χ²(1 df) = 0.42 and 1.49, P = 0.52 and P = 0.22].

Discussion

The 3HCOT/COT ratio (15) and plasma nicotine levels (5) are previously reported in ref. 14 with additional subjects genotyped in this study and are shown for comparison. White columns, CYP2B6*1 group; gray columns, CYP2B6*6 group.

Figure 2. Abstinence rates at end of treatment (EOT) and the 6-mo follow-up (6MO) were not significantly different between the CYP2B6*1 and CYP2B6*6 groups in the nicotine patch and nicotine nasal spray. The bupropion and placebo treatment arms were not significantly different between the CYP2B6*1 and CYP2B6*6 groups among all smokers, CYP2A6 genotype in nicotine patch participants who were abstinent 1 week after the quit date (n = 136), and plasma nicotine and cotinine levels by CYP2A6 genotype among all participants [F(2, 103) = 0.15 and 0.24, P = 0.86 and P = 0.79], or the CYP2A6 RM group [F(2, 27) = 0.07 and 0.49, P = 0.94 and P = 0.62; Fig. 1B].

In summary, CYP2B6 genotype does not alter nicotine metabolism, as indicated by nicotine levels from patch or the baseline 3HCOT/COT ratios even among CYP2A6 RM, nor does CYP2B6 genotype affect smoking behaviors or response to nicotine replacement therapies.

References


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