



Letter

Influence of β_2 -adrenoceptor 16 genotype on propranolol-induced bronchoconstriction in patients with persistent asthma

Polymorphic variants of the 16th amino acid position on the β_2 -adrenoceptor (B2ADR) have previously been found to influence asthma outcomes on exposure to regular β_2 -agonist therapy.^{1–3} In particular the arginine-16 allele (ie, ArgArg or ArgGly) is known to predispose patients to agonist-induced B2ADR down-regulation and associated response subsensitivity.^{4,5}

We have recently completed 2 separate randomized, placebo-controlled trials, examining the long-term dosing effects of propranolol added to inhaled corticosteroids for persistent asthma⁶ (W.J.A. et al, unpublished data, June 2013). Although we observed no changes in airway hyperresponsiveness in either trial, propranolol caused small but significant decreases in forced expiratory volume in 1 second (FEV₁) and partially attenuated FEV₁ recovery to albuterol rescue after histamine challenge. We then hypothesized that the B2ADR genotype may help identify those asthmatic patients who might fare worse in terms of propranolol-induced bronchoconstriction and hence facilitate safer prescribing.

We, therefore, performed a retrospective post hoc analysis of 25 inhaled corticosteroid-treated patients with mild to moderate asthma pooled from both propranolol trials who had given consent for their B2ADR genotype to be analyzed. We evaluated the effects of propranolol given for at least 4 weeks (maximum dose of 80 mg for at least 2 weeks) on pulmonary function (FEV₁, forced expiratory flow between 25% and 75% [FEF_{25%-75%}], and total airway resistance at 5 Hz using impulse oscillometry [R5]) and on albuterol FEV₁ recovery after histamine challenge. Comparisons were made between genotypes comprising at least 1 copy of Arg-16 (ie, ArgArg or ArgGly, n = 15, mean FEV₁ = 91.1%, mean FEF_{25%-75%} = 58.3%) vs no copies of Arg (ie, GlyGly, n = 10, mean FEV₁ = 94.1%, mean FEF_{25%-75%} = 60.0%). No significant baseline differences were found between groups for age, sex, spirometry, or impulse oscillometry indices.

Within the Arg-16 genotype there were significant effects of propranolol on FEV₁, FEF_{25%-75%}, and R5, as well as significant blunting of albuterol response, whereas in the Gly-16 genotype only the albuterol response was significantly affected (Table 1). However, when comparing the Arg-16 and Gly-16 genotypes, no significant differences were seen, which may simply reflect the post hoc nature of this analysis. Moreover, one would expect to see a greater degree of propranolol-induced bronchoconstriction after first-dose exposure compared with long-term dosing. However, we cannot dismiss the significant trend for a difference between genotypes for FEF_{25%-75%} at $P = .06$, particularly given that this is a small sample, post hoc analysis.

Trial Registration: clinicaltrials.gov Identifiers: NCT01544634 and NCT01074853.

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Table 1

Propranolol-induced pulmonary function changes by B2ADR genotype^a

Variable	ArgArg or ArgGly		GlyGly		Genotype comparison P value
	Mean (SEM) change from baseline	P value	Mean (SEM) change from baseline	P value	
FEV ₁ , %	−3.9 (1.2)	.006	−2.3 (3.4)	.51	.66
FEF _{25%-75%} , %	−5.2 (2.1)	.02	+2.0 (3.2)	.55	.06
R5, %	+17.1 (5.2)	.003	+5.7 (9.3)	.57	.27
Recovery FEV ₁ , %	−14.3 (3.0)	<.001	−8.4 (2.8)	.01	.18

Abbreviations: FEF_{25%-75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; R5, total airway resistance at 5 Hz using impulse oscillometry.

^aPaired t tests were used for within-genotype comparisons and unpaired t tests for between-genotype comparisons. The β_2 -adrenoceptor 16 genotypes were homozygous ArgArg or heterozygous ArgGly (n = 15) and homozygous GlyGly (n = 10). A decrease in FEV₁ or FEF_{25%-75%} or an increase in R5 indicates bronchoconstriction after propranolol. Recovery of FEV₁ follows nebulized albuterol, 5 mg (after histamine challenge) (ie, a more negative value indicates greater blunting of the response).

We believe that larger prospective genotype-enriched studies are required to further characterize the safety of cardioselective and nonselective β -blockers in persistent asthma, in turn moving toward more personalized prescribing.

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