Correlations between Methylldopa administration and norepinephrine levels in 14 outpatient psychiatric patients: A retrospective chart review

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Abstract

Overactive sympathetic nervous system activity may underlie many psychiatric conditions (e.g., excess catecholamines are suspected to underlie mania) and therefore should be considered when approaching treatment options. Methylldopa, a centrally acting α2 agonist that decreases production of the neurotransmitters involved in the sympathetic nervous system, became an experimental treatment of interest for certain psychiatric conditions. On the other side of the metabolic pathway, failure to break down catecholamines effectively can lead to an excess of them. One possible cause for excess catecholamines are mutations in the genes that code for enzymes involved in their catabolism. This retrospective chart review analyzed 14 patients at an outpatient psychiatric practice who received methylldopa as treatment for hypernorepinephrinemia in order to determine if significant correlations existed between methylldopa administration and changes in catecholamine levels in these patients. Out of 14 patients, 1 patient experienced a statistically significant negative correlation between methylldopa administration and catecholamine levels. The remaining 13 patients either experienced no significant change (n = 12) or a statistically significant positive correlation (n = 1). To explore why methylldopa did not succeed in effectively reducing norepinephrine levels, we examined the genomic profiles of 9 patients within this cohort who displayed non-negative slopes in their norepinephrine trend lines. Specifically, we looked for SNPs in MAO and COMT, which are two of the major genes involved in the metabolic breakdown of norepinephrine. We compared allele frequencies of 34 different SNPs within these 9 patients to that of the general population (via the gnomAD database) and found 4 SNPs of potential interest for further research. These results indicate the need for a careful approach when considering alternative treatment methods such as methylldopa for psychiatric conditions that are related to high norepinephrine levels.

Methods

Methylldopa is a centrally acting α2 agonist traditionally used for the management of hypertension (1). Methylnorepinephrine, the active metabolite of the drug, exerts its effects by stimulating negative feedback mechanisms by way of α2 receptor agonism in the central nervous system leading to decreased catecholamine signaling and thus decreased sympathetic nervous system activity (2).

Overactivation of the sympathetic nervous system is thought to underlie many psychiatric conditions (3) including depression and bipolar disorder (4). MAO-A, MAO-B, and COMT are all enzymes implicated in catecholamine metabolism (5, 6) with research revealing genetic polymorphisms that cause altered metabolism as well as documented behavioral and physiological symptoms (7), with consumer genetic reports becoming increasingly available and affordable to the public at large, reports such as the MTHFR Support Variant Analysis provide unique opportunities to screen patients for genetic polymorphisms that influence the choice of drug therapy.

This retrospective chart review analyzed 14 patients (average age 64.29 ± 17.67 years; 4M, 10 F) at an outpatient psychiatric practice that were treated with methylldopa for hypernorepinephrinemia. Inclusion criteria for consideration in this study was that the patient had a psychiatric diagnosis, was being treated with methylldopa, had labs tracking their catecholamines over time, and had a MTHFR Support Variant analysis in their chart with information on their MAO and COMT polymorphisms.

We used point-biserial correlation testing to assess statistical significance (significance level of 0.05) of the slopes of norepinephrine trend lines over time. Amongst patients (n = 9) where methylldopa was ineffective, we compared allele frequencies of 34 different SNPs with those of the general population using the Genome Aggregation Database (gnomAD), measured with a Fisher Exact test and a Bonferroni correction.

Results

The observed trend of catecholamine levels in these patients was paradoxically high, with only one participant showing the theorized decrease in catecholamine levels with methylldopa administration. One explanation could be that certain psychiatric disorders skew baseline catecholamine levels. Bipolar Disorder, Generalized Anxiety Disorder, and PTSD are associated with elevated catecholamine levels on 24-hr urine analysis (8). A meta-analysis of existing literature of catecholamine-cholinergic hypothesis studies showed elevated catecholamine levels in relation with anxiety disorders (9).

Amongst the patients where methylldopa did not have a downward trend line (n = 9), 4 different SNPs had a frequency that was different than that of the general population: rs933277 (p = .0399), rs757666 (p = .00653), rs714699 (2.966-9), and rs1021432 (p = .00927). In particular, rs714699 actually had a statistically significantly lower frequency than the general population.

Conclusions

Across 14 patients, 5 had a trend line with a negative slope, while 9 had a positive slope.

Figure 1. Norepinephrine curves over time for three patients on methylldopa. Case D (left) shows an increase over time, Case M (middle) shows a steady oscillation over time, and Case E (right) shows a decrease over time.

Figure 2. Slopes of trend lines present in 14 patients norepinephrine levels over time while on methylldopa.

After Point-Biserial correlation testing was performed on the slopes using p<0.05 as a threshold for statistical significance, only Case B (negative correlation) showed a significant negative correlation between methylldopa and norepinephrine levels.

Figure 3. A comparison of allele frequencies in 34 different SNPs for COMT and MAO between those where methyldopa was ineffective (had non-negative slope) at decreasing NE and the general population.

References

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