Correlations between Methyldopa 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. Methyldopa, 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 methyldopa as treatment for hypernorepinephrinemia in order to determine if significant correlations existed between methyldopa administration and changes in catecholamine levels in these patients. Out of 14 patients, 1 patient experienced a statistically significant negative correlation between methyldopa 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 methyldopa 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 methyldopa for psychiatric conditions that are related to high norepinephrine levels.

Introduction

Methyldopa is a centrally acting α2 agonist traditionally used for the management of hypertension (1). Methylnoradrenaline, 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.

Methods

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 methyldopa for hypernorepinephrinemia. Inclusion criteria for consideration in this study was that the patient had a psychiatric diagnosis, was being treated with methyldopa, 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.

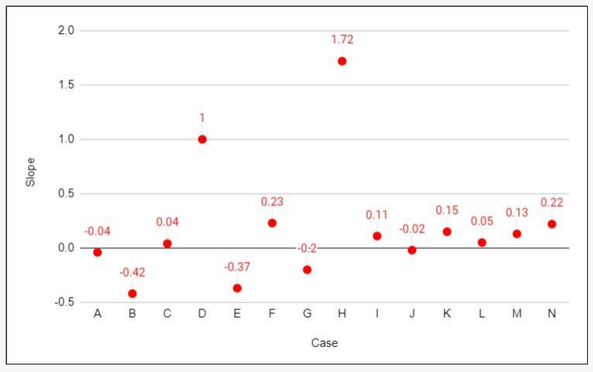
We used point-biserial correlation testing to assess statistical significance (significance level of 0.05) of the slopes of norepinephrine trend lines over time. Amongst patients (*n* = 9) where methyldopa was ineffective, we compared allele frequencies of 34 different SNPs with those of the general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

Results

Figure 1. Norepinephrine curves over time for three patients on methyldopa. 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.

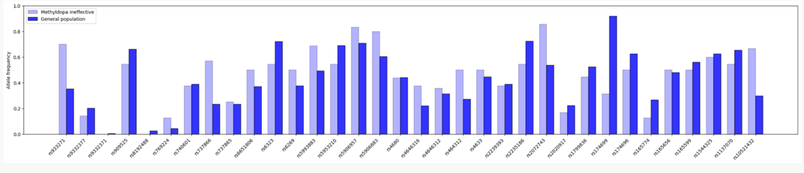
Across 14 patients, 5 had a trend line with a negative slope, while 9 had a positive slope.

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



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 methyldopa 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.



Amongst the patients where methyldopa did not have a downward trend line (*n* = 9), 4 different SNPs had a frequency that was different than that of the general population: *rs933271* (p = .03993), *rs737866* (p = .006513), *rs174699* (2.96e-9), and *rs10521432* (p = .009027). In particular, *rs174699* actually had a statistically significantly lower frequency than the general population.

Conclusions

The observed trend of catecholamine levels in these patients was paradoxically high, with only one participant showing the theorized decrease in catecholamine levels with methyldopa 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).

A majority of our study participants had at least one of three aforementioned ICD codes, which may have contributed to elevated catecholamine levels even in the presence of a centrally acting alpha-2 agonist. Further research could explore the catecholamine/disease correlation to a more statistically significant degree, and analyze its response to various drug treatments. Additionally, there is evidence of methyldopa serving as a precursor of methylnoradrenaline/methylnorepinephrine in the body. Dopamine is converted to noradrenaline, and therefore treatment with methyldopa results in depletion of noradrenaline stores in the tissues. This ultimately can lead to lower blood pressure especially in such patients with preexisting hypertensive conditions. A prior study highlights a patient being treated with methyldopa that showed an increased excretion of norepinephrine (14); this can be further investigated as a different pathway of methyldopa. This methylated version of noradrenaline/norepinephrine could be considered as a confounding variable in the catecholamine labs that were ordered to assess patient dopamine and norepinephrine levels.

Another possible explanation for these results is a drug interaction between methyldopa and other psychoactive pharmaceuticals. Prior research demonstrates a slowing of Lithium clearance when taken alongside methyldopa (10). Research shows that Lithium toxicity increases norepinephrine (NE) levels in the synapses of the central nervous system by inhibiting the norepinephrine-sensitive adenylate cyclase (11). Increased NE levels are proposed to be the therapeutic mechanism of action of lithium-containing medications (12). So, methyldopa may enhance lithium efficacy and duration, leading to an increase in baseline catecholamines. In the future, we hope to collect data on the medications each patient in our sample was taking, research the drug interactions present, and observe whether the results display a significant pattern.

A third potential confounder is the multitude of SNP polymorphisms in catecholamine metabolism. These variations could explain the unorthodox response to methyldopa and potentially other psychoactive drugs. With genetic testing becoming cheaper and more ubiquitous, this could be a very important avenue to explore when it comes to the dosing and selection of pharmaceutical psychotherapy (10). By screening uncommon alleles, we would be able to identify which diseases the patient is at risk for as well as what medication would be most effective in treating them (11). We would be able to minimize the trial-and-error strategy of determining the best medication and dose for the patient and would allow us to personalize each patient's plan based on their polymorphisms.

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