Midodrine Efficacy in Orthostatic Hypotension

W. Singer, MD[1], M. J. Joyner, MD[2], P. Sandroni, MD, PhD[1], E. E. Benarroch, MD[1], R. D. Fealey, MD[1], J. Mandrekar, PhD[3], and P. A. Low, MD[1]

[1]Department of Neurology, Mayo Clinic, Rochester, MN, USA; [2]Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA; [3]Department of Biomedical Statistics, Mayo Clinic, Rochester, MN, USA.

J Gen Intern Med 29(11):1440–1
DOI: 10.1007/s11606-014-3014-7

To the Editors—We recently came across the review article by Parsaik et al. "Midodrine for Orthostatic Hypotension: A Systematic Review and Meta-Analysis of Clinical Trials" (J Gen Intern Med 28(11): 1496–503), and feel obligated to comment on several deficiencies of this work. Unfortunately, the article was published under the Mayo Clinic name by former trainees without expert supervision, since none of the autonomic experts at Mayo who author this letter were in any way involved in conducting the study or guiding its interpretation. The deficiencies are major and reflect poorly on Mayo Clinic investigators. Furthermore, this article needs rectification—both of content and interpretation—to avoid potential damage to the future of the first US Food and Drug Administration (FDA)-approved and arguably single most efficient pharmacologic intervention for orthostatic hypotension (OH) to date.

First, the article has a main focus on the effect of midodrine on the orthostatic change in blood pressure (delta BP from supine to standing). This focus reflects an apparent misconception of autonomic pharmacology. Midodrine is a prodrug that is hydrolyzed to its active metabolite desglymidodrine, a pure alpha-1 agonist, resulting in arteriolar and venular constriction, which has the same effect on supine and standing BP.[1] It is NOT expected to selectively increase standing BP (or affect delta BP), which has never been used as primary trial endpoint, and therefore cannot be used as a primary focus of a meta-analysis.

Second, meta-analyses are typically undertaken when a treatment of interest has been studied, but the findings are equivocal or negative. The rationale is that a combination of comparable studies might improve power. In this paper, the studies are far from comparable. Nine studies are included in this meta-analysis. The studies range from small open-label case series to large double-blind, placebo-controlled multicenter trials. Trial design ranges from simple pre-post assessments, parallel group design, and crossover trials to pharmacologic dose–response studies. The studies are inhomogeneous in terms of primary endpoints, orthostatic challenge (45-degree head-up tilt versus active standing), patient population (young familial dysautonomia cohort versus neurodegenerative patient cohorts), as well as definition of OH. Those data simply cannot be meaningfully pooled.

Third, the four double-blind, placebo-controlled trials on midodrine in OH were pooled for an assessment of the actual variable of interest, the effect on standing BP. In spite of the different trial designs, all four trials reported midodrine to significantly increase standing BP in patients with neurogenic OH (all $p < 0.002$). [2–5] Due to "significant heterogeneity" of the effect, the evidence for midodrine improving standing BP was rated as "low." When marked trial design differences exist (trials with 171 versus trials with eight patients; parallel-group versus cross-over studies; differences in dosing; differences in timing of effect assessment—three trials assess the drug-effect one hour after administration, while one trial averages hourly measurements throughout the day without specific timing relative to administration), it would be most adequate to conclude that a meta-analysis is not appropriate, and that the available evidence is better assessed by considering each study independently, since the apparent heterogeneity merely reflects the combination of trials that should not have been combined. Each trial concluded that midodrine is an effective treatment for OH, and each trial documented—beyond a significant increase in standing BP—associated improvement in symptoms and/or functional capacity. A meta-analysis that comes to the opposite conclusion based on those same trials has to be flawed.

Fourth, there are numerous smaller errors that further emphasize the low quality of this review. The studies by Schrage and Axelrod are described as being performed "in 23 patients who received placebo and midodrine separated by a wash out period"—neither of these studies used placebo or a wash out period, both were simple pre/post-dose assessments.[6,7] Among the nine studies included in the meta-analysis, between two and four studies were included for pooling the different endpoints, although data would have been available from more of these studies for each endpoint. As outlined above, pooling data from these highly inhomogeneous studies is a mistake regardless, yet it is entirely unclear why some studies were chosen for pooling data for one endpoint, and others for another endpoint, although the information was similarly available for both. Of particular concern is also the uncritical inclusion of apparent outliers. For example, in the

Published online September 9, 2014

(inappropriate) assessment of systolic BP change from supine to standing, three studies show, as expected, no difference or a mildly decreased BP drop comparing placebo/baseline and midodrine, while one study (Jankovic et al.) shows an apparent large increase in the BP drop following midodrine compared to placebo (30mmHg).[3] Careful analysis would have revealed that this parallel group study was problematic, due to marked baseline differences between the placebo and the 10 mg midodrine group. Baseline (pre-medication) evaluations revealed an average systolic BP drop of only 33 mmHg in the placebo group versus an average systolic BP drop of 67 mmHg in the 10 mg midodrine group, which accounts for and readily explains the difference after medication, which was 28 mmHg in the placebo group and 58 mmHg in the midodrine group. Considering this baseline difference, the study findings are well in line with the other studies, but the authors conclude "effect heterogeneity."

Fifth, the authors find that midodrine caused a higher incidence of adverse events than placebo. That really should not be surprising, as side effects that include pilomotor erection, pruritus, urinary hesitancy, and supine hypertension are well known, widely and homogeneously described, and all are directly attributable to pharmacologic effects of an alpha-adrenergic agonist.[1] Rather than advising caution in the light of these side-effects, it would have been most appropriate to consider the universal expert conclusion of the trials that were reviewed, that "the side-effect profile indicates that midodrine is safe and well tolerated in patients with autonomic insufficiency." Because it does not cross the blood–brain barrier, midodrine has none of the central side-effects observed with other sympathomimetic agents, and due to its alpha-1 selectivity, it does not directly affect cardiac function.[1] Midodrine is generally well tolerated and side effects are generally only a mild inconvenience to patients. Due to the short half-life of desglymidodrine of 3–4 hours, adequate timing of dosing, avoiding doses prior to recumbency/nighttime, can further increase the safety margin of this medication and further lessen concerns over supine hypertension. Side effects need to be considered in the context of the risk/benefit ratio of a medication for a specific indication—considering the severity of symptoms, the often severely limiting and disabling nature of OH, and the associated risk of injuries related to falls, the majority of patients with this condition are more than willing to tolerate the side effects related to midodrine.

In conclusion, this review on midodrine in OH by Parsaik et al. is flawed by addressing and emphasizing inappropriate endpoints, by inadequate application of meta-analytic techniques, by various errors and inconsistencies, and most importantly, by incorrect interpretations and conclusions of available data. The effect of midodrine on standing BP in patients with OH due to autonomic failure is not in question considering the evidence, and—considering the methodological heterogeneity of available studies—a meta-analysis on this topic is therefore unnecessary, inadequate, and error-prone, quod erat demostrandum. An adequate summary and interpretation would have been that review of available evidence confirms that midodrine increases standing BP and symptoms in patients with OH due to autonomic failure in a dose-dependent fashion. Although dose-dependent side effects are well known and homogeneously described across studies, midodrine is generally considered safe and well tolerated. The question of whether midodrine provides sustained improvement over weeks and months in standing BP, symptoms and functional capacity has not been addressed, and represents an important question to answer in the future.

Corresponding Author: *W. Singer, MD; Department of Neurology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, USA (e-mail: singer.wolfgang@mayo.edu).*

REFERENCES

1. **McTavish D, Goa KL.** Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. Drugs. 1989;38:757–777.
2. **Fouad-Tarazi FM, Okabe M, Goren H.** Alpha sympathomimetic treatment of autonomic insufficiency with orthostatic hypotension. Am J Med. 1995;99:604–610.
3. **Jankovic J, Gilden JL, Hiner BC, et al.** Neurogenic orthostatic hypotension: A double-blind, placebo-controlled study with midodrine. Am J Med. 1993;95:38–48.
4. **Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA.** Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA. 1997;277:1046–1051.
5. **Wright RA, Kaufmann HC, Perera R, et al.** A double-blind, dose–response study of midodrine in neurogenic orthostatic hypotension. Neurology. 1998;51:120–124.
6. **Axelrod FB, Krey L, Glickstein JS, Allison JW, Friedman D.** Preliminary observations on the use of midodrine in treating orthostatic hypotension in familial dysautonomia. J Auton Nerv Syst. 1995;55:29–35.
7. **Schrage WG, Eisenach JH, Dinenno FA, et al.** Effects of midodrine on exercise-induced hypotension and blood pressure recovery in autonomic failure. J Appl Physiol (1985). 2004;97:1978–1984.