Drug Combinations in the Treatment of Hypertension
Never-Ending Novelty

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Not uncommonly, to effectively treat hypertension, multiple drugs must be given. Multidrug combinations that dominate clinical practice typically include a thiazide-type diuretic together with either an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, or less so a β-blocker. On the other hand, there are several approaches that can also incrementally reduce blood pressure (BP) but are used less regularly and, as such, go underappreciated as to their effectiveness. Such approaches may include within-class switching of diuretics, combining a thiazide-type diuretic with a calcium-channel blocker (CCB), using 2 CCBs from different subclasses, adding a peripheral α-blocker to an angiotensin-converting enzyme inhibitor, or tacking on an aldosterone receptor antagonist or nitrate therapy to any of several other drug classes. All of these presumably novel approaches offer useful options for treatment in the otherwise difficult-to-control hypertensive patient.1

These aforementioned fresh therapeutic approaches succeed in lowering BP based on the nature of the pharmacokinetic and pharmacodynamic interplay between select drug classes. A pharmacokinetic interaction that can be exploited clinically in the patient with difficult-to-treat hypertension is that of combining a dihydropyridine CCB, such as nifedipine, with a nondihydropyridine CCB, such as diltiazem or verapamil. The latter 2 compounds are known inhibitors of the cytochrome CYP3A4 isozyme. The dihydropyridine CCB nifedipine, as is the case for all CCBs, is extensively metabolized by CYP3A4 with little inhibitory effect on this isozyme itself. When nifedipine is combined with diltiazem or verapamil, the latter dose-dependently inhibits the clearance of nifedipine. This interaction occurs quickly, relates to the relatively steep dose-response relationship for nifedipine plasma levels and BP reduction when nifedipine is given in submaximal doses, and is nearly optimized within 3 days of dosing.2 Another such pharmacokinetic interaction of some clinical use is that of combining verapamil with eplerenone, with the former inhibiting the CYP3A4-mediated metabolism of eplerenone.3 This can be viewed as the “poor man’s” way of reaching higher plasma levels of eplerenone without incurring the substantial cost of higher prescribed doses of the “pricey” eplerenone.

Drug-drug interactions that display pharmacodynamic additivity for BP lowering most typically rely on 1 drug blocking counterregulatory responses prompted by the other; this has been the basis for the development of a number of fixed-dose antihypertensive combinations.4 Acute and chronic BP reductions often activate an interlinked series of mechanisms designed to restore BP. Reflex increases in cardiac output, peripheral vasoconstriction, and salt/water retention can result from baroreflex-mediated activation of the sympathetic nervous and renin-angiotensin systems (RASs).

This pattern of response is illustrated by the greater reduction in BP when a vasodilating drug, such as hydralazine or minoxidil, is coadministered with a pulse-rate-controlling compound, such as a β-blocker or a diuretic. An additional and very popular drug-drug interplay, used to good effect in the treatment of hypertension, is that of combining a volume-depleting drug, such as a thiazide-type diuretic, with a compound that interferes with RAS activity. The mechanism by which a diuretic enhances the BP-reducing effect of a RAS inhibitor relates to the induced volume changes and thereby the creation of a system sensitized to RAS inhibition.

A final consideration in how a patient with difficult-to-treat hypertension is brought to goal BP relates to the guesswork in choosing the first 1 or 2 medications in a treatment regimen. In that regard, the common failure of the first or second medication selected for the treatment of hypertension relates to the fact that many patients have their hypertension mediated by excess activity of the α-adrenergic system or the aldosterone axis. Because drugs that block the α-adrenergic system, such as doxazosin, and the aldosterone system, such as spironolactone or eplerenone, are viewed as fourth- or fifth-line therapies, the truly effective therapy for a patient’s hypertension is often added only as a last resort.5 In point of fact, either of these drug classes might have been the primary hypertension therapy in such patients if chosen initially. In uncovering the effectiveness of either of these drug classes, other minimally effective compounds in an existing regimen can be removed and the patient’s designation as being “resistant” or “difficult to treat now dropped.

It is into this cluttered therapeutic arena for resistant or difficult to treat hypertension that the combination of a nitrate and a phosphodiesterase type 5 inhibitor tries to gain entry. Oliver et al6 are to be commended for the cleverness with which they deploy an established adverse drug-drug interaction in a proof-of-concept study to show that BP can be lowered in treatment-resistant hypertensives. The authors are quite careful to point out the many issues that remain to be

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resolved with this combination before it is ready for prime time.

Such proof-of-concept studies allow room for speculation as to the basis for additivity in lowering BP with a nitrate and a phosphodiesterase type 5 inhibitor. The observed response can be conceptualized in both pharmacokinetic and pharmacodynamic terms. First, it is unlikely that there is a pharmacokinetic interaction between these 2 compounds based on their known pattern of systemic clearance, as well as the fact that these were single-dose studies. As to the pharmacodynamic exchange between these 2 drug classes, yet to be clarified is the degree to which counterregulatory systems activate with this combination. Available data in this article cannot answer this question completely, because these were single-dose studies, and RAS activity was not assessed. Heart rate responses apparently did not change with each drug individually or with their being given in combination; however, this may have been a function of the doses selected in that each of these compounds would be expected to increase heart rate at higher doses.7

Two critical issues are of some particular significance with this combination: the persistence of the BP-lowering effect of this combination with chronic dosing and the mechanism by which there is BP additivity with both drugs. The first of these questions can only be answered in the course of chronic dosing studies, which, if undertaken, would end up being quite complex in their design. The number of patients studied by Oliver et al6 was very small and the BP fall quite variable with mean systolic and diastolic BP drops of 21.8 mm Hg (range: 12 to 35 mm Hg) and 7.2 mm Hg (range: −2 to 13 mm Hg); thus, there were some patients in whom the response observed was modest at best. Mindful of this broad range of responses, interindividual variability, and the absence of predictors of response, the number of patients required for chronic dosing studies would indeed be quite large.

As to the mechanism of this additivity for these 2 drug classes, Oliver et al6 theorize that the response may be relate to targeting of the NO-cGMP pathway, which, as a vasodilator mechanism, would be little influenced by traditional therapies. This is an attractive hypothesis but one with scant supporting information. Because there are only single-dose studies to evaluate, it is unclear as to whether the observed BP lowering with this combination reflects a physiological rather than a pharmacological effect on the NO-cGMP pathway or whether it is a byproduct of rectifying the endothelial dysfunction common in difficult-to-treat hypertension.8,9 More-over, this combination would be of the greatest use in patients having failed other more traditional therapies for the resistant hypertensive, such as spironolactone. These 2 drugs given together are not necessarily a benign combination, and there will be a subset of excessive responders raising for consideration whether the first time the combination is given that it is under supervised conditions.10

The authors are forthcoming in stating that this is a proof-of-concept study and are to be commended for emphasizing the limitations to be placed on their work; however, the entry of this work into the published literature will create a “buzz,” with those seeking the “magic bullet” in combination therapy embracing it. Such is inevitable even if it is at the current time a shortsighted approach. If this combination of drug classes is advanced experimentally and the correct dose-response relationships uncovered, then this will become another one of the numerous therapies that a hypertension specialist can use in the truly difficult-to-treat hypertensive but not the inadequately treated hypertensive.

Disclosures

None.

References

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