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See related article, "Screening for Albuminuria Identifies Individuals at Increased Renal Risk," on pages 852–862.

Drug Dosing for Renoprotection: Maybe It's Time for a Drug Efficacy-Safety Score?

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The maximum recommended therapeutic dose (MRTD) of a drug is an important limit not only for the manufacturer but also for physicians and their patients.[1] Limits are derived from a dose-response curve that represents the combination of optimal efficacy and highest safety. The MRTD is established during the developmental phase of a drug. An error in that process may be very costly for both the manufacturer and patients. For example, when looking at the development of drugs altering the renin-angiotensin-aldosterone system (RAAS), there are interesting examples of "mistakes." Captopril was the first practical drug to target the RAAS in the angiotensin-converting enzyme inhibitor (ACEI) class. During initial testing, the drug was given at dosages of 450 mg/d. Although BP was very effectively lowered, these dosages produced adverse effects such as decreases in renal function, increases in albuminuria, and skin rashes.[2] Too high a dosage was later determined as the reason for these unwanted effects. Ironically, subsequent ACEIs, including lower dosages of captopril, were used to reduce albuminuria and provide renoprotection.[3] When the first drug in a second new class targeting RAAS, the angiotensin II receptor blockers (ARBs), was launched, the manufacturer and regulators did not want to make the same mistake twice, and care was taken in establishing the MRTD for losartan at 50 mg/d. The choice of this dosage may have been too cautious, because, nowadays, the MRTD for losartan is 100 mg/d.[1] First-in-class drugs seem to suffer from this trial and error. Thus, manufacturers and regulatory agencies have established even more rigorous protocols to establish an MRTD for optimal efficacy at maximum safety for a new drug. Many physician groups are also guiding proper use by implementing best practice guidelines.

Nevertheless, current regulatory protocols for establishing an MRTD are challenged by at least two recent findings. First, the maximum dosage of a drug may not be the same for different targets, and, second, individual patients may show a different dose-response curve and thus need a dosage that differs from the recommended one.

The obvious goal of antihypertensive drugs such as ACEIs and ARBs is to lower BP; however, organ protection is the ultimate goal of the treatment. What now is the MRTD for these two classes of drugs for nephrologists: Is it the optimal dosage for BP control or the optimal dosage for improved long-term renal outcome?

Recent data show that BP response to RAAS intervention may not be the best "surrogate" for estimating the efficacy of renoprotection. In diabetic nephropathy, Eijkelkamp *et al.*[4] found that long-term renoprotection is related more to the lowering of albuminuria and not so much to the lowering of BP. This suggests the optimal renoprotective dosage of an antihypertensive drug such as losartan should be established not

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only by its optimal BP-lowering efficacy but also by its ability to reduce albuminuria. To complicate things even further, the study by Eijkelkamp *et al.* found a large number of patients have a nonparallel response to the lowering of BP and albuminuria. Thus, fixing a recommended dosage to a BP response is not going to be very effective for optimizing the renoprotective effects of ARBs in patients with diabetes.

Would targeting of albuminuria with antihypertensive ARBs or ACEIs result in better long-term outcome? Two studies of patients with diabetes and hypertension and with microalbuminuria give some indirect evidence. A higher dosage of ACEIs and ARBs gave better renoprotection at the same BP response.[5,6] More direct proof was given by the ROAD study of patients with proteinuria and without diabetes. Hou *et al.*[7] found that titrating the dosage of an ACEI or an ARB to the maximal lowering of albuminuria results in markedly better renoprotection than using the maximal recommended antihypertensive dosage.

Burgess *et al.*[8] also elegantly demonstrate this dosing problem in this issue of *JASN*. The maximal recommended antihypertensive dosage of candesartan is 16 mg/d. Indeed, further titration up to 128 mg results in no further effect on BP; however, the dose-response for the antiproteinuric effect is clearly missed at the 16-mg dosage; a dosage of 128 mg still shows an additional antiproteinuric effect compared with 64 mg. One could even ask whether 128 mg is the upper limit for an antiproteinuric response. Interestingly, these supramaximal dosages, as the authors call them, do not seem to be associated with a marked increase in adverse effects. The latter should be taken with caution, because this is a relatively short-term study in a selected population, and long-term exposure to such high dosages may give different results.

How do we advance patient care with current knowledge that the MRTD for hypertension may not be the maximal dosage for renoprotection? Burgess *et al.*[8] call for more studies on optimal renoprotective and cardioprotective dosing. Indeed, there may be other issues such as whether these outcome differences will be true for all drugs in these two classes or true for each type of underlying disease or disease severity. Current evidence suggests that long-term dose-response trials probably are warranted. A good example of this is seen in heart failure treatment with ARBs; lacking an MRTD for heart failure requires dosing trials for hard outcomes.[9] We seriously doubt whether the pharmaceutical industry, which is currently the major initiator of hard outcome trials, will start such dose-response trials now having the hypertension indication, because every extra arm of a study necessary to establish a dose-response relation dramatically increases cost. This additional work will have to come from other means, eventually leading to new guidelines for regulatory authorities. A more useful approach, which still needs to be tested in practice, would be to establish a dose-response curve on an efficacy-safety score combining a set of factors such as BP, albuminuria, cholesterol, and serum potassium. Such an efficacy-safety score for a drug would indicate the combined effect of the tested dosages of a drug on these various factors, and both protective as well as detrimental changes on markers for hard outcome would be recorded at different dosages.

In conclusion, the currently registered MRTD of an ACEI or an ARB can be gauged only for its antihypertensive effect, except in heart failure. To be sure that we are not underdosing such drugs for cardiovascular or renoprotective effects, we need to establish maximum dosages in hard outcome trials. Until we find a way to do these trials, we will have to keep on working with the currently recommended maximum therapeutic dosages of ACEIs and ARBs in our patients.

DISCLOSURES

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