TROUGH-TO-PEAK RATIO AND THE REGULATORY PROCESS

Dr. Lipicky: I would like to ask Dr. Uscinowicz about the approval process for new antihypertensive drugs in Canada. If you were evaluating drug A and found that it lowered blood pressure at the end of the dosing interval by 5 mmHg more than placebo, would you then approve the drug without knowing its effects during the remainder of the 24 h period?

Dr. Uscinowicz: Until now, we have confined our interest in blood pressure lowering effects to the trough values in addition to other aspects of the approval process, such as appropriate safety data. In future, this approach may change and we may require more specific information on the trough-to-peak ratio of an antihypertensive drug or other data on its effects over 24 h.

Dr. Carruthers: There is currently a trend toward the harmonization of drugs on the international scene. I wonder if Dr. Uscinowicz or Dr. Lipicky could comment on where you see the process for approving drugs in the future. Will there be more standardization of submissions and protocols with greater cooperation between countries?

Dr. Uscinowicz: We have had a very close working relationship with the U.S. Food and Drug Administration (FDA) for many years, including the joint review of drug submissions. Recently, new guidelines have been established by the International Conference on Harmonization, such as reporting on adverse reactions, and Canada will be implementing these guidelines in the near future.

Dr. Myers: I understand from an earlier comment of Dr. Lipicky's that the FDA has no difficulty with 'draft' guidelines, such as those for trough-to-peak ratio. Is there not a down side to this approach, in that various pharmaceutical companies will develop their own interpretation of 'draft' guidelines and may exaggerate their importance to the submission of new drugs?

Dr. Lipicky: There is some truth to your statement. We try to avoid misconceptions and misunderstandings by inviting companies to approach us with any concerns or questions they may have so that these can be clarified. The apparent guideline for trough-to-peak ratio is more of a concept for addressing the duration of a drug's effect. It is not essential for a company to submit data on trough-to-peak ratio, but they should be able to define the duration of action of a drug in some way and this could then substitute for the trough-to-peak ratio.

Dr. Myers: If we could look into a crystal ball and see events over the next year or two, what do members of the panel think will be the impact of recent reports on calcium antagonists and, more specifically, the dihydropyridine calcium antagonists and possible adverse effects on cardiovascular outcome?
Dr. Lipicky: There are currently meetings scheduled both internally at the FDA and involving the National Heart, Lung, and Blood Institute to discuss the recent work of Psaty et al and the review by Furberg. Case control studies and metaanalyses raise the issue of hypothesis testing versus hypothesis formulating. I believe the current process is useful, but randomized controlled trials are often needed to answer specific hypotheses before regulatory decisions can be made.

Dr. White: When it comes to the nifedipine capsule, I am less concerned about the use of the drug in the management of chronic hypertension in the community than I am about its inappropriate use in the hospital setting. Recently, we have completed a study in hospitalized patients showing that the nifedipine capsule is frequently used in situations that are quite inappropriate. Leaving that aside, I do believe that it is important to know that the longer-acting formulations of the dihydropyridine calcium antagonists are as safe as other classes of drugs in the management of chronic hypertension.

Dr. Myers: When this symposium was initially planned, its main objective was to examine the methodologic issues in the estimation of trough-to-peak ratio with the involvement of regulatory authorities from Canada and the United States. From what I have heard from the speakers and discussants, I believe that we have come a long way toward developing criteria for studies on trough-to-peak ratio. Trough-to-peak ratio may not be the final word on describing an antihypertensive drug's effects over a 24 h period. However, the ratio does identify exaggerated responses that could potentially be detrimental to the patient. In the future, we will likely see other approaches to delineating the time-course of a drug's effect on blood pressure.

REFERENCES