Editorial Comment

Patients who have undergone organ transplantation or are otherwise immunocompromised present many therapeutic problems. The reviews in this issue highlight the necessity for clinicians to be aware of the pharmacology and pharmacokinetics of all drugs used in these complicated cases, as well as to be familiar with the best methods of monitoring and individualizing treatment with immunosuppressant drugs and antifungal agents. To do so requires the ability to properly obtain and interpret drug concentrations.

Kahan et al review the use of therapeutic drug monitoring (TDM) of immunosuppressant drugs to improve outcomes after transplantation. The authors focus on cyclosporine TDM, particularly the use of concentrations 2 hours after dosing, to predict efficacy and/or toxicity and to adjust individual therapy. Although this focus may be justified by the greater availability of published information on cyclosporine relative to other immunosuppressant agents, this is not to say that TDM of these other drugs may not be equally necessary (as evidenced by some transplant centers' routine use of Bayesian modeling of various immunosuppressant drug concentrations and in vitro measures of drug effects). Much work remains to be done to determine optimal methods of measuring and interpreting data on drug concentrations and effects after transplantation. Additional topics to be addressed include pharmacodynamic measures of drug effect, computer modeling of data, and use of TDM as a means of assessing drug–drug interactions.

In their review of the new echinocandin antifungal agent caspofungin, Stone et al make the point that tacrolimus concentrations should be monitored during coadministration with caspofungin, incidentally underscoring the importance of monitoring drug concentrations for signs of drug–drug interactions. This review also illustrates some of the difficulties of assessing new agents for which there are few published data, particularly tolerability data. For example, based on a single pharmacokinetic study of caspofungin in a limited number of elderly and nonelderly adult volunteers, we are told the investigators concluded that "dose adjustment . . . based on age was not necessary," although no studies in infants or children are described. Because of caspofungin's extensive binding (97%) to serum albumin, studies are necessary in pregnant women, icteric infants, patients with low serum albumin levels or taking drugs that displace bilirubin or other drugs from albumin-binding sites, patients with renal failure, and other populations in whom altered drug disposition and/or effects may occur. Similarly, further pharmacokinetic data are needed. Volume of distribution data, for instance, are given only in liters rather than liters per kilogram. As I have mentioned in past Editorial Comments, investigators and regulators need to recognize the large interindividual differences in mg/kg doses, achieved drug concentrations, and probable drug effects that can occur when a given milligram amount of drug is administered to "all adults." There is a 3- to 4-fold difference in body weight among adults, and without knowing the volume of distribution in liters per kilogram, it is difficult to dose children or "nonaverage" adults. Although US Food and Drug Administration guidelines may not require such adjustment, I believe this to be a correctable omission in both the federal guidelines and the drug-development process.

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