We read with interest the paper by Wu et al. (1) purporting to show that blockade of P-glycoprotein with verapamil or itraconazole increased brain concentrations of amphotericin B (AMB). Because virtually all P-glycoprotein blockers also block other transporters, we chose to compare P-glycoprotein knockout (KO) mice (Mdr1a/1b) with isogenic FVB wild-type mice. After administration of intravenous AMB, we found brain AMB concentrations were significantly lower in the KO mice (2). We also found that AMB serum levels were lower in the KO mice, as did Wu et al. in their verapamil- and itraconazole-treated mice. The cause of our latter finding was not obvious, as our studies of 11 other tissues, as potential explanations for where the intravascular compartment AMB might be localizing, were not definitive (2). This issue was not studied by Wu et al.

In addition, with the sequence employed by Wu et al., where AMB is given for 5 days, and then verapamil or itraconazole given 24 h later, is the effect of the latter drugs on P-glycoprotein influence on AMB crossing the blood-brain barrier, or are the higher AMB brain concentrations owing to a block of pumping out AMB already present?

The effect on brain AMB concentrations reported by Wu et al. could be explained by effects on other drug transporters. Our findings suggest that it would be counterproductive to block P-glycoprotein, in contrast to what Wu et al. suggest, in hopes of increasing brain AMB concentrations.

REFERENCES