Why effective drugs don't work for everyone

On page 49 in this issue, Drs. Nezzar Falluji and Steven Steinhubl review the variable response to antiplatelet therapy seen in patients with cardiovascular disease. Their paper raises the broader question of why effective drugs don't work for everyone.

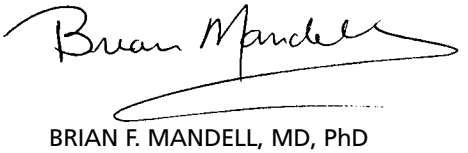
Many factors might account for drug failure in a given patient. For example, he or she may metabolize the drug differently than the average responder in clinical trials, and since we rarely measure blood levels of drugs and their metabolites, we would not know it. Differences in metabolism may be genetic or due to comorbidities or to other substances the patient is ingesting.

Furthermore, the drug's binding site may differ in number or structure among individuals. Structural differences could be due to polymorphisms, which are not routinely looked for. Specific polymorphisms that influence drug binding might be linked to race or geographic distribution, accounting for differences in drug responses in different populations. Other substances that the patient is taking can interfere with drug binding: just recently it was learned that ibuprofen interferes with the binding of aspirin to its target site on platelet cyclooxygenase.

In addition, variously expressed biological processes may counteract a drug's action: counterregulatory mechanisms may blunt the drug's effect, and parallel physiologic pathways may bypass it.

Perhaps resistance to aspirin and other antiplatelet drugs can be predicted, but the methodology must be carefully evaluated. Which is the "right" assay to use in predicting aspirin's cardiovascular protection? What percent inhibition of which platelet assay is sufficient to prevent stroke or myocardial infarction? The assay details are critical. As Drs. Falluji and Steinhubl discuss, the assay must be capable of correlating a pharmacologic effect with a clinical outcome.

For now, the concept of antiplatelet resistance is useful and probably biologically relevant, but it isn't ready to be incorporated into our clinical practice.



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