Gene-based, rational drug-dosing: An evolving, complex opportunity

We often dose drugs empirically, starting at a historically defined dose and then titrating to a desired effect, drug level, or absolute amount. Some drugs we dose on the basis of weight or estimated glomerular filtration rate, but many drugs we start with a "one-strength-fits-most" approach. For relatively few drugs can we measure circulating or relevant tissue levels or a real-time pharmacodynamic response such as a change in blood pressure or in the level of serum glucose or low-density lipoprotein cholesterol.

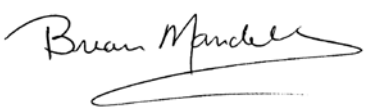
For some drugs there is a key step in metabolism, often in a rate-limiting pathway, with an enzyme that has known and detectable polymorphisms that differ dramatically in their ability to affect the drug's degradation. In theory, by determining the patient's specific genotype ahead of time, the initial dose of the drug can be determined more rationally. In this issue of the *Journal*, Kitzmiller et al (page 243) describe several drugs for which this may be true.

However, for this approach to be practical and cost-effective, several conditions should be met. The drug must be one that needs to be dosed to its therapeutic level rapidly: if there is time to titrate slowly, then there is little need for the extra expense associated with genotyping in order to titrate it more rapidly. Also, it should be proven that dosing based on advance knowledge of the genotype of the target actually results in safer or more efficacious dosing.

For carbamazepine (Tegretol, Equetro) and allopurinol (Zyloprim), specific human leukocyte antigen haplotypes are associated with a strikingly increased frequency of serious hypersensitivity reactions. In some patients, these should be checked before giving the drug.

But the concept of pharmacogenomics is broad, and it may yet explain many vagaries of drug-responsiveness in individual patients. Polymorphisms in renal anion transporters may dictate the level of anionic drugs. Drug-receptor polymorphisms may determine the affinity of a drug for its target and, hence, its efficacy. Cell-membrane transporters, which may have functionally different stable alleles or polymorphisms, may regulate intracellular drug levels by pumping the drug into or out of cells with different efficiencies.

As the entire human genome is dissected and analyzed, and as more and more genes (with their polymorphisms) are linked to specific functions readily detectable in specific patients, we will have more opportunities to match the right drug and dose to the right patient. We are not there yet, but that day is coming.



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