Commentary: Testing patients to allow tailored drug treatment

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The application of pharmacogenetics in preventing adverse drug reactions as illustrated by Konstantopoulou et al¹ is not new. In 510 BC Pythagoras observed that only some individuals—those with a deficiency of glucose-6-phosphate dehydrogenase (G6PD)—developed a potentially fatal reaction after ingesting fava beans. For nearly 50 years anaesthetists have been identifying patients who may have a deficiency of normal plasma cholinesterase (leading to prolonged suxamethonium neuromuscular blockade or “scoline apnoea”) by taking a simple patient history.²

Although the development of modern pharmacogenetic assays designed to reduce the incidence of adverse drug reactions is still its infancy, the case presented by Konstantopoulou et al illustrates that where these assays do exist, it is important that clinicians use them. Konstantopoulou et al acknowledge that many papers and guidelines on screening for thiopurine methyltransferase (TPMT) levels before starting azathioprine have been published, yet they failed to follow the guidelines in this case. Why? Through this omission a preventable serious adverse drug reaction occurred. Although the authors are to be applauded for disseminating the lessons from their oversight, surely it is a system failure that allowed the near fatal reaction to have occurred in the first place? Will publication of this case in the *BMJ* lessen the likelihood of a similar event in another patient? We might like to think it will, but until we all routinely prescribe treatment tailored to the individual as well as the disease, it seems unlikely.

Many other adverse drug reactions can occur and be prevented by screening before giving treatment—not just checking for G6PD deficiency before primaquine therapy or slow acetylation and hydralazine, but also less clearcut phenotypical variation such as with warfarin metabolism. Starting warfarin therapy is always potentially hazardous, yet screening for CYP2C9 polymorphism could explain varying drug clearance to enable tailored therapy.³

However, we need to consider not only avoiding adverse drug reactions but also enhancing therapeutic response. If we look at another regularly prescribed drug—codeine (usually manufactured in compound form with paracetamol or aspirin)—and study the metabolism, patients with inactivity of cytochrome P450 (CYP) 2D6 do not hydrolyse codeine (inactive) to morphine (active).³ This makes the drug essentially ineffective (in about 10% of the population)—but who routinely screens for this in clinical practice, let alone in community pharmacies, where vast amounts are purchased over the counter?

In fact, tailoring therapy is perhaps what pharmacogenetics is all about. In cases of acute asthma an understanding of the individual's phenotype could determine likely response to therapeutic interventions.⁴ In disorders as varied as hypertension, HIV infection, and malignancy, improved therapy is but a gene probe away.⁴

But is this really the future? Apart from major phenotypical variations such as with TPMT, or specifically tailored therapy such as trastuzumab,⁴ many other genetic tests lack clinical utility for either the individual or the population as a whole. Indeed, the resistance to their use is soundly supported by the complex arguments of cost, perception and acceptance, ethics, and overall utility.⁵ If the promise of pharmacogenetics comes to pass, perhaps we should start with avoiding the simple, life threatening reactions first.

Competing interests: None declared.

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Basic instinct

Seneca's view—"A hungry person listens not to reason, nor cares for injustice, nor is bent by any prayers"—found an exemplary application with one of our middle aged patients. He had had a contracted eye socket, a sequel of surgical removal of the orbit, and underwent socket reconstruction surgery—with an autologous, full thickness skin graft from the buccal mucosa—under general anaesthesia. After the surgery, the patient was shifted to his ward bed. As per the anaesthetist's instructions, he had had no food overnight before the operation and was to starve for a further two hours or so postoperatively.

We were therefore somewhat surprised when we visited the patient during the evening rounds to find him tucking into a substantial meal of spicy salted

vegetables, pulses, and bread, apparently quite oblivious to his reconstructed socket and, more amazingly, to the raw denuded buccal area. Anybody who has had an aphthous ulcer knows how painful is the touch of salt and spice on it, but here was our man with a raw patch in his mouth about 50 times larger steadfastly indulging his culinary desire.

Wilson said, "No one can worship God or love his neighbour on an empty stomach." Obviously, neither can he love his doctor—the urge for food reigns supreme.

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