Editorial IV

Do genes influence outcome from anaesthesia?

The last decade has seen an improved understanding of hepatic, xenobiotic metabolizing enzymes and how they may be affected by environmental influences, both natural and synthetic. These include pollutants such as solvents and petrochemicals, and enzyme inhibitors such as flavonoids in citrus fruits. Among these environmental factors, both alcohol and tobacco play an important role in determining the degree of liver enzyme induction, which determines the rate of metabolism of some medications, including volatile anaesthetic agents, thus influencing outcome from anaesthesia.

Since the dawn of the biotechnology era, culminating in the successful unravelling of the human genome, it has become increasingly apparent that subtle inter-individual genetic differences underlie differing responses to both illness, and to pharmacological challenges. Indeed, the last decade has seen the emergence of a new cottage industry, based upon the latest techniques of DNA sequencing, whose main aim is to discover genetic polymorphisms, which hold the key to the validation of new targets for drug therapy. The term genetic polymorphism now relates to monogenic traits that exist in the population in at least two phenotypes. The simplest type of polymorphism derives from a single base mutation in the double-helix of DNA, that substitutes one nucleotide for another. This is called a single nucleotide polymorphism in the double-helix of DNA, that substitutes one nucleotide for another. This is called a single nucleotide polymorphism (SNP) (colloquially termed a snip).

The observation that individuals may exhibit a varied drug response was made in antiquity. The ancient Greeks noted, for example, that some individuals might suffer haemolytic anaemia following the ingestion of fava beans. Haemolysis associated with the antimalarial, primaquine, was described in the Second World War primarily as an affliction of black soldiers. It was subsequently determined that the underlying disorder was a genetic deficiency of the enzyme, glucose-6-phosphate dehydrogenase. Another early observation was the occurrence, among some patients taking the antituberculous drug, isoniazid, of peripheral neuropathy. This is now known to be a result of an inherited defect in the activity of N-acetyltransferase and is associated, in addition to isoniazid-induced neuropathy, with procainamide-induced lupus, sulphonamide-induced hypersensitivity, and dye-associated bladder cancer. Patients whose acetylation ability is impaired are now designated ‘slow-acetylators’.

It has also been known for many years, that around 5–10% of Caucasians have a defect in their ability to metabolize the antiarrhythmic drug, sparteine. This was first recorded as a result of a chance observation in a pharmacokinetic study of the antiarrhythmic in question; one volunteer experienced affects such as nausea and diplopia, which are characteristic of intoxication with Group 1 antiarrhythmics. Subsequently, it was recognized that plasma clearance of the drug in this subject was one-fifth of that in the other individuals being studied. It is now known that the defective metabolism, that is sparteine oxidation, is inherited as an autosomal recessive trait. Individuals who have the defective gene are labelled poor metabolizers (PMs), in contrast to those with the normal gene who are called extensive metabolizers (EMs). A similar chance observation led to the discovery of debrisoquine polymorphism. Debrisoquine is a now outmoded antihypertensive agent whose side-effects, for example orthostatic hypotension, were noted in a volunteer. Subsequent family studies revealed the nature of the inherited defect.

The defective metabolism of sparteine and debrisoquine would, in itself, be primarily of academic interest, as neither of the drugs are unique in their effect and better, cleaner substitutes are now available. However, a number of commonly used drugs, some of which are used by anaesthetists, are metabolized by the same enzyme, namely CYP2D6. Examples of these are: the beta-blockers metoprolol, and alprenolol; the class 1C antiarrhythmic, propafenone; the analgesics, codeine and tramadol; various antidepressants; antipsychotics such as droperidol, thioridazine, and haloperidol; and 5HT3 inhibitors such as ondansetron and tropisetron. It is now recognized that the enzyme defect stems from a mutation leading to faulty expression of the enzyme, and that poor metabolizers either have complete deletion of the CYP2D6 gene (null mutations), or, more commonly, replacement of a single nucleotide leading to aberrant gene splicing (e.g. CYP2D6*10). (There is now consensus that the ‘wild-type’ or reference allele related to the respective isoenzyme should be designated *1.) There are a number of possible clinical sequelae for patients who are poor metabolizers of codeine. It is known that codeine is a prodrug, and its action is determined by the CYP2D6-dependent formation of morphine. In affected individuals, the ingestion of codeine results in undetectable or barely detectable amounts of morphine with little or no analgesic effect. Based on this observation, it has been suggested that codeine should not be used in patients with this gene defect. In contrast, there is a genetic variation which occurs in some Caucasian, Middle Eastern, and African populations which have been shown to produce an ‘ultrarapid metabolizing’ phenotype (URM). This phenotype results in abnormally high levels of morphine being produced from codeine. Such patients rapidly present with morphine-associated side-effects when
given standard doses of codeine. Similarly, tramadol is also metabolized by CYP2D6 and, like codeine, its effects will be determined by the underlying genotype of the recipient. In poor metabolizers, there is a significant loss of the analgesic effects of the drug. This is clearly of considerable importance to anaesthetists who may fail to understand why an individual patient is apparently resistant to standard doses of a moderately potent analgesic. Similarly, in the case of antipsychotics such as haloperidol, an unexpected response to standard medication may occur, which may take the form of either failure of therapy or the production of toxicity, depending on whether the individual is a PM, EM, or URM.

The hepatic enzyme CYP2C19 is also expressed in a polymorphic fashion. To date, eight alleles of CYP2C19 have been identified. Of these, CYP2C19*2 and CYP2C19*3 are best characterized. CYP2C19*2 occurs in 25% of the Asian population in comparison with 13% of Caucasians, while the CYP2C19*3 allele occurs in 8% of Asians in comparison with 1% of Caucasians. Those patients who are homozygous for the ‘null’ alleles of CYP2C19 are highly sensitive to substrates of the enzyme such as diazepam, the proton pump inhibitor, omeprazole, propanolol, and the antidepressive, amitriptyline. Those patients receiving such medication will require dosage modification to achieve therapeutic blood levels and avoid toxicity. Similarly, CYP2C9 has several allelic variants. CYP2C9*2 and CYP2C9*3 are expressed in this case at a greater frequency among Caucasians than among Asians (10 vs <3%). These enzyme variants can result in the impaired metabolism of a number of important substrates such as warfarin, tolbutamide, and diclofenac, which is an important postoperative analgesic.

In a recent study, Apfel and colleagues demonstrated that volatile anaesthetics are the main cause of postoperative nausea and vomiting (PONV) within the first 2 h after surgery, when pharmacokinetic effects are most likely to account for any perceived differences in recovery. All volatile anaesthetic agents are metabolized by CYP2E1, which is also expressed in a polymorphic pattern. The implications of this are clearly that certain individuals may have an innate and predetermined advantage in terms of recovery from anaesthesia. Certainly, there is a genetic component, which, inter alia, determines risk of PONV. This may simply represent the individual activity of the enzyme CYP2E1. It is interesting to speculate that a SNP at the CYP2E1 locus may either be associated with protection against, or susceptibility to PONV. Environmental–genetic interactions play a pivotal role in determining the outcome from, as well as the susceptibility to disease, such as cancer. Different levels of expression of the enzyme CYP2E1 may explain individual susceptibilities to both alcohol-related and halothane-related liver disease. Both sevoflurane and methoxyflurane related renal dysfunction are probably also related to the activity of CYP2E1. In the case of recovery from anaesthesia, smoking has been established as a significant factor protecting against PONV. This is probably a result of CYP2E1 induction. Alcohol also induces CYP2E1, and it is probable that this induction also confers protection, especially in individuals with the correct genetic background.

Genetic polymorphisms have been associated with other key areas related to anaesthesia, such as pain thresholds and the resulting requirements for analgesia. For example, Bond and colleagues have discovered a polymorphism at position 118 of the mu opioid receptor gene in 10% of their study population. The variant protein was three times more potent in its interaction with beta-endorphin than with the wild-type allele. This may have implications for determining both the need for, and the response to opioid analgesics. Another polymorphism has been found in the ryanodine gene (RYR1), which encodes the key channel regulating calcium release in muscle, and which is thought to account for susceptibility to malignant hyperthermia. Recently, there has been considerable interest in the wider question of the study of candidate genes as markers for outcome following cardiac surgery. These genes include not only those responsible for the development of cardiovascular disease, but also those that determine coagulation and inflammation.

Inter-individual variability in drug response is a major clinical problem. Clinical experience tells us that there is great heterogeneity in the way patients recover from uncomplicated anaesthesia as well as their requirements for postoperative analgesia. It is now clear that much of the observed variability in drug response has a genetic basis, arising as a result of genetically determined differences in drug disposition, metabolism, and receptor interaction. Many drugs used by anaesthetists, including volatile agents, are metabolized by enzymes, which are expressed differently among individuals and among ethnic groups. One of these enzymes, CYP2D6, metabolizes one-quarter of all prescribed drugs and is essential for the analgesic effects of codeine and tramadol.

Recent technological advances using gene clones from the Human Genome Project, have enabled gene sequence analysis to become fully automated. Analysis of up to 5000 genotypes per day is routine in many laboratories, with automated multiplex assays extending this to 100 000. This has created a new field of in-silico research, in which mining of computer databases for genomic information is performed without recourse to experimentation. This approach has revealed nearly 100 000 new polymorphisms. Individuals at risk of developing adverse drug reactions, as a result of genetically determined variation in genes such as CYP2D6, can now be easily identified using DNA-based tests. Such patients will benefit from a personalized choice of medication with individual, or tailored dosage regimens. Henceforth, this new approach to pharmacogenetics, termed pharmacogenomics, may provide the basis for a more rational approach to drug prescription.
It is conceivable that, in the not too distant future, patients undergoing anaesthesia, will have as part of their preoperative screening, genetic profiling to detect life-threatening risk factors. In addition, genetic profiling of drug metabolizing enzymes, carrier proteins, and receptors, using technology currently available, will enable anaesthetists to provide personalized care using agents whose pharmacokinetic profile are best suited to those individuals. Ultimately, a secured online database could be produced with each individual’s genotype available to the respective health-care provider. Such a system would raise important ethical and social questions, but it is potentially of major clinical and economic importance.

B. P. Sweeney
Poole and Royal Bournemouth Hospitals
Department of Anaesthesia
Royal Bournemouth Hospital
Castle Lane East, Bournemouth
Dorset BH7 7DW
UK
E-mail: bpsween@aol.com

References
1 Nebert DW, Russell DW. Clinical importance of the cytochromes. P450. Lancet 2002; 360: 1155–62
2 Sweeney BP. Why does smoking protect against PONV? Br J Anaesth 2002; 89: 1–4
6 Hughes HB, Biehl JP, Jones AP. Metabolism of isoniazide in man as related to the occurrence of peripheral neuritis. Am Rev Tuberculosis 1954; 70: 266–73
15 Yue Q, Alm C, Svensson J, Sjow J. Quantification of the O- and N-demethylated and the glucuronidated metabolites of codeine relative to the debrisoquine metabolic ratio in urine in ultrarapid, rapid, and poor debrisoquine hydroxylators. Ther Drug Monit 1997; 19: 539–42
19 Aithal GP, Day CP, Leathart JBS. Relationship of polymorphism in CYP2C9 to genetic susceptibility to diclofenac-induced hepatitis. Pharmacogenomics 2000; 10: 511–18
21 Kharasch ED, Thummel KE. Identification of cytochrome P450 2E1 as the predominant enzyme catalysing human liver microsomal defluorination of sevoflurane, isoflurane and methoxyflurane. Anesthesiology 1993; 79: 795–807

DOI: 10.1093/bja/aeg103