

Pharmacogenetics is improving care but creating new dilemmas for practice

A new report examining the ethical issues surrounding pharmacogenetics was published this week. Clare Bellingham finds out what pharmacogenetics offers and the dilemmas it raises

IT IS widely known that people respond differently to medicines. Why does one patient suffer an adverse reaction and another not? And why does a particular drug work well for one patient yet have little or no effect on someone else? Take warfarin, for example. The dose of warfarin required varies from patient to patient, and a therapeutic dose for one person can cause severe bleeding in another. Although it will not provide all the answers, pharmacogenetics should increase understanding of how people respond to medicines and then help increase efficacy and improve safety. In warfarin's case, response is known to be related to variations in metabolism via the enzyme cytochrome P450 (CYP) 2C9. These variations are determined by genetics.

Few examples of the use of pharmacogenetics in clinical practice exist. Even if the technology becomes available, the use of pharmacogenetics raises a host of questions. This week, the Nuffield Council on Bioethics attempts to answer a number of these questions through the publication of its report "Pharmacogenetics: ethical issues". It hopes that its recommendations will ensure that future delivery of pharmacogenetics tests is "as straightforward as possible". The report is available at www.nuffieldbioethics.org.

Professor Peter Lipton, chairman of the working party that produced the report, commented: "It is too early to predict whether 'personalised medicines' will become a reality. Claims of 'the right medicine for the right patient at the right dose' may be overstated. But it is important to encourage discussion of ethical and policy issues raised by the introduction of pharmacogenetics."

Professor Tony Moffat, chief scientist at the Royal Pharmaceutical Society, said: "The Society's working party on pharmacogenetics is examining the role of the pharmacist in pharmacogenetics and what the Society can do to assist pharmacists in developing the new knowledge that they will need for the wider roles in counselling and information provision that they will perform."

Next week, a national strategy for genetics education for health professionals is expected to be recommended by a new report. This ties in with concerns raised in the Nuffield Council report that initiatives to provide independent and impartial information about pharmacogenetic tests are needed. Next week's report — called "Addressing genetics, delivering health" — is written by the Public Health Genetics Unit in Cambridge and was commissioned by the Department of Health and the Wellcome Trust. It says that all health care professionals need to be better informed about how genetics affects a patient's likelihood of

developing a disease or response to medicines. It recommends that a genetics education centre should be set up to support this.

HOW PHARMACOGENETICS CAN HELP

"Some common treatments for conditions including diabetes, depression and asthma are only effective in around 60 per cent of patients, and for medicines used to treat cancer this figure may be as low as 25 per cent," the Nuffield Council says.

Pharmacogenetics could help improve understanding of these responses. It can be used to identify an individual's genetic variations that are associated with adverse reactions or with differing metabolism so that medicines could be tailored accordingly. It can also provide information about the genetic characteristics of a disease, which could be used to improve drug design.

Whether or not pharmacogenetics will be used to improve existing medicines is unclear. There is a long list of currently prescribed medicines where genetic variations are known to play a part in the drug's metabolism (see Panel overleaf). How significant some of these variations are is not known, but some do have an impact on response to therapy yet routine testing for genetic variations does not occur.

"We recommend that efforts should be made to encourage pharmacogenetic research on existing medicines, where there is reason to believe that such research could significantly improve efficacy or safety," the Nuffield Council report states. It acknowledges that in some cases it might be quicker and easier to continue today's practice of giving a medicine and observing its effects instead of developing pharmacogenetic tests.

However, a first step towards routine use of pharmacogenetics was made this summer. A diagnostic test for cytochrome P450 was launched in the United States in June. The AmpliChip CYP450 microarray is manufactured by Roche Diagnostics. It enables genetic variations in two CYP enzymes to be identified. Speaking at the time of the launch, a company representative commented: "The launch of this product heralds the emergence of pharmacogenetics as a medical and commercial reality." Initially it will only be available in specialist clinics.

The ability to determine more accurately which patients will benefit from treatment could also have an impact on drugs that have been withdrawn. Withdrawals tend to be on safety grounds and if a pharmacogenetic test could identify patients at increased risk of an adverse reaction then the drug could be avoided in these patients.

The report notes that an example of this is alosetron (Lotronex), a treatment for irri-

table bowel syndrome approved in the United States three years ago but subsequently withdrawn because some patients experienced adverse reactions. The Food and Drug Administration and the drug's manufacturer are currently re-examining the medicine, including using a pharmacogenetic analysis.

What about new medicines? One drug that came to the market recently — and represents one of the few current uses of pharmacogenetics in practice — is trastuzumab (Herceptin). Used in the treatment of breast cancer, it can only be given to patients who over-express the human epidermal growth factor receptor 2 (HER2) gene.

The Nuffield Council report says that it might be discovered that some conditions currently thought of as single disorders might have different causes. "It may turn out that the nature and efficacy of treatment depends on which type of the disease is present. Such heterogeneity may be behind some of the well-known variation in efficacy of medicines given to people affected by what appears superficially to be the same disorder," it states.

Better targeting of drugs could make the market smaller and the report warns that some medicines may not be developed if the number of patients who would benefit is too small to be profitable. On the other hand, it could also encourage drug development by preventing early halts to clinical trials if a subgroup of patients with a particular genetic profile for whom the drug appears to be effective can be distinguished.

USE IN PRACTICE

Use of pharmacogenetics in practice will pose challenges for many aspects of health care. Where tests will take place will have to be decided. The Nuffield Council predicts that this will depend on the test itself with some carried out in a pharmacy or GP surgery and others requiring more specialised testing facilities. It warns that if testing takes up too much time then it might impede the delivery of health care.

Some tests might become available to buy over the counter but only if they provide clear, readily interpretable information. The Nuffield Council report comments: "The majority of pharmacogenetic tests will be more complex, providing less certain predictions. In these cases, professional advice is likely to be needed both before and after taking the test which means that the direct commercial provision of tests will be inappropriate."

Pharmacogenetic testing will introduce a new raft of decisions about a patient's treatment: decisions around whether to take the test, whether the medicine should be

available after the test and what to do if the patient refuses to take the test. If a patient refuses a test that is part of a licence condition then it is unlikely that the patient will be prescribed the medicine. In other cases, it might only form part of the decision-making process. But the Nuffield Council warns: "We note that advances in pharmacogenetics can be expected to lead to the licensing of medicines that would not have been licensed had there been no associated test, because of the serious danger those medicines pose to a sub-population. To allow prescription without the test in such a case would be wrong."

Consent will become an increasingly important issue with the possibility that some pharmacogenetic tests will require patient consent. However, information generated by a pharmacogenetic test is likely to be less predictive of health outcomes than genetic tests so consent might not be such a thorny issue as has been previously imagined. The report recommends: "If information about unrelated medicines or diseases is likely to be obtained, or if the results of the test will have significant impact on the health or lifestyle of the patient, written consent may be appropriate. We take the view that, in most cases, written forms will not be required."

Patients will certainly need access to information about pharmacogenetic and health professionals will have to be able to provide it.

Variations with existing drugs

How people metabolise drugs is determined by genes. The causes of these differences can be grouped into three categories: enzyme variations, transportation differences and receptor variations. What is not known is how significant these variations in metabolism are.

Professor Tony Moffat, chief scientist at the Royal Pharmaceutical Society, explains that if one route of metabolism is affected then the body can compensate by changing the rate of metabolism by another route. So although a list of drugs with known genetic variations in metabolism can be produced, it does not mean these differences will have any significance. "The clinical outcome in most cases is unknown," says Professor Moffat.

There are only four drugs where evidence has demonstrated that genetic variations do have a clinical effect on metabolism: warfarin, omeprazole, triptans and metoprolol.

- **Enzyme variations** Differences in enzyme status can result in a lack of efficacy or toxicity at standard doses as a result of altered absorption, distribution or metabolism. The most important affected enzymes are the cytochrome P450 (CYP) group since many drugs are metabolised by them. For example, CYP2D6 metabolises 30 widely used drugs, including β -blockers, antidepressants, antiarrhythmics, loratadine and codeine. Warfarin is metabolised by CYP2C9.
- **Transportation variations** Differences in transport of a drug from the gastrointestinal tract into the systemic circulation or across the blood-brain barrier can alter a drug's efficacy or toxicity. An example is anti-infective agents.
- **Receptor variations** Variations in a drug's target receptor — such as its abundance or function — can affect the drug's efficacy and toxicity. Drugs affected include astemizole, β -agonists, clozapine, cyproterone, glucocorticoids, halothane, insulin, oestrogen, sulphonylureas, terfenadine and warfarin.