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Patient profiling — the key to successful treatment?

The European Society of Clinical Pharmacy symposium on patient profiling focused on the potential benefits and problems of pharmacogenetics and pharmacogenomics,

Christine Clark reports

Pharmacogenetics is unlikely to lead to personalised treatment in the immediate future, except in the field of cancer chemotherapy, according to Geoff Tucker, professor of clinical pharmacology, University of Sheffield. Appropriate trials and professional cost analyses are still needed, he added.

Pharmacogenetics has been defined as “the study of inter-individual variations in DNA sequence related to drug response”, whereas the closely-related field of pharmacogenomics has a broader definition: “the study of the variability of the expression of individual genes related to disease susceptibility as well as drug response at cellular, tissue, individual or population level”.

Genomics holds out the promise of precise, personalised medicines and this has been fuelled by the pace of advances in molecular biology and gene sequencing. The Amplichip cytochrome P450 (CYP450) test — a pharmacogenomic micro-array designed to test for variations in 2D6 and 2C19 that is now available for *in vitro* testing in both the US and the EU — exemplifies this progress. However, some of the predictions have amounted to little more than enthusiasts extrapolating beyond small, proof-of-principle studies and retrospective studies, said Professor Tucker. There have been some notable exceptions, such as trastuzumab (Herceptin), which is now known to be effective only in the 15-20 per cent of breast cancer patients who over-express the human growth factor receptor, HER-2. Another success is abacavir (Ziagen) — variations in the HLA-b gene in about 50 per cent of white male HIV positive patients predispose them to the development of adverse reactions to abacavir.

Drug response is likely to be more heavily influenced by factors such as compliance, poor prescribing and drug interactions than

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Geoff Tucker: more functional studies are required

by genetic variation alone, but these factors are not sufficiently acknowledged outside clinical pharmacy, cautioned Professor Tucker. Whereas 3 per cent of pharmacodynamic variance might be accounted for by genetic differences, 30 per cent variance could arise from other factors and easily obscure the genetic effect, he said.

In the UK £4m has been allocated to fund genetic testing that had a greater than 50 per cent chance of reaching the bedside in the next five years. In contrast, in the US a sum of \$20m has been allocated.

In order for a pharmacogenetic test to be cost-effective, a number of conditions need to be satisfied. They are:

- Severe clinical or economic consequences that could be avoided
- Difficulty in monitoring drug response using current methods
- Lack of alternative drug with equivalent therapeutic index and price
- Well-established association between genotype and clinical phenotype
- Availability of a rapid and inexpensive genetic test
- Relatively high frequency of the variant gene(s)

One good example is the test for genetic variations in thiopurine methyl transferase — the enzyme responsible for the metabolism of azathioprine and 6-mercaptopurine. Routine testing can identify 90 per cent of the poor metabolisers who are at risk of developing signs of toxicity, although direct measurement of red cell enzyme activity might be better for intermediate metabolisers.

Another example is CYP2C9 mediated metabolism of warfarin. One researcher has developed an algorithm that takes into account the genetic variation in CYP2C9 activity, and shown that fewer patients were overdosed when it was used. However, the greatest danger with warfarin is when other drugs are added to established treatment and here there is no substitute for careful monitoring, suggested Professor Tucker. CYP2D6 is inactive in 5-8 per cent of Caucasians but there is still so much variation amongst extensive metabolisers that a genetic test is a little help in clinical practice. One study had shown that in patients receiving thioridazine, which is metabolised by CYP2D6, twice as many poor metabolisers as extensive metabolisers required anti-parkinsonian treatment. Genetic testing could potentially identify those at risk. The same enzyme is involved in the metabolism of tricyclic antidepressants and it has been calculated that 1,500 to 2,000 patients would need to be evaluated over a one-year period to determine whether the CYP2D6 genetic variation significantly alters the duration of hospital stay and costs.

In psychiatry, multiple drug therapy and poor prescribing are bigger influences than genetic variation, said Professor Tucker. The effect of drug interactions is to push many more patients into the “poor-metaboliser” category, he said. Asked if pharmacogenetic data could be used to remove a drug such as thioridazine from the market, Professor Tucker said that there are no examples so far. Solid evidence would be needed before this could happen; in particular, more functional studies are required to help understand the clinical significance of pharmacogenetic data. Another question concerned the prac-



CHRISTINE CLARK

Sandy Thomas: pharmacogenetics offers people a better future

tical application of pharmacogenetic information in a pharmacy. Professor Tucker said that a measure of exposure, that is whether or not the patient was taking the drug, would always be essential. Even in clinical trials only 50 per cent of participants take the drugs as prescribed. He also recommended that much more effort should be directed towards encouraging good prescribing.

— Drug response

Genomics affects all stages of drug action and the data that we have now should be used as the basis for further prospective trials, Heyo Kroemer, dean of the medical school and professor of clinical pharmacology at Ernst Moritz Arndt University, Greifswald, Germany, told the audience.

In drug treatment we expect a uniform response but sometimes there can be large variations between individuals who are given similar doses of drugs. The differences can arise because of genetically-determined variations in pharmacokinetic and pharmacodynamic responses. Moreover, although we conceptualise these aspects separately, in real life they happen together and can reinforce or oppose each other.

Genomics affects the uptake, processing and elimination of drugs, said Professor Kroemer. One example is the uptake of drugs from the gastro-intestinal tract into the liver. The transport protein, organic anion transporting polypeptide-C, mediates the absorption of some compounds, including statins. If there is a defect in the

transporter protein then some of the drug is not absorbed and is left free in the bloodstream. The high peripheral concentrations of drug are associated with increased frequency of side effects. Thus certain genotypes have high peripheral levels of pravastatin along with reduced liver levels and reduced therapeutic effects.

The next stage of drug handling is intracellular processing and here the CYP450 family of enzymes is important. For some of these, such as CYP2D6, there is considerable genetic variation. For example, in two patients of similar weight given similar doses of propafenone after myocardial infarction, a 16-fold difference in plasma drug levels had been observed and this was explained by the genetically-determined absence of CYP2D6 in one patient. This is not an "all or nothing" phenomenon, said Professor Kroemer. In a population sample, 5-10 per cent will be ultra-rapid metabolisers, 70-80 per cent will be extensive metabolisers, 10 per cent will be intermediate metabolisers and 5 per cent will be poor metabolisers. The people at highest risk are not the poor metabolisers, but the ultra-rapid metabolisers because these people often have no circulating drug left. Numerous drugs, including anti-arrhythmics, neuroleptics, beta-blockers and antidepressants are substrates of CYP450, but response cannot always be predicted on this basis, warned Professor Kroemer.

Elimination is an aspect of variation that is often overlooked. When drugs are metabolised, for example by glucuronidation, the metabolites are hydrophilic and require active transport proteins to remove them. If there are genetic variations in the transport protein then elimination will be variable. The multidrug resistant protein MRP2 is responsible for elimination of conjugates into bile. If the MRP2 elimination route is not working then conjugates are shunted to MRP3, which excretes them to the blood instead. This is the case in Dubin-Johnson syndrome, which manifests clinically as jaundice due to conjugated hyperbilirubinaemia. If the MRP2 transport protein were functioning normally conjugated bilirubin would be excreted in the bile and patients would not be jaundiced.

Turning to the question of whether genomic information can be abused, Professor Kroemer pointed out that research has now been published that shows links between CYP450 genotype and behaviour. In one study that compared poor metabolisers with extensive metabolisers, poor metabolisers were shown to be significantly more likely to have low harm avoidance scores, to exhibit fear of uncertainty and to suffer from fatigue. The authors had concluded that CYP2D6 polymorphism might impact on personality, and one potential mechanism for this would be by influencing the generation of endogenous neurotransmitters in the brain.

— Ethical issues

We want people to feel that pharmacogenetics offers them a better future; it need not be threatening because it involves genetics, explained Sandy Thomas, director of the Nuffield Council on Bioethics. It is important to discuss the ethical legal and social implications, she continued. A number of assumptions have to be made about the context in which pharmacogenetics will develop. This is not easy because there are still many areas of uncertainty.

Pharmacogenetics is likely to have a considerable impact on both clinical trials and treatment but it is likely to be 20 years before the impact is felt. In the meantime, it will be important to assess claims about what pharmacogenetics will achieve and to consider ethical and policy issues. There is a common perception that genetic information raises specific ethical issues and is fundamentally different from other medical information, but this is not the case. After all, blood tests can also provide information about response to medicines, and testing for HIV and cholesterol can raise similar issues to genetic testing. It is the nature of the information that is key to considering its implications, not whether it is genetically derived, said Professor Thomas.

The ethical issues surrounding pharmacogenetics can be divided into three major areas, namely the research and development of medicines, public policy and the use and storage of genetic information.

It is likely that pharmacogenetic tests will be carried out by hospital doctors, GPs and pharmacists and the results would be stored in medical records. The Human Genetics Commission has said that special arrangements for storage of genetic information are not feasible. Considering whether written consent would be needed for pharmacogenetic tests, Professor Thomas said that each test needs to be evaluated according to the type of information that it will yield. In most cases written consent will not be required but patients should be provided with written information, particularly if the tests are likely to reveal complex or probabilistic information, such as susceptibility to other diseases in future.

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