THE ROYAL SOCIETY

Study on pharmacogenetics

Response by the Royal Pharmaceutical Society of Great Britain

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Dr John Clements, Science Secretary

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The Royal Pharmaceutical Society of Great Britain is the regulatory and professional body for pharmacists in Great Britain. It has responsibilities in relation to the education, registration, conduct and practice of pharmacists, and it registers and inspects pharmacies. The Society is also a Chartered body with objects concerning the advancement of science and the application of pharmaceutical knowledge.

The Royal Pharmaceutical Society is pleased to respond to the request from the Royal Society to seek submissions for its investigation into the potential for designing drug treatments based on a person's genetic makeup.

Overview

Current practices in clinical therapeutics result in medicines being used in a rather non-targeted manner in which the selection of the therapeutic agent is based on diagnosis but generally does not take account of inter-subject differences. This is understandable because until quite recently we have not had the ability to identify these critical differences and measure them.

There is a clear need to use medicines more effectively. Many classes of drugs have quite a low efficacy rate in clinical practice. These range from the Selective serotonin reuptake inhibitors (where the efficacy is about 62%) to those for treating Alzheimer's disease (about 30%) and cancer (about 25%) (Table 1, from Roses, 2004).

A number of factors can influence the efficacy of a particular treatment in any one individual (Table 2). Although the relationship between therapeutic response and genetic variation is complex, the variations between individuals in levels of metabolising enzymes and transporter proteins are now recognised as important determinants of therapeutic outcomes from treatments with some drugs.

For some enzymes and proteins, the levels of activity are genetically determined and genetic profiling offers a way to assess these levels. The key enzymes are those where the level of enzyme activity is genetically determined and where the enzyme level is an important determinant of the rate of removal ("clearance") of the drug. Table 3 lists some enzymes, together with examples of drugs that are cleared by these enzymes.

Advances in pharmacogenetics have the potential to improve the targeting of drugs, guiding both the choice of drug and dose in an individual, to avoid the use of drug regimens that cause adverse drug reactions, or drugs that are ineffective in the individual.

The future role of pharmacists

The Government wants to see more use made of point of care diagnostic testing and pharmacies are convenient locations for patients to visit to be tested. Pharmacists are well placed to play their part in the individualisation of therapeutic treatments because of their knowledge of medicines, experience of dealing with patients and the trust that the public puts in them.

There are a number of pharmacogenetic services that can be performed by pharmacists. These include advising and counselling, taking samples (such as buccal swabs) and conducting tests, interpreting results, prescribing and advising, monitoring and reviewing the treatment prescribed, recording results and educating the public and other healthcare professionals. The Royal Pharmaceutical Society will soon be providing practice guidance to pharmacists who plan to set up such services. This guidance will include information on clinical governance issues, choice of equipment, training and advertising of the services, and sources of funding.

Pharmacogenetic testing is currently carried out in central genetics laboratories using semi-automated equipment and technologies such as gene-chips, real-time polymerase chain reactions or sequencing. However, the development of new technologies and the identification of relevant single nucleotide polymorphs should allow appropriate pharmacogenetic tests to be performed at the point of care, such as in a pharmacy.

The potential of pharmacogenetics to improve the use of medicines is not confined to those available on prescription. Patients taking over-the-counter medicines containing codeine, for example, could benefit from testing. The test would only be required on a single occasion and the individual advised to use other analgesic drugs. With the Government's clear intention to deregulate more medicines from prescription-only to pharmacy status, people purchasing medicines in pharmacies would benefit from point-of-sale advice.

Last year, the UK Government published a white paper on "*Our Inheritance, Our Future – Realising the potential of genetics in the NHS*" looking broadly across genetics and health. It recognised the important role that pharmacists have to play in pharmacogenetics in the future.

As part of this initiative, the Department of Health recently announced the six winning bids for £4M to fund cutting edge research into pharmacogenetics. These research projects are expected to last one to three years and the results of half of the projects are expected to be used by the NHS or industry within five years of completion. The widespread clinical use of pharmacogenetic information for the benefit of patients is some years away, however.

Clinical applications

Responses by individuals to drug treatment are recognised as being multi-factorial (Table 2). Where the pharmacogenetic effects are large, and the specific genetic differences are readily detectable, genetic information would

have a role in drug and dose selection. There are just a few established drugs (including warfarin, omeprazole, tricyclic antidepressants, codeine, fluorouracil, mercaptopurine, azathioprine, isoniazid and irinotecan) that fall into this category, but they are widely used.

Most commonly, the use of a standard regimen may cause toxicity in a small group of individuals (such as occurs with azathioprine). However, some drugs are pro-drugs and may be ineffective when used in conventional dose regimens because the enzyme systems have reduced activity in some individuals. An example is codeine, which may lack activity in about 7% of Caucasian populations.

It is difficult to forecast the time-scale for the introduction and routine use of pharmacogenetic testing allied to drug therapy. However, the U.S. Food and Drug Administration (FDA) has started to address the issue. It has recognised the risk of toxicity of drugs metabolised by the endogenous enzyme thiopurine methyltransferase (TPMP) in some individuals. It now requires pharmacogenetic information to be added to the labels of two of these (mercaptopurine and azathioprine) to improve their risk/benefit ratio in clinical use, and is considering changes for two others (warfarin and irinotecan).

For new drugs, the pharmaceutical industry takes account of any important functional polymorphisms in developing dose regimens, and is developing pharmacogenetic test methods, if these are needed.

The British National Formulary

The British National Formulary (published jointly by the Royal Pharmaceutical Society and the British Medical Association) will contain relevant pharmacogenetic information to assist in the correct selection of medicines. The Editor has advised that the information will be provided on a drug by drug basis as the evidence base emerges (Mehta, 2004). (For an example, see Appendix 1).

Specific examples

Mercaptopurine and azathioprine

It has been observed that the toxicity of mercaptopurine and azathioprine (a pro-drug for mercaptopurine) is increased in individuals who are deficient in an endogeneous enzyme thiopurine methyltransferase (TPMP). Mercaptopurine is metabolised by at least three enzyme systems to inactive metabolites. One of these is an intermediate metabolite (thioinosine-5' monophosphate) that is itself metabolised to further metabolites including thioguanine (TG) nucleotides. The TG nucleotides can produce bone marrow toxicity (which can be fatal). TG formation involves enzymes ***other than*** TPMP whereas the metabolites formed from TPMT are non-toxic. This accounts for the observed inverse relationship between TG accumulation and the level of activity of TPMP.

The incidence of "poor" and "intermediate" metabolisers of mercaptopurine amongst the population are about 1:300 and 1 in 10 respectively, and poor metabolisers are particularly at risk from conventional doses of mercaptopurine (Baker, 2003). Because tests to identify TPMP genotype (or phenotype) are available, the results can be used to detect metabolic status and select the appropriate dose regimens for mercaptopurine in an individual.

Atomoxetine

Atomoxetine is a recently discovered selective noradrenaline re-uptake inhibitor that has been tested in clinical trials for Attention deficit hyperactive disorder (ADHD). It was approved for use in ADHD in the USA in July 2003.

Atomoxetine is primarily metabolised through the cytochrome P-450 2D6 pathway and the major metabolite is also active. The activity of the CYP 2D6 system can vary widely in healthy people; there are extensive metabolisers (EM) and poor metabolisers (PM). Individuals who metabolise it slowly will build up a higher level of atomoxetine faster than those who metabolise it rapidly. The plasma clearance ratio in EM is about ten times that in PM.

Clinical experience has shown that the rate of adverse drug reactions (ADRs) is 9% in PM and 6% in EM. Studies have shown that 3.5% of PMs and 1.5% of EMs discontinued atomoxetine because of ADRs. The FDA has suggested that genetic tests should be conducted in patients before prescribing atomoxetine, the first time that this approach has been taken by the FDA.

Irinotecan

Irinotecan was introduced in 1996 as a treatment for metastatic colo-rectal cancer. However, severe diarrhoea and neutropenia occur in 20 – 35 % of patients treated (Rougier at al, 1998; Saltz et al, 2000).

The metabolism is complex and involves many proteins. Briefly,

- human carboxylesterase isoforms 1 and 2 (hCE1, hCE2) activate irinotecan to its metabolite SN-38 (7-ethyl-10-hydroxycamptothecin);
- cytochrome P450 isoforms 3A4 and 3A5 (CYP3A4, CYP3A5) mediate the oxidation of irinotecan;

- uridino-glucuronosil transferase isoform 1A1 (UGT1A1) catalyses the glucuronidation (and inactivation) of SN-38;
- the multi-resistance protein isoform 2 (MRP2) allows the cellular excretion of the SN-38 glucuronide (SN-38G) (Toffoli and Cecchin, 2003 a); and
- the multi-drug resistance gene (MDR1), encoding for P-glycoprotein, is responsible for the excretion of irinotecan from the cell.

Polymorphic structures in the genes encoding for all these proteins have been described and multiple genes may play a role in irinotecan activity.

However, the UDP glycuronosyltransferase 1 family, polypeptide A1 (uridine diphoshate-glucuronosyltransferase 1A1 (UGT1A1)) enzyme has been most strongly associated with toxicity. A common dinucleotide repeat polymorphism in the UGT1A1 promoter region (UGT1A1*28) has been correlated with severe toxicity in patients with cancer receiving therapy containing irinotecan. The measurements used in the clinic, such as body-surface area, are considered no longer a sufficient determinant of the dose regimen ((Ando et al (2000); Iyer et al (2002); Toffoli et al 2003 b).

Patients with Gilbert's syndrome phenotype have reduced inactivation of the active topoisomerase I inhibitor 7-ethyl-10-hydroxycamptothecin (SN-38) caused by a mutation in the UDP-glucuronosyltransferase 1A1 gene promoter. This subset of patients is more likely to be exposed to irinotecan toxicity and could be identified by genotyping for gene promoter variants (Innocenti et al, 2000)

Therefore, the screening of patients before chemotherapy selection could identify those carrying the UGT1A1*28 polymorphism who could be given alternate therapy to avoid severe toxicities (Marsh and McLeod. 2004).

Appendix 1. Example of an entry in the current British National Formulary

"Azathioprine. The enzyme thioprine methyltransferase (TPMP) metabolises azathiorine; the risk of myelo-suppression is increased in those with a low activity level of the enzyme, particularly in the very few individuals who are homozygous for a low TPMP activity."

Table 1: Drug efficacy rates (%)

• Depression	62
• Asthma	60
• Cardiac arrhythmias	60
• Schizophrenia	60
• Migraine (acute)	52
• Alzheimer's disease	30
• Cancer	25

Table 2: Non-genetic determinants of therapeutic outcomes

Intrinsic determinants:

- Body weight
- Age
- Sex
- Organ dysfunction

Extrinsic determinants

- Timing of dose (in relation to food intake)
- Timing of dose (diurnal variations)
- Concomitant medication(s)
- Diet

Table 3: Enzymes and candidate drugs

Enzyme	**Drug**
CYP2C9	Warfarin
CYP2C19	Omeprazole
CYP2D6	Tricyclic antidepressants, codeine
DTP	Fluoracil
TPMT**	Mercaptopurine
NAT2	Isoniazid
UGT1A1	Irinotan

** TPMP = thiopurine methyltransferase

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