Editors' view

Characterizing variability in cardiovascular drug responses

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Optimizing the therapeutic response for an individual patient is at the heart of good clinical decision-making, but for most drugs the prescriber has very little information about clinical, demographic, or metabolic factors that influence outcome. Nowhere is this better illustrated than in cardiovascular therapeutics, where pharmacodynamic and pharmacokinetic variability accounts for significant inter- and intra-subject differences in drug response (see Figure 1). For example, antihypertensive and cholesterol-lowering drugs are prescribed extensively, but only a fraction of treated patients achieve target blood pressures and serum lipids [1, 2]. Clinical decisions about drug and dosage selection, combination therapies, and drug sequencing are largely empirical. This issue of the *Journal* contains several research studies that use different approaches to characterize cardiovascular drug responses and investigate factors that contribute to variability in treatment outcome.

MacFadyen *et al.* (pp 622–631) undertook a longitudinal study in patients with stable chronic heart failure (CHF) to investigate factors that contribute to within- and between-patient differences in response to furosemide. Changes in diuretic therapy or effectiveness may account for some episodes of CHF hospitalization, and diuretic resistance seems to indicate a poor prognosis [3]. The thrust of the study was to investigate whether over 2 years diuretic resistance, changes in diuretic absorption, and/or non-adherence to treatment contributed to the outcome (e.g. hospitalization or death from CHF). There were several important conclusions: (1) although furosemide dosage requirements varied widely (20–370 mg/day), there was a linear relation between dose and urinary furosemide excretion and the within-subject variability in furosemide excretion was relatively low; (2) there was a progressive rise in the pre-

scribed doses of furosemide over time, but diuretic responsiveness (calculated as mmoles of Na⁺ excreted per mg of furosemide in the urine) within an individual remained constant, despite variations in prescribed dose and outcome; and (3) patients who died during follow-up had evidence of furosemide resistance (i.e. impaired sodium excretion per unit drug reaching the renal tubules). Another interesting observation was that non-adherence to medication among CHF patients seems to be selective.

Statins are another major class of drugs used in long-term therapy for patients with cardiovascular disease, but there are considerable inter-individual differences in lipid-lowering responses, dosage requirements, and

Figure 1

Pharmacodynamic and pharmacokinetic variability accounts for the large inter- and intraindividual differences in cardiovascular treatment responses. Genetics, clinical factors and disease-related mechanisms may affect circulating drug concentrations and/or drug responsiveness

disease-modifying effects. The clinical and cost-effectiveness of statin therapy has been evaluated in different patients, e.g. in primary versus secondary prevention of coronary heart disease (CHD), in older patients, in those with diabetes, and in those who have had a stroke as opposed to a CHD event. Crucial public health decisions about the balance of benefit and harm and the availability of statins are often based on estimates of the number needed to treat (NNT) for different patient subgroups and different cardiovascular outcomes, but conclusive analyses require tight confidence intervals [2].

Cheung *et al.* (pp 640–651) report a meta-analysis of 10 placebo-controlled trials of statin therapy in 79 494 subjects, to derive more reliable estimates of the treatment effect on different end-points, e.g. major CHD events, strokes, all-cause mortality, and non-cardiovascular mortality, in specific patient subgroups. Statin therapy reduced major CHD events by 27% (95% CI 23, 30), stroke by 18% (95% CI 10, 25), and all-cause mortality by 15% (95% CI 8, 21). In addition, there was a non-significant 4% reduction in non-cardiovascular mortality. This meta-analysis has shown that the magnitude of reduction in major CHD events with statin therapy is independent of sex and the presence of hypertension or diabetes. But the risk reduction was significantly greater among smokers. This study also provides information about the comparative effects of different statins. Pravastatin reduced stroke incidence by only 12% (95% CI 1, 21), whereas the other statins reduced it by 24% (95% CI 16, 32) ($P < 0.04$).

Pharmacokinetic factors also influence inter- and intra-individual differences in drug response, as do adverse effects. Calcium channel blockers exemplify this. Clinical observations in the 1980s first suggested that the antihypertensive effect of calcium channel blockers may be greater in older patients [4], but this was not solely due to an effect of age on pharmacodynamic sensitivity to calcium channel blockers, since reduced hepatic metabolism accounts for higher plasma drug concentrations in the elderly [5]. Minami *et al.* (pp 632–639) have shown how pharmacokinetics, especially the rate of drug absorption, can have an important effect on the pharmacodynamics of calcium channel blockers. They compared 24-hour blood pressure and heart rate profiles in hypertensive patients taking two modified-release formulations of nifedipine, one taken once a day and one twice a day. Although 24-hour blood pressure reduction was similar in the two groups, there was much less evidence of reflex sympathetic activation (i.e. increased heart rate) after treatment with controlled-release nifedipine. Since reflex autonomic stimulation

often causes the adverse effects of headache, flushing, and palpitation, these observations may have important implications for improving the tolerability profile of nifedipine.

Characterizing treatment responses using an integrated approach to pharmacokinetic and pharmacodynamic modelling provides a more scientific basis for analysing factors that account for inter- and intra-subject differences in drug effects. Persky *et al.* (pp 552–562) have applied pharmacokinetic–pharmacodynamic modelling to the unwanted effects of ephedrine on blood pressure and heart rate. Ephedrine is a key ingredient in some popular aids to weight reduction, which have been associated with serious adverse cardiovascular effects (e.g. hypertension, myocardial infarction). During 8 hours after a single dose of ephedrine there was clockwise hysteresis – i.e. the change in blood pressure lagged behind the change in plasma drug concentrations. There was a linear concentration-effect relation for the increase in heart rate, and there was tolerance to the effect of ephedrine on blood pressure. Such information will undoubtedly help to define the relation between ephedrine dose and adverse cardiovascular effects, and therefore reduce the likelihood of serious adverse events. In a similar study Cantarini *et al.* (pp 657–660) have used pharmacokinetic–pharmacodynamic modelling to characterize the pressor effect of intravenous tyramine and to investigate inter-subject variability. They measured the dose of tyramine required to increase the systolic blood pressure by 20 mmHg in each healthy volunteer and found no evidence of tachyphylaxis. These results will be of practical benefit for the future design of phase I safety studies to characterize possible interactions between tyramine and new drugs in the pipeline.

There is much interest in genetic effects on pharmacokinetic and pharmacodynamic variability of cardiovascular drugs [6]. Several DNA polymorphisms have been implicated in specific mechanisms responsible for such variability (see Table 1). For example, P glycoprotein, which is encoded by the MDR-1 gene, is involved in the acquisition of multidrug resistance phenotypes in cancer cells and various other tissues, but P glycoprotein also limits intestinal drug absorption and oral drug availability (e.g. digoxin). Single nucleotide polymorphisms of the MDR-1 gene have been associated with lower intestinal P glycoprotein activity [7]. Two polymorphisms of the MDR-1 gene had no effect on the oral availability and disposition of risperidone (pp 569–575), although this gene seems to have widespread effects on the absorption profiles of orally administered drugs.

Table 1

Examples of DNA polymorphisms implicated in the variable treatment outcomes with cardiovascular drugs; adapted from [6]

Drug	Gene	Effect
<i>Pharmacokinetic variability</i>		
Digoxin	MDR-1	Variable systemic availability
Warfarin	CYP2C9	Increased anticoagulation
Losartan/irbesartan	CYP2C9	Greater blood pressure response
Metoprolol	CYP2D6	Poor metabolizers—greater beta-blockade
<i>Pharmacodynamic variability</i>		
Drugs that prolong the QT interval	KCNHZ/ KCNEZ	Increased risk of torsade de pointes
Beta-blockers	β 1 and β 2 adrenoceptors	Blood pressure and heart rate responses
ACE inhibitors	ACE	Reduced response with DD genotype
Beta-blockers	ACE	Increased response with DD genotype
Diuretics	α -Adducin	Variable stroke incidence and blood pressure response
Antihypertensive drugs	GS α	Variable blood pressure response
Pravastatin	CETP	Variable regression of atherosclerosis
Fluvastatin	ABCA1 transporter	Fluvastatin resistance
Lipid lowering drugs	Hepatic lipase	Variable lipid lowering

These six papers in this issue of the *Journal* illustrate a variety of scientific approaches in characterizing therapeutic responses and adverse effects of cardiovascular drugs. Their common goal is to provide more information about variability in outcome, so that decisions in routine practice can be more informed and less empirical.

References

- Marques-Vidal P, Tuomilehto J. Hypertension awareness, treatment and control in the community: is the rule of halves still valid? *J Hum Hyperten* 1997; 11: 213–20.
- Shepherd J. Statins for primary prevention: strategic options to save lives and money. *J R Soc Med* 2004; 97: 66–71.
- Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002; 144: 31–8.
- Buhler FR, Hulthen DL, Kiowski W. The place of the calcium antagonist verapamil in antihypertensive therapy. *J Cardiovasc Pharmacol* 1982; 4: 5350–7.
- Robertson DRC, Waller DG, Renwick AG, George CF. Age related changes in the pharmacokinetics and pharmacodynamics of nifedipine. *Br J Clin Pharmacol* 1988; 12: 401–4.
- Roden M. Cardiovascular pharmacogenomics. *Circulation* 2003; 108: 3071–4.
- Segmund W, Ludwig K, Giessmann T, et al. The effects of human MDR-1 genotype on the expression of duodenal P-glycoprotein and disposition of the probe drug talinolol. *Clin Pharmac Ther* 2002; 72: 572–83.