Pharmacogenomics of hypertension: a realizable goal?

It is common clinical experience that individual patients vary in their response to different types of anti-hypertensive drugs. The best recognized example of this is the much poorer response of black subjects to angiotensin-converting enzyme (ACE) inhibitors compared with that of Caucasians. However, even within a relatively homogeneous group, individual responses vary greatly. This was shown recently by Dickerson et al. [1] in their study of 56 white patients (aged 22–51 years) from the East Anglia region of the U.K., with previously untreated essential hypertension, who were rotated through the four main classes of anti-hypertensive drugs (diuretics, \( \beta \)-blockers, calcium antagonists and ACE inhibitors). Only 22 out of 56 (39\%) individuals achieved the target blood pressure with their first drug, but this increased to 41 out of 56 (73\%) when the best response was considered, supporting the concept of individual variability in anti-hypertensive response. There was some correlation between the responses to ACE inhibitors and \( \beta \)-blockers \( (r^2 = 0.25) \) and between those to diuretics and calcium antagonists \( (r^2 = 0.36) \), but not between the other four pairings of treatments.

Currently few, if any, clinical or biochemical parameters provide a useful guide as to whether a subject will respond well to a particular class of anti-hypertensive drug. Renin–sodium profiling has been advocated as a means of distinguishing hypertension that is volume dependent (and therefore likely to respond to diuretics) from hypertension that is renin dependent [and therefore likely to respond to drugs that inhibit or antagonize the renin–angiotensin system (RAS)] [2]. However, such profiling has, so far, found little utility in routine clinical practice. Therefore, from an efficacy viewpoint, the choice of initial anti-hypertensive drug is largely empirical. A variety of factors influence the decision, including cost, trial evidence or perceived benefit, guidelines from learned bodies, the presence of other disorders which may encourage (e.g. ACE inhibitors when there is left ventricular dysfunction) or exclude (e.g. \( \beta \)-blockers in presence of asthma) the use of particular drugs, and fashion. The study of Dickerson et al. [1] shows the shortcomings of the current empirical approach. Their findings suggest that, unless one is prepared to go through the laborious process of rotating those patients who do not initially respond adequately through different classes of drugs, many patients will either remain inadequately treated or have additional drugs unnecessarily added in when one would have sufficed. The potential cost, both financially and in terms of morbidity, is enormous.

The reasons for the inter-individual variation in responses to anti-hypertensive agents are poorly understood. Although genetically determined variation in drug metabolism that could impact on bioavailability has been documented for some anti-hypertensive agents, this is likely to be only a minor factor. Most of the variation is probably a direct consequence of the heterogeneity of mechanisms underlying ‘essential’ hypertension. Since genetic factors make a significant contribution to this heterogeneity, a hope that is often expressed is that elucidation of the nature of the inherited factors and a better molecular characterization of hypertension may allow a more informed therapeutic choice to be made. Indeed, this potential provides a key reason for justifying research funding in this area.

Several genes have now, at least tentatively, been linked and/or associated with essential hypertension [3]. In the RAS, these include polymorphisms in the angiotensinogen gene, the ACE gene and the angiotensin II subtype 1 receptor gene. However, current evidence that these genetic variants significantly influence blood pressure responses to drugs that antagonize or inhibit the RAS is weak. This is particularly surprising as, at least in the case of the angiotensinogen and ACE genes, the polymorphisms influence plasma levels of their respective protein products. A likely explanation is that, under normal circumstances, these changes are not sufficient to affect the activity of the RAS. A more exciting observation has recently been reported in relation to the adducin gene. Adducin is an \( \alpha/\beta \) heterodimeric protein found in the renal tubule, and is thought to regulate ion transport through changes in the actin cytoskeleton. A Gly–460 → Trp polymorphism in the \( \alpha \) adducin gene has been variably associated with hypertension, and the Trp460 allele has been shown to increase proximal tubular reabsorption [4]. In two separate hypertensive Italian cohorts, subjects carrying the Trp–460 variant have been found to show a much greater fall (by as much as 70–100\%) in blood pressure after a thiazide diuretic than subjects carrying only the Gly–460 allele [5]. The findings require replication in other populations but, if confirmed, could provide a valuable means of identifying individuals who are more likely to show a greater blood pressure response to diuretic treatment, since the Trp–460 allele occurs in up to 20\% of European Caucasians. A further example relates to the epithelial sodium channel. A mutation in the \( \beta \) subunit (T594M) has been reported to be almost four times more common in hypertensive compared with normotensive black subjects living in
London (8.3% and 2.1% respectively), with those carrying the 594M variant showing evidence of sodium retention, presumably due to increased channel activity [6]. Since amiloride is a direct antagonist of the epithelial sodium channel, those patients carrying the mutation may show a particularly good blood pressure response to this agent. This needs to be formally assessed.

The search for gene variants that may predict an enhanced blood pressure response need not be confined to those genes that have been associated or linked with hypertension. Indeed, the adducin story [5] illustrates the vagaries of trying to associate a polymorphism with a complex heterogeneous trait such as hypertension. Responses to drug treatment are likely to be more predictable and hence easier to demonstrate and replicate. However, analysis should ideally focus on plausible candidate genes, and especially variants that have been shown to directly influence the level or activity of the gene product. In this issue of Clinical Science, O'Shaughnessy and colleagues [7] describe a first assessment of whether a common polymorphism in the \( \beta_1 \)-adrenoreceptor gene, G389R, influences the blood pressure (and heart rate) response to \( \beta \)-blockade in hypertensive subjects. The polymorphism has not been associated with hypertension. However, in vitro studies have shown that it markedly affects G-protein coupling of the receptor and resulting cAMP production, with a 3-fold greater cAMP level following receptor activation with the R389 compared with the G389 form [8], making it a worthwhile candidate to investigate. However, in a total of 147 subjects in two study groups, they found no evidence that the G389R variant influenced the clinical blood pressure response to 1 month of \( \beta_1 \)-receptor blockade. The authors carefully discuss their findings and why an effect may not have been seen, including the possibility of a Type II error. The pretreatment plasma renin level was found to be a predictor of the blood pressure response to \( \beta \)-blockade. However, the effect was modest (13% of variance), suggesting that a further search for functional genetic variants in the \( \beta_2 \)-adrenoreceptor signalling pathway may yet prove worthwhile.

What then of the future? As illustrated by the study of O'Shaughnessy et al. [7], the drive to identify genetic factors that influence blood pressure responses to anti-hypertensive drugs is definitely on. Several factors could aid this process. First, there should be a focus on functional genetic variants, or at least the use of haplotypes to define more accurately variation at a gene locus. Technically, this is becoming easier with the advent of chip-based genotyping. Secondly, use should be made of more precise methods of assessing blood pressure response, such as 24-h ambulatory blood pressure recording. Thirdly, there should be more active collaboration in this area with the pharmaceutical industry. Although their main aim in any clinical evaluation of an anti-hypertensive agent is to demonstrate overall efficacy, the same data set could be used to identify those who respond well and those who do not. If a register of such studies, together with a DNA bank, could be built up, then progress in identifying responsible genetic determinants of the variable response could be quite rapid. Equally, as the study by O'Shaughnessy et al. [7] demonstrates, if hypertension clinics set up protocols that dictate the introduction or addition of anti-hypertensive drugs and allow the subsequent blood pressure response to be monitored accurately, then much of the information necessary to identify genetic factors could become available through routine clinical practice. Although much more work needs to be done, the emerging data make one optimistic that common genetic variants will be identified that will improve the prediction of the blood pressure response to each class of anti-hypertensive drug, and that in 10 years’ time, if not sooner, our choice of anti-hypertensive agent for individual patients will be much better informed.

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REFERENCES

5 Glorioso, N, Manunta, P., Filigheddu, F. et al. (1999) The role of \( \alpha \)-adducin polymorphism in blood pressure and sodium handling regulation may not be excluded by a negative association study. Hypertension 34, 649–654