Variability in Human Drug Response
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Ethnic differences in drug response: A model for understanding interindividual variability

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ABSTRACT

The mission of clinical pharmacologists is to understand interindividual variability in drug response in order to allow optimization of therapy for the individual patient. In the quest to improve such individualization it is important to identify patient groups whose characteristics put them at special risk from either excessive or reduced pharmacologic effects. It has long been recognized that such inappropriate response may be due to either pharmocokinetic or pharmacodynamic variability so that the individual may have an appropriate pharmacological response to an abnormal drug concentration at the effect site (pharmocokinetic variability), or may have an inappropriate response to a normal drug concentration at the effect site (pharmacodynamic variability). Recent advances in molecular biology have allowed us to understand many of the molecular mechanisms responsible for such interindividual variability in drug response and to explain the differences in drug response among different ethnic groups.

Key words: ethnicity, drug response, pharmacokinetics, pharmacodynamics, receptors.

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INTERETHNIC DIFFERENCES IN DRUG METABOLISM

Interethnic differences in drug metabolism may be due to one of the following:

- Interethnic differences in distribution of a polymorphic trait.
- Mutations which code for enzymes with abnormal activity which occur with altered frequency in different ethnic groups.
- Interethnic differences in metabolism within a phenotype.
- Interethnic differences in substrate specificity.

The effects of these differences will depend on whether the drug in question produces its effects directly or through a metabolite, examples of both situations have been found to result in interethnic differences in response.

Many of these differences are well illustrated by the effects of ethnicity on the analgesic codeine which is metabolized by CYP2D6 to morphine (Figure 1). Most of codeine's thera-

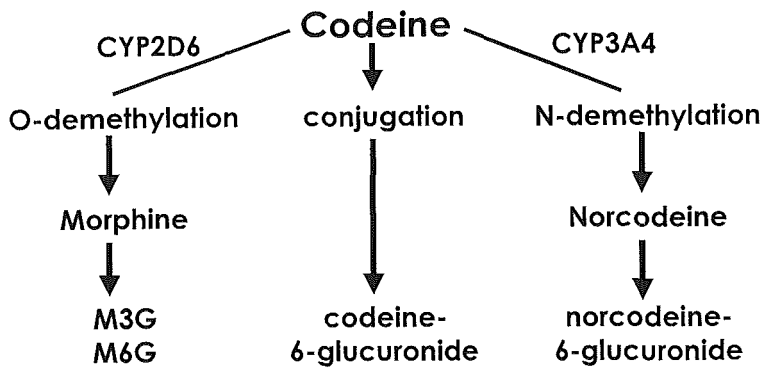

Figure 1. Routes of codeine metabolism

peutic effects are due to the production of this active metabolite, so that the therapeutic effect produced in an individual is dependant on the combination of that individual's CYP2D6 activity and their sensitivity to morphine. Individuals who lack active CYP2D6, poor metabolizers, produce minimal amounts of morphine (Figure 2) [1] and achieve little opiate effect [1] (Figure 3). Because of the interethnic differences in the distribution of the poor metabolizer phenotype (Table 1) the proportion of individuals who fail to produce morphine will also show marked interethnic difference.

Table 1.
Frequency of CYP2D6 poor metabolizers in different ethnic groups [2]

Population	Poor metabolizer frequency
US Caucasian	7%
Nigerians	8%
Chinese	0,7%
Japanese	0,5%

Thus altered frequency of a polymorphic trait is an important determinant of interethnic differences in response. However even within a phenotype interethnic differences may occur. Again this can be illustrated with codeine. In Chinese extensive metabolizers the partial

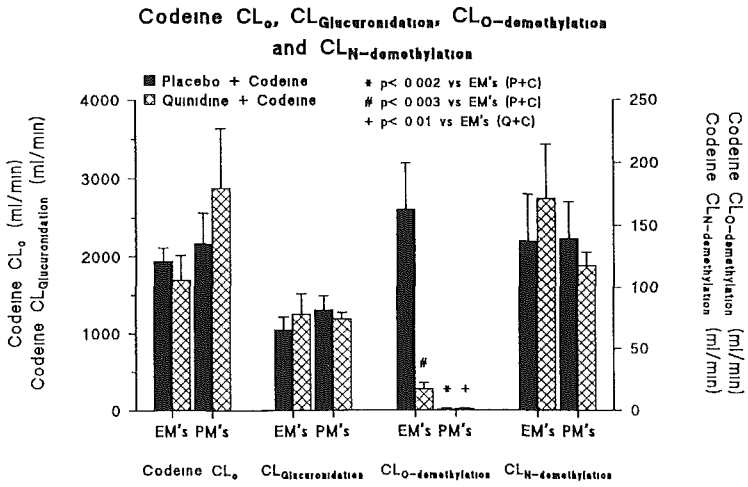

Figure 2. Partial metabolic clearance of codeine by various routes in extensive (EM) and poor metabolizers and following quinidine [1]

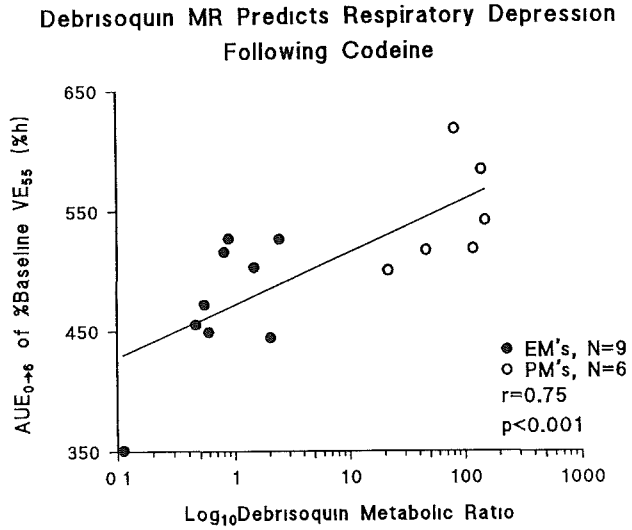

Figure 3.
Relationship between debrisoquin metabolic ratio and codeine induced respiratory depression[1]

metabolic clearance of codeine by the O-demetylation pathway (the pathway responsible for the production of morphine) was substantially lower in Chinese EMs than in Caucasians [3].

The explanation for this is also now clear and has a genetic basis. Chinese individuals have a high incidence of the allele CYP2*10 [4] which codes for an enzyme with reduced metabolic activity [5], so that even though they are phenotypically extensive metabolizers they have a lower enzyme activity.

ETHNIC DIFFERENCES IN DRUG SENSITIVITY

Ethnic differences in drug response also occur due to altered sensitivity at the receptor level even when corrections are made for drug concentration. Sensitivity to morphine is decreased in Chinese individuals [6] resulting in less respiratory depression in response to both direct morphine administration [6] and in response to the morphine produced by metabolism of codeine [3].

ETHNIC DIFFERENCES IN VASCULAR RESPONSE

It is well recognized that mortality and morbidity from hypertension and other vascular disease is higher in Blacks. This led us to investigate role of ethnicity in determining vascular response. Vascular tone is determined by both vasodilation and vasoconstriction and ethnic effects have been shown on both. The vasodilatory response to $beta_2$ stimulation by isoproterenol is impaired in African Americans [7] (Figure 4). Again exploration of the genetic

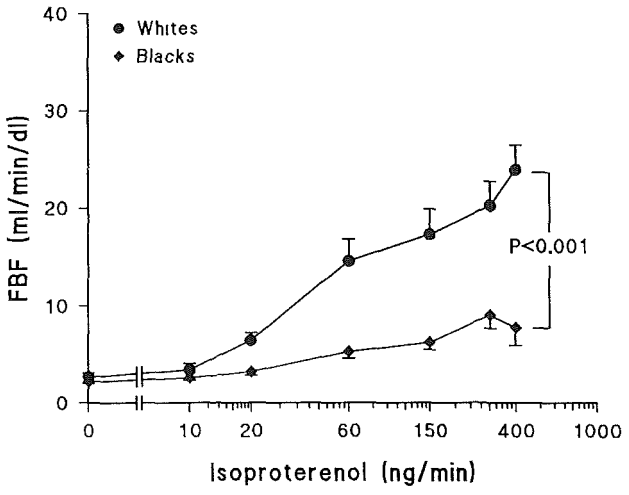

Figure 4. Impaired vascular response to $beta_2$ receptor mediated vasodiation [7]

basis for this difference has become possible, with recent data suggesting that this interethnic difference may be due to an altered frequency of a mutation for the $beta_2$ adrenergic receptor

gene. Response to vasodilation induced by nitric oxide is impaired in Blacks whether the generation of NO is endogenous (produced following methacholine administration) or whether produced following sodium nitroprusside [8]. Vasoconstriction produced by intra-arterial administration of phenylephrine is markedly increased in Blacks so that the combination of impaired vasodilation accompanied by enhanced vasoconstriction will result in additive effects and increased vascular tone.

CONCLUSION

Thus in conclusion, understanding the basis for ethnic differences in drug response have significantly enhanced our ability to define the underlying basis for interindividual variability in responses to drugs.

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Discussion: Ethnic differences in drug disposition and response

P. du Souich:
Just to confirm some of the data presented, the Mexicans have shown that the need of nifedipine among them is almost half the dose of Caucasians. This fact has been associated to the widespread use of corn in their meals.

A.J.J. Wood:
We are currently looking at midazolam in Mexico and we are not seeing huge differences, though there have been data in the past that suggested that such differences might exist. When you are looking at ethnic differences it is difficult to know whether they are due to the environment or to the genotypic differences.

H.K. Kroemer:
Related to this morphine story in Chinese, it could be a pharmacokinetic phenomenon due to the production of glucuronides or to the P-GP transport through the blood-brain barrier. Do you have further details on how that works? My second question is: Do you know whether the development of tolerance to morphine effects in Chinese is different from in Caucasians?

A.J.J. Wood:
The point is that morphine is metabolised to an active glucuronide and that might explain these differences. We performed this study but the differences in morphine glucuronidation and in plasma glucuronide concentrations did not explain these differences. We also thought that morphine-3-glucuronide might be a P-GP substrate, but unfortunately through our studies *in vitro* we could not confirm that. The anaesthetic literature had said that Asians were much more sensitive to morphine than Caucasians, however this goes the wrong way with what we were led to expect. In fact, Asians appear to be much more sensitive to the nausea-producing effects of morphine than were Caucasians. But as the anaesthesiologists were not measuring CO_2 response curves, perhaps what they had was a different effect. We also do not know whether that is due to some different receptor responses.

M. Lader:
I am wondering whether we are not being a little over-facile with this issue. For example, one of the problems in the development of drugs for schizophrenia is the possible over-representation of Afro-Caribbean origin patients, who are treatment-refractory. They end up in locked wards and on high doses of anti-psychotic drugs. There may be an over-representation of Western African origin people but not for people of East African origin. We need to have much more precise ways of defining ethnic groups than talking about blacks and Caucasians. The same happens when you refer to about Indians, without taking into account that there is a great deal of ethnic difference here. I think we are in danger of missing important data if we just put all people together by geographical origin, instead of doing some more biological analyses to typify what these groupings are.

A.J.J. Wood:

I agree with that completely. On the other hand, I think part of our purpose as clinical pharmacologists is to try to identify factors that we, as physicians, can use to better individualise dose. That can range from genotyping people, some sort of intervention we make before we give someone a dose, to more superficial measures, which include gender, age, frailty or ethnic background. We ought not to ignore the opportunity to try to use these techniques. For example, knowing somebody is from China, Japan or Korea, tells you they are very unlikely to be a poor metaboliser of debrisoquine, and secondly, it tells you that they are likely to have a higher incidence of the alleles that metabolise CYP2D6 substrates more poorly. There are some data actually also from side-effects of different anti-psychotic agents that show quite marked differences in the frequency, which may reflect expectation in different ethnic groups. Therefore, we need to try to find clues.

I.P. Hall:

When you have a polymorphism which is fairly common in a given population, it is relatively likely to be distributed events across that racial group. That is true for the β-receptor polymorphisms, which have a similar prevalence in all black South Africans or Afro-Caribbean populations and also in Japanese population, which have been studied. I have also a question that refers to the work on vasodilator properties of isoproteronol. It always worries me that there is a circular argument in saying that there is a causality link when you have got a population with a reduced vasodilator response and with a different prevalence for polymorphism. You have got in your population the key individuals, which are those who have the Glu-27 polymorphism in the blacks. Would you predict that those people would have the same response as the white Caucasians?

A.J.J. Wood:

I do not know the answer, but that is precisely what we are studying. We are trying to evaluate the sensitivity to desensitisation in previously genotyped individuals of both populations. As you said, it is possible to predict that individuals of different ethnic backgrounds but of similar genotypes would respond to desensitisation similarly. And hence, would respond to vasodilation in desensitised or not desensitised states similarly. As you can imagine, it is not a trivial experiment to undertake, so we have to find the homozygotes, and we have to convince them to undertake a desensitisation experiment.