Variability in Human Drug Response
G.T. Tucker, Editor

Variability in human drug response. Age as a source of variability

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ABSTRACT

Changes in liver size and volume, organ blood flow, enzyme activity and function, kidney function, receptor function, sensitivity, coupling mechanisms and second messenger responsiveness have all been elucidated and shown to influence responsiveness to ageing.

Phenotypic differences in drug handling were explained by genetic variations in drug metabolising enzymes such as the cytochrome P450 system (CYP). Using phenotypic probes for CYP2D6, CYP2C9 and CYP3A4 did not demonstrate any age related difference, yet CYP 2E1 has been shown to vary with age.

Recently, we have examined the impact of age and phenotype on CYP2D6 using propranolol as a model substrate. This showed a 55% decline in clearance of the propranolol in elderly PMs when compared to young EMs. This highlights the importance of the environment on differences in drug response.

More recently, frailty has been put forward to link the 'functional phenotype' with the 'physio-pharmacological phenotype'. Significant reduction in drug metabolism in frail elderly and not in well elderly has been noted. This separation based on function needs further research. Other areas include interaction studies to clarify the impact of genetics on drug response to such components as induction, inhibition and organ related age changes in CYP function.

Key words: age, pharmacokinetics, pharmacodynamics, variability, elderly.

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INTRODUCTION & HISTORY

This paper will summarise briefly the principle findings in relation to age as a co-variable in drug responsiveness. A detailed description is beyond the remit of this manuscript. The

review will focus on both pharmacokinetic and pharmacodynamic aspects of human pharmacology.

PHARMACOKINETICS

There are no consistent clinically meaningful changes in relation to age in drug absorption. This is principally because of the enormous surface are for absorption overwhelms any changes (decline) in the ability of the small intestine to absorb drugs. Changes in gastric acid production for the large part do not impinge on drug absorption. Less is known of ageing and alternative routes of drug absorption such as skin and d nose.

DISTRIBUTION AND HALF LIFE

On of the earliest human studies on ageing was from the Dundee group. O'Malley and colleagues published a study of half-lives between young and elderly [1]. This showed a significant trend in half-life with age for antipyrine.

Half-life is directly related to volume of distribution and inversely related to clearance.

Volume of distribution increases with lipophilic drugs with advancing years. This understanding explained in part the pronounced effects of benzodiazepines with age due to increased half-life [2]. As half life was dependent on Vd, subsequent work shifted the emphasis from half-life to clearance of drug [3].

CLEARANCE

Clearance, (litre/min) is a measure of the efficiency of an organ (or organism) to irreversibly remove a drug from the perfusate [3]. Systemic clearance is independent of drug. The liver is the main metabolising organ in the body. Hepatic clearance is dependent the ability of the liver to extract the drug from the blood and the amount of blood delivering drug to the liver, (LBF). This can be expressed accordingly.

$$Cl_{hepatic} = Q\,\frac{[Ca - Cv]}{[Ca]} = QE$$

E	=	steady state extraction ratio
Q	=	liver blood flow
Ca	=	concentration of drug in portal vein and hepatic artery
Cv	=	concentration of drug in vein leaving liver in hepatic vein
$Cl_{hepatic}$	=	clearance by the liver

Clearance is therefore dependent on two physiological parameters: LBF and the extraction ratio (E). E is dependent on the hepatic metabolic enzyme capacity otherwise known as intrinsic clearance (Phase 1 and/or phase 2 enzymes). Standard pharmacokinetic studies can determine E for an individual drug. Drugs can be classified into three groups by their E into high 0.7, low 0.3 or intermediate 0.3 - 0.7.

LIVER SIZE AND BLOOD FLOW AND AGE

Liver volume declines by approximately 30 % [4,5] in the over 65 yr. LBF falls by 20% - 35% in healthy elderly compared to young [5,6,7]. As LBF is important in high E drugs such as propranolol, triazolam, and chlormethiazole predictable decline in hepatic clearance occurs.

INTRINSIC CLEARANCE AND AGE

Intrinsic clearance of a drug is a measure of the clearing organ to remove that particular drug. It is estimated by E. It is independent of blood flow [3]. Reduction in intrinsic clearance will produce significant changes in the clearance of low extraction drugs. This can be illustrated by equations below.

$$QE = \frac{Q \times Cl_{intrinsic}}{Q + Cl_{intrinsic}}$$

$$Cl_{intrinsic} = QE/1 - E$$

$Cl_{intrinsic}$ = intrinsic clearance of drug by the liver

Antipyrine is an example of a low extraction drug. Age related decline of 19% in the clearance of antipyrine has been reported [7]. This was due to reduction in intrinsic capacity. Therefore, low E drugs might be predicated to have reduced hepatic clearance. However, hepatic extraction does not translate into systemic clearance decline. Further the increasing complexity of the CYPs has raised the possibility of selective decline on one pathway can be compensated by metabolism down an alternate pathway. As such the role of alternate pathways needs to be considered.

CYPs AND AGE

In human metabolism there are six subfamilies responsible for most of human drug metabolism. These are CYP 1A, 2A, 2C, 2D, 2E and 3A. Of the range of subfamilies known, CYP1A1, CYP1A2, CYP2C9 & 19, CYP2D6, CYP2E1, CYP3A4 & 5 are the most important in terms of drug metabolism. The effect age has on the functional activity of the various CYPs has been an area of intense research since the 1970s [6,7]. Studies of *in vitro* enzyme levels (accepting the problems of sampling) have not documented a decline in CYP enzyme function and amount with age [8]. *In vivo* estimations are more problematic and surrogate markers such as plasma aspirin esterase activity has been used to suggest that there is no difference *in vivo* between the elderly compared to the young [9,10]. *In vivo* probes have documented a decline the dapsone recovery ratio in contrast to debrisoquine ratio for CYP2D6 and mephenytoin ratio for CYP2C9 [11]. Initially, dapsone was attributed to CYP3A4 but more latterly has been

reassigned to CYP2E1 [12]. This data would therefore support a selective decline in CYP activity with age.

PHASE II REACTIONS AND AGE

There have been few studies examining age effects on conjugation because of the complex metabolism of many drugs. Nonetheless there are drugs exclusively metabolised by phase 2 reactions and these include lorazepam, oxazepam and paracetamol.

Studies with lorazepam did not find any significant reduction in the clearance of lorazepam with age following intravenous administration. [13]. Studies suggest that there is no age related decline in total clearance with oxazepam [2]. Yet a recent study of well elderly patients (80-94 yr.) noted a decline in unbound clearance compared to young. This was said to explain a pharmacodynamic difference in finger tapping between both groups [14].

Paracetamol conjugation is reduced in the elderly [15]. Similar data exists for the conjugation of metoclopramide in frail elderly but not healthy elderly. This difference persisted on correction for reduction in liver volume [16].

CYPs POLYMORPHISMS AND AGE

In a recent study, we examined the effect of age on both CYP2D6 and non-CYP2D6 pathways of propranolol's metabolism. Non-CYP2D6 pathways included conjugation of propranolol to its glucuronidated metabolite. We were unable to find any selective loss in capacity of either pathway when comparing young to elderly (65 - 81 yr.). However, the reduction in clearance of total propranolol in older patients who are deficient in CY2D6 pathway was greater than 50% compared to young subjects with functioning CYP2D6 (Kinirons *et al.* submitted). This indicates that elderly subjects who are deficient on CYP2D6 are at considerably greater risk of a drug related adverse effect because of increased demand on alternate pathways. This potential is further increased when the known changes in LBF and liver size further diminish the reserve in patients on chronic dosing of drugs metabolised by CYP2D6. All the elderly subjects studied in the above protocol where well healthy subjects.

There have been some interesting studies in frail elderly, a more clinically appropriate population to consider. Induction and inhibition in response to age is an area that needs to be re-examined in the light of our current understanding of the complexity of enzymes involved in drug metabolism.

ENZYME CHARACTERISTICS AND AGE

Based on only a small amount of data examining a few enzymes, no decline in Km and Vmax has been noted. In particular studies of the plasma esterase activity in the elderly has shown no difference compared to the young [10].

FRAILTY

Frailty has been defined as "persons over 65 yr., dependent on others for activities of daily living" [17]. Formal pharmacological studies on frail elderly have reported reductions in the metabolic activity of plasma aspirin esterase [9,10,18] and paracetamol conjugation [15] and in the metabolism of metoclopramide [16]. Studies with theophylline have documented increased variability in frail compared to healthy elderly [19]. These studies all emphasise the concept of frailty over age as a determinant of drug disposition and response.

Explanations for frailty might include greater reduction in liver volumes and /or blood flow compared to well elderly. This is supported by some studies. For example, Swift noted a decline in liver volume between well elderly and hospitalised elderly (990 ± 166 ml vs. 838 ± 242 ml) [4]. However, as mentioned above, correction for liver volume did not remove differences in phase 2 metabolism of metoclopramidde. There are no specific studies compared subjects with frail patients for liver blood flow.

ENZYME MODULATION AND AGE

Enzyme modulation is discussed in more detail by other speakers at the symposium and elsewhere [20]. Nonetheless, a few general points can be made.

The original studies on induction determined the inducibility of drug metabolising enzymes for antipyrine and propranolol's metabolism. This suggested that there was loss of inducibility with age [7,20,21]. By contrast, plasma esterase inducibility is not affected by age [22]. This would be consistent with differential selective inducibility with various enzymes based on our increased understanding of the complexity of CYPs.

Of note is the emerging data about the effects of diet on aspects of drug metabolism, induction and inhibition. An interesting report has reported significant inhibition of drug metabolism following changes in diet [23].

PHARMACODYNAMICS

Effects of ageing on the above are much less clearly defined. This is because of the problems in what to measure and what model to study. Frequently, altered drug pharmacodynamics are explained by some of the effects of ageing on pharmacokinetics. It is frequently difficult to disentangle one from the other. Further, one is not sure whether any reported changes are due to ageing or related to age-disease pathophysiology. Much of the data collected from animal models may not be applicable to humans. The main areas are in cardiovascular and in central nervous system pharmacology. I will therefore concentrate on this area for the remainder of this paper.

BETA RECEPTOR FUNCTION AND AGEING

The lymphocyte contains beta-receptors. This cell is accessible and therefore has been studied extensively. Initially, it was thought that numbers of receptors were lower in the

elderly than the young and that this was the explanation for the [24]. However, more recent studies have not confirmed this [25]. The well-known decline in responsiveness with age is now felt to be due to decline in coupling with rather than a decline in maximal receptor activity. Because of the surplus capacity of the receptor-substrate coupling there is no discernible decline in maximal receptor activity with age. However, decreases in numbers may lead to a diminished response. This is may be termed redundancy in the signal amplification pathway. These findings demonstrate the difficulty in interpreting the pharmacodynamic data.

VASCULAR RESPONSIVENESS AND AGEING

More recently, studies have looked at ageing and the forearm vascular bed [26]. Various groups have either studied the hand vein or using phlethysmographic techniques in association with brachial artery infusions [27]. The data suggests that there is reduced responsiveness to beta agonists as estimated by changes in blood flow [28,29] consistent with the receptor data. More recent data from our unit has suggested in contrast, that there is impaired nitric oxide mediated vasodilatation with ageing. Further, ageing *per se*, was associated with reduced basal urinary nitrate excretion even when corrected for creatine clearance [30]. These finding mirror the findings of reduced acetylcholine-mediated vasodilation [31]. In regard to nitric oxide, changes in forearm responsiveness are reversible in disease states such as treated hypertension [27].

CONCLUSIONS

Ageing and understanding its effect on drug response is crucial to society. With the ageing of the population, the potential for future pharmacological problems will increase. This will most likely be seen in increased admissions to acute hospitals with drug related problems or in more serious and dramatic effects such as has been seen with terfenadine. Therefore, the need to pursue more aggressively the underlying aspects that distinguish the well young from the sick older person and to apply this understanding to improve selectivity and specificity of drugs is a challenge we must continue to pursue.

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Discussion: Variability in human drug response: age as a source of variability

P. Rolan:
In the Vanderbilt's University paper (May G *et al.*, Clin Pharmacol Ther, 1994) you have shown a reduced dapsone clearance, were people of both genders included in the results stratified by gender?

M . Kinirons:
Yes, both genders. I think there was an about 40-60% split in gender distribution. A relationship with age was present in both genders.

L Aarons:
You have shown that the trends of physiologic variables with age are not linear, because they remain constant up until a certain age and then they drop off. Nevertheless, all the relationships which you showed and which are ubiquitous in the literature, show linear relationships of clearance, volume of distribution, etc., with age. Firstly, I would just like to get your comment on that. And secondly, did you measure protein-binding in your propranolol study?

M. Kinirons:
It is very hard to explain that discrepancy. I only can mention the existence of an increasing loss in liver mass and decline in liver volume with age. Arbitrarily, people have chosen 65 years as older, but perhaps if there were more detailed longitudinal studies, you would find much greater variability. About your second question, we measured protein-binding and there was no difference.

M.M. Reidenberg:
Firstly, I think that your exploration of the idea of frailty versus chronologic age is important, and I hope you will expand on that a little bit. Secondly, I would point out that virtually all of the studies in this field are cross-sectional studies, looking once at each person and then stratifying by age. The only longitudinal studies I am aware of are from the Baltimore Longitudinal Study of Aging in renal function (Lindeman RD *et al.*, J Am Geriat Soc, 1985). Here it is very clear that some people have virtually no decline in renal function as they get older, where other people have a slow and still others, a more rapid decline. So, when you look at a cross-sectional study, it appears as if people have a decline in renal function as they age. But in fact, some do and some do not. Clinically we can see people of the same age, and some obviously are frail and these are the ones who have trouble therapeutically. Has your thinking gone farther in coming up with criteria for defining frailty, in terms of research studies?

M. Kinirons:
No, I am afraid not. We are currently trying to look at those people who get admitted to hospital with drug-related adverse reactions and trying to equate with frailty, just to see if this concept persist in a different selected population. It has not caught on, so people have not taken up the idea put forward by Ken Woodhouse to try and translate from socio-functional

definition to a physiological definition. I have only tried to put forward some suggestions that there are links, because obviously changes in liver blood flow and liver mass cannot fully explain frailty.

G.T. Tucker:
You mentioned some work on debrisoquine suggesting that CYP2D6 activity does not change with age. This is based on constancy of the urinary metabolic ratio which, as I said, is also a function of renal drug clearance. What I believe happens with CYP2D6 with age is that enzyme activity and renal clearance tend to decline in parallel. Hence, the metabolic ratio does not change.

M. Kinirons:
It is very difficult sometimes to separate out those two aspects. Nonetheless, if you take debrisoquine as an estimate of CYP2D6 and you accept it for that, it is obviously important that we try to develop estimates or probe estimates for systemic clearance. What happens actually in the internal milieu is almost secondary because, even if it is important, the final line must be what comes out. So there could be a decline in hepatic metabolism, which is corrected by renal retention.

G.T. Tucker:
The fact is the enzyme may deteriorate with age, but you cannot see it with the index that you are using.

M. Kinirons:
From some of the data that I have shown, it is hard to imagine that if you get a 30% reduction in liver mass, the enzyme has upregulated with ageing, because you have now lost one third of all the cells that are metabolising CYP2D6. So in a sense one could speculate that this is what is happening, that there is some increased activity, but the individual data does not suggest that.

A. Breckenridge:
I would like to express the frustration of the drug regulator on this question of age and drug response. Nearly, every agency will have guidelines that a new drug should be studied in the elderly. But too often one gets results of investigations in what you might call geriatric "supermen". If a company came to you for advice on how to study a new drug, and they said they wanted to examine the effect of ageing, what advice would you give them?

M. Kinirons:
The pharmaceutical industry has failed to study the right population. The FDA's guidelines concerning studies in older people, have pushed up the age requirement as the realisation of the demographic trends have become apparent.There has got to be a need to study the real-world patients for your own practice. All the trials for donepezil in dementia were done in very clean patients, but the reality is that lots of these patients are on multiple drugs. Rivastigmine has moved forward in that because they have given the drug in their trials to a more varied population.

J. Urquhart:

The pharmacoepidemiology should inform regulators on what ought to be looked for in the studies with aged people. Because much of what you do as a regulator is to look at me-too drugs, so there are already drugs in the market-place that represent that class of therapy. It is possible to consult in data-bases those people who get that class of drug and to see what is the age distribution, and their current and past prescription drug histories profile. For example, basic community pharmacy records can give you a picture of what the dominant drug usage patterns are, how old the patients are, and what the gender distribution is. That is possible in the Netherlands where you have a reimbursement system, and where the basic system requires patients to designate a single pharmacy for their reimbursed prescriptions. If we are going to approve another drug in this class, we ought to have data in patients who have this and that sort of concomitant drug usage, age distribution, etc. And that will be representative of what is going to happen with the new product, because presumably it will go in unless the sponsor has compelling evidence for how they are going to label it differently and force the drug into a different usage pattern. But even in that situation you can look at it as soon as it goes in the market, to see where it goes, and then come back and hope for Phase IV studies to fill in the blanks. So I think that is a very realistic subject and it has not been done to my knowledge.

A. Breckenridge:

The role of the drug regulator is not to prevent a drug from coming to the market if it is going to benefit patients. The evidence of its safety must be gathered from wherever it can be obtained. However, one would submit that it is the role of the pharmaceutical company to produce that evidence, and a lot of them would be very happy to support it. If they produced evidence in what we were calling the geriatric supermen, the most severe comment would be that this drug had not been studied in an appropriate group of subjects, therefore it is not indicated in them. But most drug regulators would be unhappy about that, if it was seen not to be benefiting patients. But the plea that I was making is for more realistic studies to be carried out by the industry or better information to be obtained by them.

M.M. Reidenberg:

Let me ask for advice on issues I face as an editor. We will get a paper looking at either age or gender or some disease's effect on a drug. There will be 6 to 8 subjects in a group. The elderly people will range in age from about 60 to 69 with a median of perhaps 62 or 63. If the variability in a group is small, then sometimes a small difference can have a statistically significant $p<0.05$. If it is $p<0.1$, then they claim a trend has occurred. And the real issue I have as an editor is: Should these be rejected or am I simply contributing to publication bias? They are certainly not definitive, and if somebody does enough of these studies, some will have a $p=0.05$; and as you look at the data, it is because they were lucky and had small variability between one of the groups so that they could get statistical significance.

A.J.J. Wood:

The reason we study healthy elderly is to be sure we are studying only one variable, that is age and not frailty, ill health, nor other drugs. Similarly, if you were studying renal failure, presumably you would try and study patients who had renal impairment, but not other variables. Hence, we have to be careful that we do not get ourselves into a situation where

we study patients who happen to be elderly, but have cardiac failure, ischaemic heart disease or whatever else.

M.M. Reidenberg:
I am unwilling to accept people between 60 and 65 as being an elderly group for the purpose of clinical decisions with respect to drug therapy.

J. Urquhart:
Why do not you set a policy for what age means ? I vote for 85 and up.

M.M. Reidenberg:
This is what I am inviting advice on. These are decisions that have to be made. For the journal, I would rather we do it publically than that I personally make an arbitrary decision.

M. Lader:
One group of drugs is often given to people in their 50s and then they are continued on a regular basis into old age. The hypnotic drugs are amongst the most widely used of all the medications. The elderly lose their tolerance to these medications and they then end up either with a broken hip or pseudo-demented. And this is another area where we need longitudinal rather than cross-sectional studies.

T. Salmonson:
What I meant by publication bias is that interesting data may not be published by industry, because of other reasons. If you do pick up an effect in a small number of 60-65 year old people, it would be very interesting to see how that would translate into an 85-year old one. But if we had all the time and resources that we wanted, I am sure we could do a lot of work on existing data. There is plenty of data in regulatory agencies, where you can look at the effect of age in a number of drugs, and perhaps get the magic age number or year you are after.

U. Klotz:
Recently, an article (Fliser *et al.*, Kidney Internat, 1997) about aging and creatinine clearance was published which comprised a sufficiently high number of subjects. Included were the so-called fit elderly, just to find out an age effect, and different patient groups (elderly with hypertension and elderly with congestive heart failure). I think this is the type of study you were looking for and you will be happy to accept it because it is the way to clearly distinguish age *per se* and the effects of diseases.