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

Can we design drugs with low variability

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ABSTRACT

The reasons for inter-subject variability in dose response can reside within the pharmacokinetic (PK) or the pharmacodynamic phase (PD) of the classical PK/PD model. Thus concentrating solely on pharmacokinetics may not result in markedly reduced variation in response. However, some reasons for variability in the pharmacokinetic phase are additive and therefore should be targets for drug design. For instance, unreliable or erratic absorption can be overcome by correct physiochemical properties. Extremes of variation in clearance can be limited by avoiding metabolism by polymorphic cytochrome P-450, such as CYP2D6 and CYP2C19. However, clearance will always remain a large source of variability and has to be addressed by having sufficient selectivity for the target to avoid side effects. Patient compliance probably represents one of the largest reasons for variability in drug effect and design has to focus on medicines that have convenient twice or once a day dosage regimens, that are not complicated by food effects or concomitant administration with other drugs.

Key words: Pharmacodynamics, absorption, food, P450, polymorphism, compliance.

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PHARMACOKINETIC VARIABILITY AND PHARMACODYNAMICS

When one considered the question "can we design drugs for low variability?" further clarification of what constitutes variability is needed. Variability can only really be considered from the point of view of dose and pharmacological effect. Attenuation of the variability in a single event in the cascade that follows the swallowing of an oral dose and observing the pharmacological effect of the drug may not have the desired outcome in an overall reduction in variability of dose response. Figure 1 illustrates a typical PK/PD model, dividing drug activity into the pharmacokinetic phase and the pharmacodynamic phase. The pharmacodynamic phase is further subdivided into the interaction with the drug receptor triggering post receptor events, eventually leading to actual drug effect. The impact of considering this model is that variability in the pharmacokinetic phase may not be the

dominant factor in the overall variability of response [1]. To exert an effect drugs must occupy the receptor to differing degrees. For instance, many 7 trans-membrane spanning receptor/anatgonists (7-TM's, such as β-adrenoceptor antagonists, dopamine antoagonists, etc) require around 75% occupancy to trigger efficacy [2]. In contrast ACE inhibitors are often dosed to maximally (95-100%) inhibit the enzyme (occupy the receptor). With their high degree of selectivity, considerable attenuation of the effects of any variability in pharmacokinetics occurs with this "maximal" dosing strategy. Noticeably the actual effects on lowering blood pressure still shows variability even when the degree of ACE inhibition is constant. This variability is the result of post-receptor events referred to above.

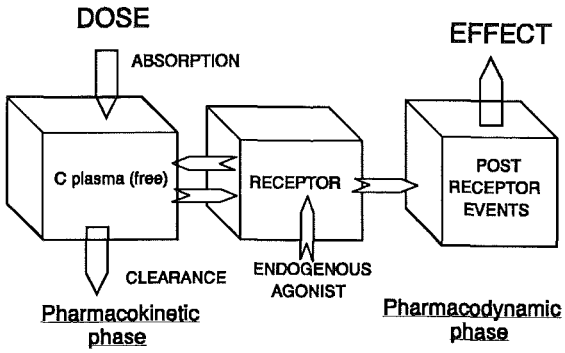

Figure 1. Pharmacokinetic/pharmacodynamic model linking administration of an oral dose of a drug and pharmacological effect.

For most drugs only a proportion of the target receptor is normally occupied for efficacy. Moreover drug concentration and effect can be modelled to provide sigmoidal or linear dose response relationships. Study of these relationships shows how variability in the pharmacokinetic phase can be exaggerated by the pharmacodynamic phase. Hill numbers, which refer to the steepness of dose response curves can range from 1 (Fenoterol, albuterol and noberastine), 2 (diazepam), 4-5 (midazolam, alfentanil, morphine and meperidine) to 20 (tocainide). The numbers are a summation of receptor occupancy, post receptor events, plus the actual effects observed, but do give an indication that pharmacokinetic variability is more critical to some pharmacological mechanisms than others.

It is clear that solving pharmacokinetic variability may not in itself rectify inter-individual variation. Nevertheless it is an appropriate target for some aspects of drug design as outlined below.

ABSORPTION, AN UNNECESSARY SOURCE OF VARIATION THAT IS AMENABLE TO DRUG DESIGN

It would seem a reasonable premise that variability is drug absorption is an unnecessary complication, regardless of the outcomes of the analysis above. In essence, drugs should have adequate aqueous solubility for dissolution of the compound to occur, followed by an ability

to rapidly traverse the gastro-intestinal tract epithelium and enter the blood stream. Solubility is broadly inversely proportional to the number and type of lipophilic functions within the molecule and the tightness of the crystal packing of the molecule. Absorption across the gastro-intestinal tract normally involves the diffusion of the molecule through the apical and basolateral membranes of the cells lining the gastro-intestinal tract (transcellular absorption). To traverse this route the compound has to have sufficient lipophilicity to "dissolve" within the lipid core of the cells membranes. If a molecule has sufficient lipophilicity the large surface area of the microvillic means that absorption is rapid. Tight junctions formed by the proteins that act as the junction between cells, offer an aqueous channel (pore) for (paracellular) absorption. These pores are estimated to be a size of 3-10A and represent only 0.01% of the total absorptive surface area. Thus whilst available for small molecules, the aqueous pore paracellular pathway is an inefficient route. Moreover, adequate pores for drug absorption are only present in the upper gastro-intestinal tract, thus creating an "absorption window".

A number of drugs have very low aqueous solubility, mainly due to very high lipophilicity, but also due to lack of ionisable centre, and also the tight crystal packing referred to above. These drugs are erratically and incompletely absorbed due to this inability to dissolve in the gastro-intestinal tract following oral administration. Examples of low solubility, dissolution limited drugs include danazole [3], griseofulvin [4], halofantrine [5], ketoconzaole [6], nitrofurantoin [7], phenytoin [8] and trianterene [9]. Poor dissolution is responsible for both intra- and inter-patient variability.

Low or negligible lipophilicity compounds which rely on the paracellular aqueous pore pathway include atenolol, nadolol, pirenzipine, and ranitidine [2]. These compounds range in absorption from 51-13%, and are all simple, low molecular weight structures (266-351) as is necessary for acceptable absorption by this mechanism [10]. Whilst not highly variable per se, the incomplete absorption renders the mechanism particularly influenced by motility effects due to the "absorption window [11]".

Food is a complicating factor in drug absorption but its effects are largely limited to the above types of drugs, those either of very low lipophilicity, or those of very low aqueous solubility. Due to increased secretion of acid, bile, etc., the dissolution of poorly soluble drugs can be considerably increased (e.g. halofantrine, 1200% increase) [5]. In comparison food can reduce the absorption of low lipophilicity drugs due to effects on motility and shorter residence of the dose in the upper gastro-intestinal tract (e.g. atenolol, 20% reduction). The effect of food to increase the variability of absorption is shown schematically in Figure 2. To overcome these problems compounds in the "mid-ground" of the lipophilicity (log $D_{7.4}$ 0-2.0) offer the best chance for the optimal balance of properties to ensure rapid dissolution and subsequent efficient and complete transcellular absorption. Similarly such compounds are unlikely to show complications due to food, other than a delayed Tmax due to lengthened

Fluconazole is an example of a drug design programme aimed at producing an antifungal agent [2] with superior pharmacokinetics to the first orally active azole antifungal drug. ketoconazole (Figure 3). Ketoconazole is cleared primarily by hepatic metabolism and is difficult to formulate to obtain consistent absorption, due to poor aqueous solubility due to its high lipophilicity log P>5. Fluconazole is the least lipophilic (log P 0.5) member of a series of metabolically stable bis-triazoles. This ideal physicochemical profile gives fluconazole rapid dissolution and complete transcellular absorption. This complete absorption is not affected by food, achlorhydria, etc.

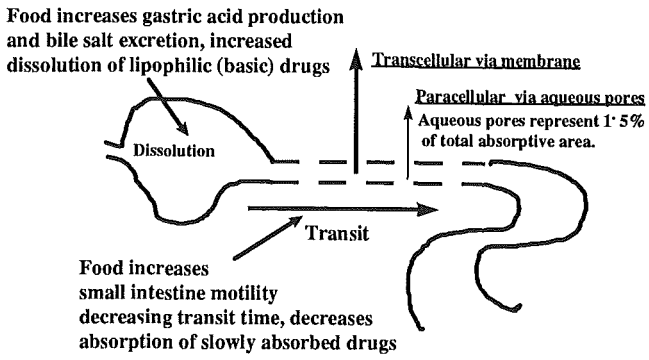

Figure 2. Schematic illustrating effect of food on the absorption of drugs of high and low lipophilicity

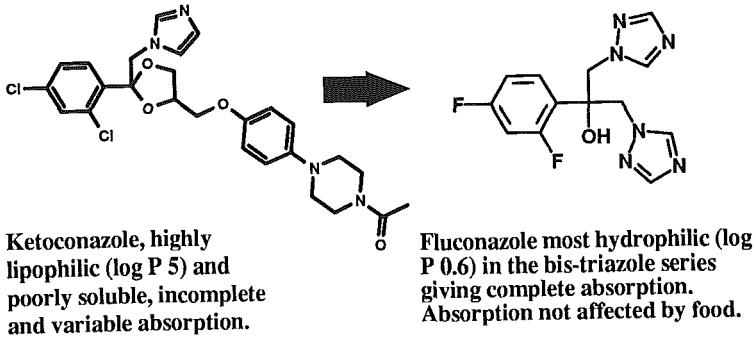

Figure 3. Fluconazole, an example of a drug discovery programme incorporating excellent absorption properties as part of the structure activity relationships.

CLEARANCE AND DESIGNING DRUGS TO LIMIT VARIATION

Given complete absorption, then the major sources of variation in the pharmacokinetic phase must reside in metabolic clearance, including first pass effects, and renal clearance. Minimal variation should be encountered with a drug that is 100% absorbed by the transcellular route and undergoes clearance by passive glomerular filtration (GF). Fluconazole is a rare example of such a drug. Base-line variation for such a compound is indicated by studies in healthy males [13]. In one such study (n=10), create clearance as an indicator of GF was 115 ml/min (90-140 ml/min) whilst fluconazole plasma clearance was 20 ml/min (15-23

ml/min). In such a study there is therefore a 1.5 fold range in fluconazole clearance values, directly reflecting a similar variation in GFR. In larger populations of patients [14] GFR varies more widely in patient populations. In a study in AIDS patients receiving fluconazole, GFR varied 4-fold from 36-138 ml/min, resulting in greater variation in fluconazole clearance [14]. Moreover, lower fluconazole values were also associated with lower CD4 cell counts. These studies indicate that variability in the pharmacokinetic phase is intrinsic in any drug and that the degree of variation is likely to increase from healthy volunteers to the wider patient population. Perhaps equally important, a large part of the variation is predictable from GFR measurements allowing dosage adjustment.

An examination of Pfizer compounds [15] undergoing early clinical studies and also going on to wider clinical studies indicated variation from 1.5 to 4.5 in Cl/F for 12 out of 15 drugs cleared by a variety of mechanisms. Lowest variation was seen for renally or partially renally cleared compounds, whilst higher variation was seen for those relying on metabolism. Compounds with wide variation (5-100 fold) were cleared by the polymorphic cytochrome P-450 isoenzymes CYP2D6 and CYP2C19. Where data was available, wider variation was encountered as a greater number of patients were studied

The substrate structure requirements of both these polymorphic isoforms is understood, particularly CYP2D6, and it is possible to include this knowledge in a drug design programme. For instance, the compound with 100 fold variation, UK-84,149(16, Figure 4), was identified by selective microsomal inhibition experiments as a CYP2D6 substrate. "First in man" studies included volunteers phenotyped and genotyped for CYP2D6 polymorphism and the results are shown in Figure 4. The unacceptably high variation led to termination of

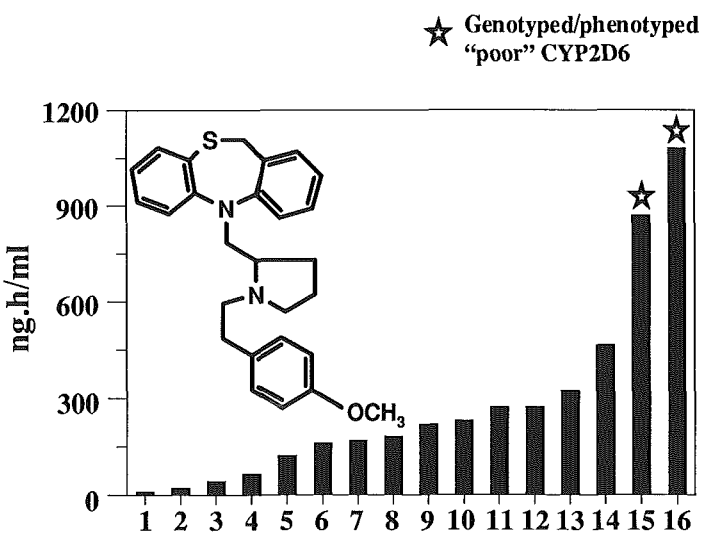

Figure 4. Variation in area under the plasma concentration time curve (AUC) following a single oral dose of UK-84,149, a compound metabolised by CYP2D6 (O-demethylation)

the development of the compound. Today protein homology and template overlay models exist that would have allowed the propensity for CYP2D6 metabolism for compounds of the UK-84,149 type to be predicted "in-silico" and the resultant structural features changed to avert metabolism by this isoenzyme. Alternatively, one could envisage that "population genotyping" would allow these variations to be predictable, in similar terms to GFR measurement.

In the wide patient population, variation in compounds metabolised by other P-450's is larger than expected. For instance, clozapine in small patient studies (n=16) shows a 6 fold variation [17] in CL/F (24.5, 11-63 L/H) and in larger studies (n=241) a 50 fold [18] variation (28.3, 5-250 L/H). Clozapine is metabolised by CYP3A4 and CYP1A2, isoenzymes [19] known to be variable, but involved in the metabolism of most basic lipophilic drugs. It seems difficult therefore that in terms of clearance to remove variation. The extremes can be removed by drug design, but "variation" will be present and needs to be accommodated in the selectivity, etc., of the compound.

REMOVING OTHER VARIABLES

Part of the extreme variability in the wide patient population is certainly the effects of patient compliance and concomitant medication. It seems prudent therefore that drugs should be designed that are convenient to take both by themselves and in combination. Thus pharmacokinetic properties should allow twice or preferably once a day administration. Drugs should be equally effective and tolerated when taken in the presence or absence of food. Whilst being a substrate for a P-450 enzyme is probably not avoidable (given the constraints of achieving activity, selectivity, absorption, etc.) the affinity for the system should be as low as possible. Thus the compound should not cause interactions either as a cytochrome P-450 inhibitor per se, or as an "efficient" substrate. Reduced affinity and greater metabolic stability go some way towards the pharmacokinetic properties for once a day therapy. Whilst not without exception metabolic stability and reduced affinity for P-450 enzymes such as CYP3A4 [2] can be gained by designing compounds in the "mid ground" of lipophilicity (log $D_{7.4}$ 0-2.0). Potent inhibition per se, can be limited by exclusion of unhindered pyridine, immidazole, or triazole functions. Duration of activity can also be enhanced by introduction of a basic group, to a neutral template, and its resultant effect on volume of distribution (2) as seen in examples such as amlodipine. Moreover such additions often bring extra benefit such as increased aqueous solubility.

CONCLUSION

Variation in dose response between patients is unavoidable. Pharmacokinetic variation can be limited but not avoided by careful drug design. Variation in the pharmacodynamic phase may in itself become attenuated as the full impact of genomics allows the sub-division of patients.

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Discussion: Can we design drugs with low variability?

G.T. Tucker:
If I can just ask a question about eliminating CY2D6 substrates or inhibitors during drug development. How good are the active site models in terms of doing this? The topography of the binding area of the dopamine receptor, for example, is very similar to that of the active site of CYP2D6.

D.A. Smith:
If you are talking about the actual part the agonist binds, then definitely you have got aspartate salt bridges in both cases. When you are looking at adrenaline or dopamine, they are of a pretty similar size and they would fit into the CYP2D6 active site model. If you are trying to look for an agonist, then it is going to be very tough to get one. If you are looking for an antagonist, it does not have to bind into the agonist site with the same way. Then you are back to actually looking through high-throughput screening for other antagonists. So there is a chance you can actually get rid of that problem. The other thing is you can make antagonists that are not polymorphic, that we can actually do on certain occasions by blocking metabolism. One example, is going from metoprolol to betaxolol, which has actually used a substituent that is metabolically stable. The one compound is rapidly metabolised because it fits the model perfectly; the other has a metabolically stable substituent, that when it is actually bound it cannot be metabolised.

J. Benítez:
You said that one should try to escape from polymorphic enzymes, but you showed the case of clozapine with quite big individual variability and a lot of problems in clinical practice. Would not it be useful to look for drugs that could be metabolised by three or four different isoenzymes? So if one fails, the other one would take its place, and therefore there would be much less variability.

D.A. Smith:
It is clear there must be something extra in clozapine. I am not quite sure why it is so variable, because there is a difference when you look at different CYP3A4 substrates. The problem may be the way the data is collected. As soon as you go to sparse data, you only need someone who is not taking the drug to actually give you the low value. I think the idea of trying to get multiple metabolic routes in is an interesting one, particularly if you could perhaps use glucuronidation. That may actually damp down the variability. But the reason I was putting up the data is the recognition that variability is large rather than small with most metabolically cleared drugs. As I worked through it, I was looking for ways of getting rid of polymorphism, etc. But when one actually goes down and looks at the data, the variability is very large in all cases and we are stuck with that, and have to work through that one. Part of it, I think is getting really good selectivity in your compounds.

J. Benítez:
Did you check caffeine intake in those patients taking clozapine?

D.A. Smith:
That is a literature study and I do not know if they checked that.

U. Klotz:
Due to the lower variability if a drug is glucuronidated, one could do some drug design: if you have a handle on the molecule, like a hydroxyl group, you can improve the lipophilicity and affect the distribution volume. You might design a drug, forcing your molecule into glucuronidation pathway. On the other side, most of us are dedicated to drug metabolism, why not use more o less renally secreted drugs, where we get at least some standardisation by using creatinine clearance?

D.A. Smith:
I think the big problem there is absorption, of course, because you have to make them, in general, with low lipophilicity. Then you run into the problem of going via the paracellular absorption route, which limits you to very small molecules like atenolol, and you still have this marked reduction in bio-availability with food. Fluconazole is the pinnacle of that approach. Certainly, if it is a small molecule, it is attractive to go for the renal route if absorption problems can be overcome. Finally, it is always a balance you are looking at.

U. Klotz:
From a pharmaceutical point of view, I think the absorption can be handled by galenic tricks.

D.A. Smith:
There is no trick when you are in a poorly water-soluble compound. Once you are into a lipophilic one, you can come up with various formulations that will improve it. When people have looked for absorption enhancers of the paracellularly absorbed compounds, I am not aware there has been any advance at all in that area. There are compounds which ride this nicely, like fluconazole.

D.C. Brater:
I think no matter how much you try to custom-design things, you are not going to eliminate substantial variability. It seems that one of the themes we have here is that there is some lamenting that funding agencies do not embrace some of these concepts, and that sometimes industry and regulatory authorities do not embrace them. We cannot expect the practicing physician to pay attention to this variability in terms of how they deal with patients in the present climate of inattention. Perhaps we should discuss how we can attack this problem. Does it mean that we really need to think about a whole new different type of study, where we apply some of these concepts and conduct outcome studies? Does it mean we need to phenotype or genotype, or both, large numbers of patients and follow them prospectively over time to see if doing so has an important impact in caring for patients? It seems to me that such studies are a step that is going to be needed. After such studies, if you prove that this kind of information is helpful in terms of taking care of patients, we must then determine how we are going to get this information to practicing physicians. But they are being assaulted by all of the funding agencies and insurance companies to see patients in short periods of time. So we have to figure out ways in which we can get digestible packets of information to them,

using tools like computer information systems while they are actually taking care of the patient. If we think that all these issues are important, how are we going to convince other people that it is sufficiently important in terms of translating into patient care? We are kind of working in the trees here, and I just wonder if there is going to be an opportunity to talk about the forest, which I think is a bigger issue.

D.A. Smith:

There are few representatives from industry and from regulatory authorities in this meeting. It will have been very useful to have some of my clinical colleagues here, who actually can provide some comment as well through these issues. But I think that in general, most people feel the same way you have expressed.

G.T. Tucker:

I guess the key words are education, information and monitoring and how we implement them.