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Predicting Pharmacokinetics/Pharmacodynamics in the Individual Patient: Separating Reality from Hype[1]

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ABSTRACT

Individualization of patient drug dosing to maximize efficacy and minimize toxicity is the goal of clinical pharmacology. Here we review the history of drug dosing individualization from early predictions for renally eliminated drugs based on kidney function, the introduction of clearance concepts for metabolic processes, the differentiation of volume of distribution between pharmacokinetics and chemistry, the role of transporters, the unique pharmacokinetic aspects of oral dosing, the relevance of protein binding and the emergence of pharmacogenomics. The FDA listing of pharmacogenomic markers in approved drug labeling is analyzed with respect to the promise of genomics in terms of picking the right drug for the patient based on genetic information versus selecting or adjusting the dosage regimen based on genetic information, with the former resulting in a great advance while for the latter there is less convincing evidence of clinical relevance. Finally, new information as to why individualized predictive methodologies based on marker drugs for enzymes and transporters is reviewed. We conclude that although individualization of drug dosing will work for most drugs primarily excreted unchanged in the urine, individualization of dosing regimens is not critical for wide therapeutic index drugs, while for narrow therapeutic index drugs predictions are most often more hype than reality, with therapeutic drug monitoring required. However, continuing advances in discovering and validating biomarkers will lead to predictions of PK/PD in the individualized patient that should result in shifting the hype to reality with time.

Keywords: Individualized dosing; Pharmacokinetics; Pharmacodynamics; Pharmacogenomics

INTRODUCTION

From 1984[1], "Pharmacokinetics may be simply defined as what the body does to the drug, as opposed to pharmacodynamics, which may be defined as what the drug does to the body. A combination of pharmacokinetics and pharmacodynamics allows the clinician and the pharmacological scientists to define the appropriate drug dosage regiment in a particular patient." There is no doubt that clinical pharmacology and all of its sub disciplines, including pharmacokinetics and pharmacodynamics, have had a marked effect on the progress in therapeutics that we have experienced over the past century. [2] But here I address specifically the progress that we have made in dosing drugs in the individual patient. First, giving a history of the approaches utilized by the field, then critiquing the various methodologies employed over the last half century, critically evaluating whether these approaches to precision medicine are real advances in individualization of drug therapy or are they more appropriately characterized as "hype" and then ending this review with my assessment of the potential for future progress in utilizing pharmacokinetics (PK) and pharmacodynamics (PD) in treating the individual patient.

The Concept of Dettli

In 1976, I carried out my first sabbatical in the laboratory of Professor Luzius Dettli at the Kantonspittal Basel, Switzerland. I view Professor Dettli as the first clinical pharmacologist to systemize drug dosing in the individual patient. Dettli compiled a list of drugs[3] where he knew the fraction of the dose <u>not</u> eliminated unchanged in the urine, Q_0 (e.g., gentamicin $Q_0 = 0.02$, that is 98% of the dose is excreted unchanged), which was primarily used for iv dosed drugs. His list included 50 chemotherapeutic agents, 8 cardiac glycosides and 7 other miscellaneous drugs. Then based on the creatinine clearance in an

individual patient, Dettli recommended dose adjustment or dosing interval adjustment by calculating a Q factor as given below for gentamicin in a patient with a creatinine clearance (CL_{cr}) of 40 ml/min.

$$Q = Q_0 + (1 - Q_0) \cdot CL_{cr}/100$$

$$Q = 0.02 + (1 - 0.02) \cdot \frac{40}{100} = 0.41$$ Dettli then applied one of his rules to either modify the individual dose (Rule 1) or the dosing interval (Rule 2) or combined both Rules 1 and 2[3].

Rule 1: Dose (no renal function problems) x Q = Individual patient dose

2 mg/kg b.i.d x 0.41 = 0.82 mg/kg b.i.d.

Rule 2: Dose interval (no renal function problems)/Q = individual patient dose interval

12 hr/0.41 = 2 mg/kg every 29 hours

Or combine Rules 1 and 2: 1.64 mg/kg every day

Dettli's rules were based on drug half-life considerations and did not contemplate the possibility of non-renal elimination changes. Dettli's rules do provide reasonable individualization of drug dosing for drugs predominantly eliminated by renal elimination. However, since 77% of drugs on the market are eliminated primarily by metabolism[4] and another 3 to 4% primarily by biliary excretion of unchanged drug, Dettli's dose adjustment equations cannot provide adequate PK and PD predictions.

Rate Constants and Half-lives

Thus, 45 years ago pharmacokinetics began to evolve using more complicated models of rate constants and half-lives. Reviewing the human pharmacokinetic literature 45 years ago, almost all published studies were carried out with salicylic acid. This was because the drug was given in large doses, and primarily because we had a colorimetric assay, using the Trinder reaction, that allowed us to measure plasma and urinary concentrations. However, the mathematical models that were developed and the

equations that accompanied these models, although of interest to the cognoscenti, were incomprehensible to clinicians treating patients. Furthermore, there appeared to be no useful relationship between the changes in these pharmacokinetic parameters and a degree of disease, which would allow translation of pharmacokinetics to patient drug dosing.

A number of experimental observations in the late 1960s, early 1970s could not be explained by the pharmacokinetic theory available at the time. For example, von Bahr et al.[5] observed that for rats receiving phenobarbital as an enzyme inducing agent the elimination of phenylbutazone was increased both in vitro in liver microsomes and in vivo in whole animals vs that observed in non-induced animals. However, for the drug desipramine, although elimination was increased in microsomes from phenobarbital-induced rats, no change in plasma disappearance was noted in vivo following tail vein injection of this drug when comparing rats induced with phenobarbital and control rats. Another series of studies related to protein binding also showed discontinuities for certain drugs between in vitro and in vivo studies. Krüger-Thiemer and colleagues[6] showed that inhibition of protein binding would increase free concentrations of a large number of sulfa drugs. They reasoned, therefore, that in vivo in humans they would expect the renal elimination of these sulfa drugs to increase when protein binding was inhibited. For some sulfa drugs, this in vivo increase in renal elimination was observed, however, for a number of sulfas no change in renal elimination was found when free concentrations of the drugs were increased by inhibiting protein binding. Therefore, it appeared in the early 1970s that pharmacokinetics did not provide any predictability of changes in elimination based on induction of metabolic enzymes or through increasing free drug concentration, and thus could not be useful in individualization of drug dosing under such conditions.

The Introduction of Clearance Concepts

So 45 years ago what was wrong with pharmacokinetics? It appeared to have no relationship with clinically meaningful parameters that could help in making drug dosing decisions or that could account for differences in physiology and pathology, except for drugs predominantly excreted unchanged in the urine. For example, at steady state:

$$Rate \in ¿\, Rate\, Out$$

$$Availability \bullet Dosing\ Rate = ?\,? \bullet Average\, Concentration$$

$$F \bullet Dosing\ Rate = ?\,? \bullet Target\, Concentration$$

It was well known that at steady state the $Rate\ In$ would be the dosing rate at which the drug was administered multiplied by the bioavailability (F), which could change as a function of the route of administration. It was recognized that $Rate\ Out$ should relate to systemic concentrations or to a target concentration that was known to yield efficacy with minimum toxicity. However, the parameter that was to be multiplied by this systemic target concentration (i.e.,??) was undefined in 1972. Therefore, we invented it (or more accurately adapted it from renal elimination processes) and called it clearance (CL). So that at steady state:

$$Rate \in ¿\, Rate\, Out$$

$$Availability \bullet Dosing\ Rate = Clearance \bullet Concentration\ at\ steady - state$$

$$\frac{F \bullet Dose}{\tau} = CL \bullet C_{ss} \qquad \text{(Eq. 1)}$$

where τ is the dosing interval and C_{SS} is the concentration at steady state. From the equality in Eq. 1, it can be determined that the units of clearance are flow parameters or volume per time.

Rate of elimination for an individual organ can be defined as the blood flow to that organ (Q) multiplied by the difference between the arterial (C_A) and venous (C_V) blood concentrations as shown below:

$$Rate\,of\,elimination = Q \bullet C_A - Q \bullet C_V$$

This rate of elimination can be expressed in terms of organ clearance (CL_{organ}) multiplied by the driving force concentration for elimination.

$$Rate\,of\,elimination = CL_{organ} \bullet C_{driving\,force\,for\,elimination}$$

Beginning in 1972, Rowland[7] assumed that the driving force for elimination was C_A leading to

$$CL_{organ} = Q \bullet \frac{C_A - C_V}{C_A} = Q \bullet ER$$

(Eq. 2)

where the difference in arterial and venous concentrations divided by the incoming arterial concentration may be defined as the extraction ratio (ER) of the organ.

We have recently shown[8] that it has been universally unrecognized that when the rate of elimination is divided by the arterial concentration, this assumes the well-stirred model of hepatic elimination and that the extraction ratio is only a well-stirred model concept. However, Eq. 2 would not explain the anomalies listed above as observed by von Bahr and Krüger-Thiemer. Thus, the development of clearance in pharmacokinetics[9, 10] was advanced by describing the extraction ratio in terms of the "well-stirred" model adapted from the chemical engineering steady-state mixed flow reactor, also called the continuous stirred tank reactor.[11] The extraction ratio was defined[9,10] as a function of three parameters:

a) blood flow to the elimination organ (Q)

b) the ratio of the unbound plasma concentration to the whole blood concentration (fu_B), and

c) the intrinsic ability of the organ to eliminate the unbound drug if there were no flow and protein binding limitations (CL_{int}).

In terms of the well-stirred model, clearance (with respect to blood concentrations) for the eliminating organ then becomes:

$$Q + fu_B \bullet CL_{\int ¿}$$
$$fu_B \bullet \frac{CL_{\int ¿}}{¿}$$
$$CL_{organ} = Q \bullet ¿$$

(Eq. 3)

Equation 3 demonstrates that when the capability of the eliminating organ to metabolize the drug is large in comparison to the rate of drug presentation to the organ, i.e., $fu_B \bullet CL_{int}$ is much greater than Q, the clearance will approximate the organ blood flow

$$CL_{organ} \cong Q$$

(Eq. 4)

That is, drug elimination is limited by organ blood flow rate and the compound is called a high-extraction-ratio drug. On the other hand, when the metabolic capacity is small in comparison to the rate of drug presentation ($Q >> fu_B \bullet CL_{int}$), the clearance will be proportional to the unbound fraction of drug in blood and the intrinsic clearance, as in Eq. 5.

$$CL_{organ} \cong fu_B \bullet CL_{int}$$

(Eq. 5)

The drug is then called a low-extraction-ratio drug.

Note that the definitions for low- and high-extraction-ratio drugs are independent of the fraction of the dose eliminated by a particular organ. For example, diazepam is eliminated almost completely by hepatic metabolism (less than 1% of the drug is excreted unchanged in the urine), yet the clearance of diazepam, 27mL/min, indicates that this is a low hepatic extraction ratio drug. That is, on each pass through the liver only a small fraction of the drug (ER_H = 27/1,500 = 0.018) will be eliminated, although eventually almost all of the drug will be eliminated by the liver. The value of 1,500 is the average hepatic blood flow in mL/min for a 70kg man.

Equation 3 clarifies the unresolvable experimental results described above. For example, enzyme induction or hepatic disease may change the rate of desipramine metabolism in a hepatic microsomal enzyme system, but no change in clearance is found in the whole animal with similar hepatic changes. This is explained by the fact that desipramine is a high-extraction-ratio drug and clearance becomes limited by blood flow rate (Eq. 4), so that changes in CL_{int} due to enzyme induction or liver disease have little effect on clearance. Also, although desipramine is a relatively highly protein bound drug (fu_B = 0.18), changes in protein binding due to disease or competitive binding should have little effect on clearance. In contrast, for a low-extraction-ratio drug such as phenylbutazone (CL = 1.6mL/min/70kg), enzyme induction or changes in protein binding (fu_B = 0.039) should markedly affect elimination since Eq. 5 describes this drug's elimination.

The introduction[9] of clearance concepts to pharmacokinetics beginning in 1973 has had an immense effect on the field. Reviewing PubMed for the term "drug clearance" one finds in 1972 that there were 192 references, many of them dealing with mucociliary drug clearance. In January 2018, the number of references is greater than 69,000. Thus beginning in 1973 it was recognized that clearance, not half-life, was a measure of the body's ability to eliminate drug and changes in pathology or physiology could be

correlated with measures of clearance. Clearance concepts allowed the field to develop a basic understanding and to make predictions as to how pathological and physiological changes would influence drug kinetics and drug dosing. It provided the quantitative rationale for Clinical Pharmacology. Clearance concepts not only influenced the health professions in terms of patient care, it also had a marked influence on the regulatory agencies (e.g., FDA, EMA) and the drug development process. Clearance is now a parameter that medicinal chemists and drug delivery scientists take into consideration in their new advances with the recognition that exposure of drug in the systemic circulation is the driver that will lead to a drug or a delivery vehicle being commercialized.

Volume of Distribution (V)

In the equations above, we explain the change or lack of change in half-life ($t_{1/2}$) in terms of clearance relationships. On the left hand side of Fig 1 we depict an interesting change in half-life for diazepam with age. I have noted that on average, if one takes his/her age in years and converts it to hours, this will be the terminal half-life of diazepam in that individual. It was initially believed that the increase in half-life with increasing age was due to decreased hepatic function with age as had been seen with renal function. However, the measure of the body's ability to eliminate drug is clearance not half-life. On the right hand side of Fig 1 Klotz et al.[12] showed that clearance did not obviously change with age. It was then recognized that volume must have increased with age from the relationship in Eq. 6.

$$t_{1/2} = \ln 2 \bullet \frac{V}{CL}$$

(Eq. 6)

The introduction of clearance initially created some confusion because up to the early 1970s, half-life was well recognized in terms of basic chemical principles as an appropriate measure of the rate of elimination and reflective of changes in this rate. However, the difference between chemistry and pharmacokinetics is that in chemistry the volume in which the reaction occurs does not change. In contrast, in pharmacokinetics, disease states and differences in physiology can change the space available in which the drug may distribute in the body. Thus, it was necessary to develop a measure of volume of distribution that was independent of elimination. Such a volume term had been defined as volume of distribution at steady state (V_{ss}). Although clearance could be determined independent of the previously employed pharmacokinetic models by determining dose divided by the area under the curve (AUC), no noncompartmental method for determining V_{ss} was available until 1979. Then Benet and Galeazzi[13] defined a noncompartmental method for determination of V_{ss}. This paper was the first to describe the relationship between V_{ss}, CL and a measure of time of drug in the body, the mean residence time (MRT).

$$V_{ss} = CL \bullet MRT \qquad \text{(Eq. 7)}$$

MRT has units of time and is a parameter that reflects the overall rate of elimination at steady state for a drug following multiple compartment kinetics ($MRT = 1/k_{ss}$). We will return to this relationship when addressing why IVIVE (In Vitro-In Vivo Extrapolation) methodology does such a poor job in predicting in vivo clearance from in vitro measures. Now it was recognized that clearance and volume were the independent parameters and that half-life or MRT (a measure of inverse half-life) was the dependent parameter. Clearance is a measure of the body's ability to eliminate a drug. Volume of distribution is a measure of the space available in the body at which a drug may distribute. Pathology and physiology can change both CL and V_{SS}, thereby changing MRT or half-life.

Introduction of Transporters

So from the perspective of PK and PD, what did we know 45 years ago? First, it was recognized that there was some active process in the kidney responsible for the elimination of charged drugs, and this facilitator could be called a transporter. However, the majority of drugs were eliminated by metabolism and no one in the 1970s considered an active transfer process to be involved. Yet, we knew little of the enzyme characteristics except that most were located in hepatic microsomes and they could be upregulated by dosing phenobarbital. In 1983, I spent my second sabbatical with Professor Herbert Remmer at the University of Tübingen, Germany. Professor Remmer was one of the very early experts in Cytochrome P-450, which began to be recognized as the major enzyme for drug metabolism. A great deal of our scientific discussions in Professor Remmer's laboratory in 1983 focused around whether there was one P-450 or two P-450s, since a second spectrophotometric peak was being recognized as our instrumentation became more sophisticated. At that time Professor Remmer, and every other pharmacological scientist, believed that free drug concentrations were the driving force for pharmacodynamics and that free concentrations at peripheral (nonsystemic) activity sites in the body were the same as the free concentration measured in the systemic circulation. That is, it was a generally held dogma that free drug concentrations were equivalent throughout the body.

Yet transporters were recognized as important for endogenous mediators such as glucose in the early 1960s.[14] In 1976, Juliano and Ling[15] recognized that a transporter, identified as P-glycoprotein (P-gp) was constitutive and being upregulated in cancer tumors as a tumor protective mechanism to efflux drugs out of the tumor. In 1992, Ishikawa[16] proposed that drug metabolites were being eliminated from the body in an active phase 3 "metabolic" process via ABC efflux pumps. It was called phase 3, since

Ishikawa's original observation was that this was the mechanism for eliminating phase 2 metabolites into the bile or urine. In 1994, Schinkel and coworkers[17] from the Netherlands Cancer Institute generated mice homozygous for a disruption of the gene encoding P-gp. The mice were viable and fertile and appeared phenotypically normal, but they displayed an increased sensitivity to the centrally neurotoxic pesticide ivermectin (100-fold) and to the carcinostatic drug vinblastine (3-fold). By comparing wild-type and knockout mice, they proposed that P-glycoprotein was a major component of the blood-brain barrier and that the absence of active P-gp transport resulted in elevated drug levels in many tissues (especially in brain) and in decreased drug elimination. One year later, we proposed the potential for transporter-enzyme interplay in a paper entitled "Overlapping Substrate Specificities in Tissue Distribution of Cytochrome P-450 3A and P-glycoprotein: Implications for Drug Delivery and Activity in Cancer Chemotherapy"[18], and suggested that this CYP3A and P-gp interplay could also be important for the gut, in addition to the liver.

Oral Bioavailability

Let us return to the manuscript topic, Predicting PK/PD in the Individual Patient, first considering oral dosing from the basic concepts known 20 years ago. Exposure was given by Eq. 8:

$$AUC_{oral} = F_{oral} \bullet Dose / CL \qquad \text{(Eq. 8)}$$

The well-stirred organ clearance relationship (Eq. 2) allowed Rowland to predict the decrease in bioavailability based on the physiologic phenomena that orally dosed drugs must first pass through the liver before reaching the systemic circulation and thus bioavailability can be low based on first-pass hepatic loss in addition to poor absorption[7]:

$$F_H = 1 - ER_H = 1 - \frac{CL_H}{Q_H} \quad \text{(Eq. 9)}$$

where F_H is the hepatic bioavailability, ER_H is the hepatic extraction ratio in the well-stirred model and CL_H and Q_H are the hepatic blood clearance and hepatic blood flow, respectively.

In the 1990s, our group carried out interaction studies in humans with cyclosporine and tacrolimus evaluating inhibitors and inducers following intravenous and oral drug dosing. The results of these studies could not be explained based on hepatic first pass loss (Eq. 9) only, indicating that there may be other previously unidentified factors that must be considered. That is, the results were only consistent with the new hypothesis that the major effect of the interactions was on bioavailability as opposed to clearance and that this interaction occurs primarily in the intestine[18-26]. Therefore, in evaluating oral bioavailability the fraction of drug that gets through the gut wall unchanged (F_G) must be added to the equation and both enzymes and transporters can effect oral bioavailability.

$$F_{oral} = F_{abs} \bullet F_G \bullet F_H \quad \text{(Eq. 10)}$$

Changes in Plasma Protein Binding as a Result of Disease States or Drug Interactions Have Little Clinical Relevance

When a drug is given orally, the well-stirred model yields the following relationship for F_H for all drugs independent of the hepatic extraction ratio:

$$F_H = 1/(fu_B \bullet CL_{int}) \quad \text{(Eq. 11)}$$

Therefore:

$$AUC_{oral} = \frac{F_{abs} \bullet F_G \bullet Dose}{fu_B \bullet CL_{int}} \quad \text{(Eq. 12)}$$

The area under the concentration-time curve for total drug (AUC_{oral}) is directly related to the oral dose, the fraction of the dose absorbed (F_{abs}), the fraction of the dose that gets through the gut wall intact (F_G) and inversely related to the fraction unbound (fu_B) and the intrinsic clearance of unbound drug (CL_{int}), that is, the ability of the liver to eliminate drug independent of flow and protein binding. Now multiplying both sides of Eq. 12 by fu_B gives:

$$AUC_{oral,u} = \frac{F_{abs} \bullet F_G \bullet Dose}{CL_{int}} \quad \text{(Eq. 13)}$$

That is, the area under the curve of unbound drug ($AUC_{oral,u}$) is independent of protein binding. Since the total integrated effect (AUE) is believed to be directly related to unbound concentrations, AUC_u, changes in fu_B either due to disease states or drug-drug interactions will not be expected to influence clinical outcome, and no adjustment of drug dosing should be required for any drug dosed orally where the liver is the major organ of elimination.[27] Table 1 presents a summary of the potential for the clinical relevance of changes in protein binding. In essence, protein binding changes will only be relevant for

high extraction ratio drugs dosed intravenously and I estimate that less than 3% of drug dosings would require concerns about changes in response due to changes in binding caused by drug-drug interactions or disease states. And these drug dosings will almost be exclusively anesthetics and IV dosing of antiarrhythmic drugs, such as lidocaine. It is possible that transient changes in binding due to drug-drug interactions could be relevant but this would only be true for narrow therapeutic index (NTI) drugs where there is a rapid equilibration between pharmacokinetics and pharmacodynamics, as seen for antiarrhythmic drugs and anesthetics.

When is Protein Binding Important?

We have shown that changes in protein binding caused by drug-drug interactions or disease-drug interactions will usually not influence the clinical exposure of a patient to a therapeutic agent[27]. Therefore, no adjustment in dosing regimens will be necessary, except in the rare cases we have outlined. However, this conclusion should not be extrapolated to suggest that measurements of protein binding are not important in drug development. For example, in the scale up of pharmacokinetic and pharmacodynamic parameters from animal models to humans for new molecular entities (NME), it is essential to consider interspecies differences in binding in the prediction of volumes and clearances. Similarly, when the first dose in humans of an NME is calculated from in vitro measures of target concentrations, fu_B must be factored in to the estimated size of the dose. Furthermore, there is an important clinical reason for knowing whether protein binding measurements may occur for narrow therapeutic index drugs when therapeutic drug monitoring of plasma or blood concentrations is routinely used to adjust dosings; many routine therapeutic drug monitoring techniques measured total drug concentrations rather than unbound concentrations.

So we are left with predicting CL_{int}, F_{abs}, and F_G in the individual patient.

Pharmacogenomics

There is a great deal of interest both from clinicians and regulatory agencies in the promise of pharmacogenomics so revisiting the title of this manuscript "Individualized Patient Drug Dosing Based on Genetic Characteristics: How Much is Reality – How Much is Hype?" With the publication of the human genome, the medical promise of personalized medicine and individualized drug dosing were the watchwords frequently read in the papers and heard from genetic researchers. Many research scientists expected that just a handful of genetic mutations would explain most cases of any given major disease. Others expected that we would be able to markedly decrease the variability and tailor drug dosing to the individual patient based on their genetic characteristics. However, the mutations that have been detected in various diseases have turned out to account for a very small fraction of the overall incidents and there are only a few good examples where drug dosing based on a genetic determinant markedly improves drug therapy. One can evaluate the promise of genomics in the individualization of drug therapy in two categories:

1. Picking the right drug for the patient based on genetic information – YES a great advance.
2. Selecting or adjusting the dosage regimen based on genetic information – Less convincing evidence of clinical relevance.

One can find on the FDA website a listing of 190 drugs and drug combination in a "Table of Pharmacogenomic Biomarkers in Drug Labeling with Labeling Text"[28] that can be readily accessed at **https://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM545881.pdf** In my analysis of the table of the 190 listings, 69 were for therapeutic indications and 46 for toxicities related to a pharmacogenomic biomarker. For example: Bosutinib "is indicated for the

treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome – positive (Ph+) chronic myelogenous leukemia (CML)…". Or Abacavir "is contraindicated in patients who have the HLA-B*5701 allele". Thus, 115 of the 190 pharmacogenomics marker label texts recommend that the drug is appropriately or should not be dosed in patients exhibiting the marker.

But even with a pharmacogenomic marker, how do we predict its relevance for a newly approved drug? Let us consider antiepileptic drugs and HLA-B*15:02 for the toxicities of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). The warning concerning HLA-B*15:02 related to SJS and TEN was added to the carbamazepine label in the U.S. in December of 2007. It was subsequently added to the phenytoin label in September 2013 and the oxcarbazepine label in June 2014. The label for lamotrigine listed the potential for skin toxicity beginning in October 2010 but HLA-B*15:02 was not mentioned and thus it is not in the list of 190 drugs on the FDA website. We recently reported surface plasma resonance relative response measures of specific interaction of the antiepileptic drugs with HLA-B*15:02 using other HLA-B alleles as controls[29]. We clearly show that extensively metabolized, poorly soluble Biopharmaceutics Drug Disposition Classification System (BDDCS) Class 2 drugs all give strong response measures in our in vitro studies with HLA-B*15:02, while BDDCS Class 3 drugs (poorly metabolized, highly soluble) all show very little response measures. We believe it is inappropriate to wait for serious life threatening toxicities to appear for the Class 2 antiepileptic drugs and recommend that the label at least suggest the warning for HLA-B*15:02 for lamotrigine and eslicarbazepine. Our in vitro measures, in further unpublished studies, show ambiguity for the BDDCS Class 1 (extensively metabolized, highly soluble) antiepileptic drugs, with valproic acid showing minimal interaction but tiagabine, clonazepam and clobazam exhibiting strong interactions[30].

We raise the issue of biomarker validity to point out the necessity for strong validation. The examples above for Philadelphia chromosome-positive and HLA-B*15:02 are excellent examples of the use of genomics in individualizing drug therapy. However, recent reports of failures of other biomarkers, such as inhibition of cholesterol ester transfer protein (CETP) to lower the risk of myocardial infarction[31] and the incorrect analysis of iniparib as a first-in-class poly (ADP-ribose) polymerase (PARP) inhibitor[32] are warnings of caution.

My analysis of the listing of 190 drugs and drug combinations in the FDA "Table of Pharmacogenomic Biomarkers in Drug Labeling with Labeling Text" indicates that 102 of the listings were for drug disposition (e.g., metabolic enzymes) characteristics that could affect drug dosing. Table 2 lists the number of drug labels with pharmacogenomic implications for nine enzymes and one transporter. The values in parentheses are drugs for which a polymorphism is listed but found to be not clinically relevant, i.e. 27% of the 102 listings. It is interesting that the one drug listed for a CYP3A5 polymorphism, prasugrel, indicates no clinical relevance, while in contrast there is no indication of the importance of CYP3A5 for tacrolimus where the Clinical Pharmacogenetics Implementation Consortium (CPIC) has published guidelines for CYP3A5 genotype and tacrolimus dosing[33]. This is just another example of where FDA labeling may lag consensus pharmacogenomic dosing recommendations.

Revisiting our two subsets of the promise of genomics in the individualization of drug therapy, we can add the rationale for the discrepancy between the two categories.

1. Picking the right drug for the patient based on genetic information – YES, a great advance and it works well because it is a binary decision that is clinically relevant.
2. Selecting or adjusting the dosage regimen based on genetic information – Less convincing evidence of clinical relevance because it is not a binary decision, but rather requires a patient specific adjustment.

Why is there less convincing evidence of clinical relevance in selecting or adjusting the dosing regimen based on genetic information? First, sponsors preferably select NMEs with wide therapeutic indices where concentration variances due to pharmacogenomics differences are not relevant (e.g., the values in parentheses in Table 2). Second, for narrow therapeutic index drugs, therapeutic drug monitoring (TDM) will be necessary independent of pharmacogenomics. And third, generally, where pharmacogenomics is relevant for narrow therapeutic index drugs, pharmacogenomic recommendations are at most binary (e.g., cut the maintenance dose in half) and then monitor the patient. Phenytoin is an example of this third point. CYP2C9 accounts for 80-90% of its metabolism, with the remainder CYP2C19, both pharmacogenomics variant enzymes. CPIC guidelines for phenytoin[34] state "Consider 50% reduction of recommended starting maintenance dose in poor metabolizers. Subsequence maintenance doses should be adjusted according to therapeutic drug monitoring and response". The FDA label, as quoted in the pharmacogenomic compiliation[28], has no useful pharmacogenomic information beyond "hypermetabolizers" may have unusually low levels and "congenital enzyme deficiency" can lead to unusually high levels, and thus "Serum level determinations in such patients may be particularly helpful." There is also a nonsensical protein binding statement in the label "As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal".

With such little evidence that pharmacogenomics is useful in selecting or adjusting the dosing regimen, why do we believe pharmacogenomics will be relevant in precision medicine? The field has been strongly influenced by the life-saving importance of the polymorphism in thiopurine methyltransferase (TPMT) in dosing 6-mercaptopurine and thioquanine as antileukemic agents. Weinshilboum and Sladek[35] in 1980 reported that TMPT activity in humans, which is inherited as an autosomal co-dominant trait, exhibits

genetic polymorphism, with about 10% of Whites and African Americans inheriting intermediate (heterozygote) activity and about 1 in 300 inheriting a TMPT deficiency. As shown by Krynetski and Evans[36], knowing this polymorphism results in a dosing recommendation that is simple, works extremely well and TDM is not required. Even with this success, however, it was not obvious until 35 years later that the TMPT polymorphism was not predictive in Asians and Hispanics, where the inherited NUDT15 variant was the genetic determinant of 6-mercaptopurine intolerance[37].

In the FDA listing of 190 drugs and drug combinations with pharmacogenomic labeling[28] only rosuvastatin includes pharmacogenomic related transporter text “Disposition involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T>C). The frequency of this genotype (SLCO1B1 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of rosuvastatin has not been clearly established.”

Recently we addressed the pharmacogenomic issues related to rosuvastatin dosing[38, 39]. Asian patients receiving the HMG-CoA reductase inhibitor rosuvastatin for lowering cholesterol levels exhibit on average two-times higher rosuvastatin blood concentrations than observed in White patients. The US FDA recommends that Asians patients should receive one-half the dose of rosuvastatin given to White patients because of rhabdomyolysis and myalgia concerns. The labels state “Asian population: consider 5mg starting dose”. In Japan and China, a lower starting dose than in the US is recommended. Based on the rosuvastatin label, pharmacogenomic variance in OATP1B1 alone could not explain this difference. Therefore, we investigated rosuvastatin pharmacokinetics in Asian and White subjects wild type for both OATP1B1 and BCRP under control and when the transporters are inhibited by dosing rifampin[38]. Table 3

depicts the measures for C_{max} and $AUC_{0\rightarrow48}$ and CL/F for White and Asian subjects under control conditions and when they are given a single 600mg i.v. dose of rifampin. Our study indicates that the pharmacokinetics of rosuvastatin do not exhibit a clinical difference from Whites in Asian subjects who are wild type in both OATP and BCRP. Although on average Asians exhibit twice the exposure observed in Whites for the same dose of rosuvastatin, approximately 1/3 of Asians are actually wild-type in OATP and BCRP. These 1/3rd of Asians are being underdosed with rosuvastatin when the dosing regimen is based on ethnicity rather than pharmacogenomics. The results of our prospective clinical study implicating a pharmacogenomic basis for the difference between Asians and Whites in rosuvastatin pharmacokinetics contradicts the conclusion of ethnic variability from the analysis of the Sugiyama lab[40,41], but is confirmed by the mechanistic modeling studies most recently published by Pfizer scientists[42].

Much of what I have discussed thus far relates to predicting pharmacokinetics, which can translate to predictions of pharmacodynamics. Now, I return to a statement early in the paper concerning a belief/dogma in 1983 and still not recognized generally today.

Transporters and Unbound Concentrations

Earlier I indicated that Professor Remmer, and every other pharmacological scientist, believed that free drug concentrations were the driving force for pharmacodynamics and that free concentrations at peripheral (nonsystemic) active sites were the same as the free concentration measured in the systemic circulation. But this is not a true condition; what transporters do is cause unbound concentrations of substrate drugs to be different at different sites in the body, and this will be the case for all drugs that are transporter substrates. Much of the work from my laboratory over the last decade has addressed predictions of drug disposition and drug-drug interactions based on the BDDCS[4,43]. Thus, for many BDDCS

Class 2, 3 and 4 drugs unbound concentrations in blood/plasma may not reflect unbound concentrations at sites of efficacy and toxicity. In contrast, for BDDCS Class 1 drugs, unbound concentrations are expected to be equal throughout the body following the long-held previous supposition. There are at least two consequences to these findings:

1. Unbound concentrations in blood/plasma may not reflect unbound concentrations at sites of efficacy/toxicity for many drugs.
2. Transporter pharmacogenomics could change effect without changing pharmacokinetics.

Forty-five years ago, Professor Dettli assumed that changes in renal function had no effect on non-renal drug elimination. But early this century we began to recognize that previously unexplained effects of renal disease on hepatic metabolism can result from accumulation of substances (toxins) in renal failure that modify hepatic uptake and efflux transporters[44]. Thus, although drug dosing can be adjusted based on changes in drug renal elimination, uremic toxins can modify non-renal elimination requiring further drug dosing adjustments.

Predictive Methodologies

Up to this point, I have not mentioned quantitative translational learning from clinical studies and physiologically based pharmacokinetic (PBPK) modeling. I do believe that these are useful exercises and I agree such approaches now routinely used in pharmaceutical development programs and increasingly accepted by regulatory authorities can be used to predict drug-drug interactions, disease specific dosing modifications and risk assessment drug approval recommendations for the patient population. I view these as picking the right drug (and starting dose) for the patient and we are making great progress in this area. However, the topic of this manuscript is can we make further recommendations for the individual patient. A tremendous amount of work has been undertaken to attempt to predict drug

clearance or changes in drug clearance by administering a “cocktail” of marker drugs that are substrates of different enzymes and transporters or by measuring an endogenous metabolite marker such as 4β-hydroxycholesterol to predict the activity of various enzymes and transporters in an individual patient. But, as we have reviewed[45, 46], these efforts are not successful, and the field does not know why. To understand why a “cocktail” approach will not work, we refer to our very recent publication[46] to understand why IVIVE predictions are so poor. In that publication[46], we derive the relationship between in vitro incubation measures of metabolic clearance with in vivo clearance measures showing that a critical ratio, designated as R_{ss}, must be included:

$$R_{ss} = \frac{V_{H,ss}}{V_{hep,ss}}$$

(Eq. 14)

where $V_{H,ss}$ is the volume of distribution of the drug at steady-state in the entire heterogeneous liver, while $V_{hep,ss}$ is the volume of distribution of the drug at steady-state in the homogeneous hepatocyte water in contact with the metabolic enzymes. It is expected that each drug will distribute differently into lipophilic hepatic tissue depending on its unique physicochemical properties. Therefore, the *in vivo* volume of distribution of drug in the liver will vary from drug-to-drug, and a drug-specific value for R_{ss} should be incorporated into IVIVE in order to accurately predict human liver clearance from *in vitro* data. Thus, using a surrogate compound to account for an individual’s metabolic or transport activity will only succeed in predicting clearance of a drug-of-interest if the marker substrate has a similar R_{ss} value as the drug-of- interest.

CONCLUSIONS

Predicting PK/PD in the Individual Patient

- PD—The field has made significant advances in using individual patient characteristics to select drugs that will provide efficacy and avoid off-label toxicities.
- PD – In some cases biomarker measurements will allow doses to be selected that should be efficacious and safe.
- PK— Dose selection in the individual patient can give quality results for drugs primarily excreted in the urine.
- PK— For most wide therapeutic index drugs, the label dose will be effective in the great majority of cases, and binary predictions of dose changes (i.e., give 50% of usual dose) in potential drug-drug and drug-disease interactions will work.
- PK— For NTI drugs the predictions are most often more hype than reality, and at most binary recommendations are related to the initial dose followed by required TDM.

But despite this listing, our progress in understanding the importance of variances in metabolic and transporter processes in terms of drug PK and PD, coupled with new modeling techniques utilizing translational learning from clinical studies together with PBPK are very useful in predicting population drug dosing recommendations. I suspect that with continued advances in discovering and, most importantly, validating biomarkers, predicting pharmacokinetics/pharmacodynamics in the individual patients will lead to increased substitution of much of the hype with reality.

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