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Perspective

Drug Metabolism in Older People—A Key Consideration in Achieving Optimal Outcomes With Medicines

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Hepatic clearance plays a key role in determining the systemic exposure of drugs and metabolites, which in turn has a major effect on variability in the beneficial and adverse effects of medicines. Aging results in a number of significant changes in the human liver including reductions in liver blood flow, size, drug-metabolizing enzyme content, and pseudocapillarization. Drug metabolism is also influenced by comorbid disease, frailty, concomitant medicines, and (epi) genetics. These changes have the potential to alter the hepatic clearance of drugs but need to be interpreted in the context of the pharmacokinetic (and pharmacodynamic) characteristics of the drug of interest. There is growing evidence that the age-related changes in the liver not only result in a decrease in the hepatic clearance of unbound drug but also influence variability in response to medicines in older people.

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OLDER people display considerable variability in response to the beneficial and adverse effects of medicines (1). A person's response to a medicine is an interplay between the pharmacokinetics (dose, concentration, and time relationship) and the pharmacodynamics (relationship between concentration and pharmacological effect) of the drug or its metabolites in an individual (2). The pharmacokinetics and pharmacodynamics of a drug are in turn influenced by a range of clinical and pathological factors associated with comorbid medical conditions, concomitant medicines, and age-related changes in organ function and homeostatic control (1,2). These include major changes in body composition and a decline in renal function, both of which can impact on the pharmacokinetics and pharmacodynamics of medicines used in older people (1,2). Of all the changes that occur with aging, it is changes in the human liver that have the greatest impact on drug clearance and significantly contribute to variability in response to medicines in older people (3). A comprehensive understanding of the factors that influence hepatic metabolism in older people is critical to allow individualization of drug and dose

selection for older people and thus achieve optimal outcomes for this patient population. The aim of this review is to highlight the important physiological changes that occur in the aging liver and the impact of these changes on hepatic drug clearance (CL_H) that have important implications for achieving optimal outcomes from medicines for older people.

AGE-RELATED CHANGES IN THE LIVER AND ITS IMPACT ON DRUG CLEARANCE

Hepatic clearance of drugs and metabolites is determined by the delivery of substrates to the drug-metabolizing enzymes within hepatocytes and by the intrinsic metabolic capacity of these enzymes (3). The delivery of drugs to the hepatocyte depends on a number of key parameters such as liver blood flow, binding of drugs (and metabolites) to plasma proteins, and the distribution or transfer of the drug from the hepatic blood supply into the space of Disse via the liver sinusoidal endothelial cells (3,4). In the context of aging a number of parameters that determine hepatic clearance are altered. Significant changes occur in the hepatic

sinusoidal endothelium. This structure consists of a thin fenestrated endothelium with fenestrations clustered into what are termed liver sieve plates that act as an ultrafiltration system (5,6). These sieve plates allow some plasma proteins and smaller substances such as small lipoproteins to enter the space of Disse but excludes larger substances like chylomicrons (6,7). Le Couteur and colleagues have established that aging is associated with significant changes in the liver sinusoidal endothelial cells (a process called pseudocapillarization) (6–8). This process is characterized by the loss of fenestrations, thickening of the endothelium, perisinusoidal collagen deposition, and basal lamina formation (8,9) similar to that observed in hepatic cirrhosis (6).

The impact of aging on CL_H must be interpreted in the context of the pharmacokinetic properties of the drug involved, in particular the extent of drug metabolism and the hepatic extraction ratio (E_H) of the drug or metabolite (3).

High Hepatic Clearance Drugs

For drugs with a high $E_H > 0.7$, also termed flow-limited or high clearance drugs, the hepatic clearance is approximately equal to the hepatic blood flow (Q_H), such that $CL_H = Q_H$. Liver blood flow and size are reduced in older people (and different animal models of aging) (9,10). The age-related reduction in Q_H is expected to result in a decrease in hepatic clearance of drugs with a high E_H . This has been supported by the majority of studies of drugs that have a high hepatic clearance that demonstrate reduced hepatic clearance in older people when compared with younger people (9,11). The following medicines with a high hepatic clearance have been shown to have a lower hepatic clearance in older people: amitriptyline, desipramine, diltiazem, dosulepin (dothiepin), fentanyl, imipramine, labetalol, levodopa, lidocaine (lignocaine), metoprolol, morphine, nortriptyline, pethidine (meperidine), propofol, propranolol, and verapamil (11). Age-related changes in the liver have the potential to impact on the presystemic metabolism (first-pass effect) and therefore the bioavailability of drugs with high hepatic clearance after oral administration (12). Although the effect on bioavailability is unpredictable, the age-related changes in the liver have the potential to result in a significant and variable increase in bioavailability for some medicines after oral administration (12).

Low Hepatic Clearance Drugs

Alternatively, for drugs with a low $E_H < 0.3$, also called capacity-limited or low clearance drugs, the hepatic clearance is estimated as $CL_H = fu \times CL_{int}$ where fu is the fraction unbound in blood and CL_{int} is the intrinsic hepatic clearance, reflecting the activity of the drug metabolizing enzymes within the hepatocyte. Examples of drugs with a low E_H include naproxen, valproic acid, ibuprofen, temazepam, lorazepam, diazepam, phenytoin, and warfarin. Numerous studies have investigated the effects of aging on the content

of drug-metabolizing enzymes within the liver, which impacts on CL_{int} (9–11). One of the most comprehensive investigations of the effect of aging on drug metabolizing enzyme content in the liver, by Sotaniemi and colleagues (13), investigated the cytochrome P450 (CYP) content in liver biopsy samples in 226 people and found that CYP content declines at a rate of approximately 0.07 nmol/g of liver after approximately 40 years of age. Other studies and commentaries have not reported significant changes in drug-metabolizing enzyme content in older people but suggest that this may vary between different drug metabolizing enzymes (14–16). Reduced liver size and enzyme content observed in older people suggest that hepatic clearance is expected to be reduced in older people (specifically by a reduction in CL_{int}). However, the impact of age-related changes in the liver for drugs with low E_H provides for a more complex set of observations whereby some studies of capacity-limited drugs display a reduction (eg, lorazepam, piroxicam, and warfarin) or paradoxical increase (eg, ibuprofen, naproxen, and phenytoin) in hepatic clearance whereas other drugs with these characteristics display no significant change (eg, diazepam, temazepam, and valproic acid) in total hepatic clearance in older people (11). Butler and Begg (11) reviewed the available literature related to hepatic clearance changes that occur in older people. These authors highlighted the need to study the hepatic clearance of unbound drug (CL_H/fu) rather than total hepatic clearance (CL_H , which includes bound and unbound drug). A critical consideration is that human serum albumin concentrations (which is responsible for the plasma protein binding of many low clearance acidic drugs) declines in older people (9) leading to higher unbound fraction (fu) in older people when compared with younger people (11). Many basic drugs are bound to α_1 -acid glycoprotein and lipoproteins in plasma (11). There remains some debate about how the concentrations of α_1 -acid glycoprotein change with older age that makes interpreting the effect of aging on the plasma protein binding of basic drugs complicated. As an acute phase protein, there is some data to suggest this plasma protein is elevated or remains unchanged in older people (11). As outlined previously, an increase in fu will lead to an increase in total hepatic clearance for low clearance drugs if CL_{int} is unchanged or may counteract the reduction in CL_{int} in older people such that total clearance appears unaffected by aging. Misinterpretation of these age-related changes in total hepatic clearance could lead to recommendations to actually increase the dose rate in older people, whereas the unbound clearance is decreased, leading to a considerable risk of toxicity.

The interpretation of age-related changes in protein binding and hepatic function also needs to be considered in the context of the extent of protein binding for a given drug. For example, low clearance drugs that have a relatively low extent of protein binding typically show a reduction in total hepatic clearance in older people because the changes in binding due to reduced albumin concentration observed in

older people do not represent a significant change in f_u . For example, theophylline has a f_u of approximately 0.60, and numerous studies have demonstrated a reduction in clearance in older people by up to 50% (9,11). In this case, the age-related decline in intrinsic hepatic clearance has a major effect in reducing theophylline total hepatic clearance despite the fact that f_u increases in older people. On the other hand, low clearance drugs that exhibit extensive protein binding (with a very small f_u) demonstrate a significant increase in f_u in older people, which in turn, will increase the total hepatic clearance, highlighting the need to estimate hepatic clearance of unbound drug to evaluate the effect of aging. The nonsteroidal anti-inflammatory drugs naproxen and S-ibuprofen are examples of drugs that have both low hepatic clearance and extensive protein binding in plasma ($f_u < 0.01$). The hepatic clearance of unbound drug of naproxen was reduced by 50% and S-ibuprofen by up to 30% in older people when compared with younger people (11).

The reduced content of phase I drug-metabolizing enzymes has led to the majority of studies for low clearance drugs demonstrating reduced hepatic clearance of unbound drug in older people when compared with younger people (11). This is an important observation because it is the clearance of unbound drug that determines the multiple dose rate during chronic dosing. These observations also have important implications for pharmacokinetic studies conducted in older people and highlight the need to measure unbound concentrations of drugs and metabolites to correctly interpret the impact of aging on their pharmacokinetics. However, this is a difficult and complex area to study given the many factors that influence pharmacokinetic variability in older people (1). As an example, Wright and Begg (17) investigated the pharmacokinetics of phenytoin in older people to test the hypothesis that the 'apparent clearance' (CL/F) of unbound phenytoin is reduced in older people using a retrospective and prospective study. These researchers found older people had a trend for reduced unbound hepatic clearance of phenytoin (0.12 ± 0.02 L/kg/day in older patients and 0.18 ± 0.07 L/kg/day in the younger cohort) but this was not found to be statistically significant.

To date, the majority of studies have focused on the impact of aging on the hepatic clearance mediated by phase I drug-metabolizing enzymes, such as CYP (15,18). The impact of aging has a variable effect on phase II metabolic pathways (14). Drug metabolism by glucuronidation (involving UDP-glucuronosyltransferases [UGT]) appears to be preserved in otherwise fit and well older people. A study by Court (19) investigated the variability in UGT metabolic activity using a human liver bank. This study investigated the major UGTs (UGT1A1, 1A4, 1A6, 1A9, 2B7, and 2B15) and demonstrated a coefficient of variability in metabolic activity between 45% and 92%. Whereas genetic polymorphisms, sex, and concomitant drugs had a major effect on UGT activity in this study, older age had only a minimal effect on the variability in activity of these

enzymes (19). This is supported by a number of pivotal clinical pharmacokinetic studies (20,21) that have demonstrated no difference in the formation of glucuronide and sulfate metabolites in studies comparing younger and older healthy people. Interestingly, these studies did however highlight that glucuronidation is affected by frailty, with frail older people having significantly reduced metabolic capacity in the formation of these conjugated metabolites (20,21) (discussed subsequently).

HEPATIC UPTAKE OF DRUGS AND METABOLITES IN THE AGING LIVER

Although protein binding is a major determinant of the extent of uptake of solutes by the liver, pseudocapillarization in the aging liver (6–8) has the potential to significantly limit the distribution of some drugs and metabolites into the liver. In this way, defenestration of liver sinusoidal endothelial cells has the potential to impede the clearance of large molecular weight protein therapeutics and some extensively protein bound drugs (6,22).

The liver represents a major clearance pathway for large molecules, particulate-based drug delivery modalities (such as liposomal therapies), and protein-based therapies. However, relatively few studies have investigated the effect of older age on the pharmacokinetics of liposomal encapsulation of drugs. Drug delivery strategies such as liposomal encapsulation (eg, liposomal doxorubicin or liposomal amphotericin) have a significant effect on the hepatic disposition of the encapsulated drug (22,23). The pseudocapillarization of the liver sinusoidal epithelium and the reduced endocytic capacity (24) of the aging liver have the potential to significantly reduce the hepatic uptake and subsequent clearance of large molecular weight therapeutic proteins and liposomes. Hilmer and colleagues (22) investigated the hepatic disposition of liposomal doxorubicin in the isolated perfused livers of older rats and found that liposomal doxorubicin distribution is restricted to the sinusoidal lumen (when compared with younger rats) which is a likely consequence of exclusion by fenestrations in the sinusoidal endothelium. This provides the mechanism for the significantly different pharmacokinetics characterized by reduced hepatic extraction of liposomal doxorubicin compared with doxorubicin. The sinusoidal endothelium and fenestrations within the sinusoidal endothelium have an important role in hepatic pharmacokinetics of liposomal encapsulated drugs and are important considerations for the pharmacokinetics of these agents in older people.

Whereas the effect of age-related defenestration of the liver sinusoidal epithelial cells on the CL_H of large macromolecules is clear, the effect on highly protein bound drugs is less clear (6). This leads to the hypothesis that the impact of age-related changes in the liver on the hepatic clearance of low clearance drugs would be proportional to the extent of protein binding (6,9). In part, this has been supported by observations of detailed studies in animal models of hepatic

cirrhosis, a pathological process that mimics the effects of age on the liver. For example, carbon tetrachloride-induced cirrhosis in rats leads to a 50% reduction in the hepatic extraction for the highly protein bound drug propranolol (25). A recent study involving paracetamol, a highly soluble drug that has minimal protein binding, provides more data on the impact of age-related pseudocapillarization on hepatic uptake. Mitchell and colleagues (26) compared the hepatic uptake of paracetamol in young and old rats using the isolated perfused rat liver model and multiple indicator dilution technique. These researchers found that paracetamol uptake was significantly less in the old rats when compared with young rats. In a separate study, these researchers found that the hepatic extraction of paracetamol was also reduced by approximately 10% in Poloxomer 407-treated rats (Poloxomer 407 induces changes in the liver that reflect age-related defenestration) (27).

For the majority of drugs, the healthy liver sinusoidal endothelium is unlikely to pose a significant barrier to hepatic uptake for most substrates; however, the structural changes within the liver as a result of aging have the potential to also reduce the hepatic extraction of high clearance (flow-limited) drugs. Similarly, clearance of drugs that are highly bound to albumin may be impeded by reduced access of the drug to the space of Disse (and the hepatocyte) via a defenestrated endothelium. These novel observations provide further insight into the complex interplay of pharmacokinetic and age-related physiological changes that occur in the liver. The clinical impact of these observations is the subject of considerable ongoing research and investigation.

DRUG METABOLISM IN OLDER FRAIL PEOPLE

Frailty is a clinical phenotype that is associated with adverse health outcomes (28,29) and is characterized by an excessive reduction of lean body mass, sarcopenia, chronic under-nourishment, reduced function, and poor endurance (28). Frailty is likely to increase the age-related heterogeneity in the pharmacokinetics and pharmacodynamics of drugs (1). There are a relatively limited number of investigations on the effect of frailty on the pharmacokinetics of drugs in older people (20,21,30,31); however, interpretation of these studies is complicated by inconsistent assessment of frailty. In these studies, the investigators have used a variety of methods to assess the frailty status of participants. These range for clinical assessment by investigators (20,21) to more systematic metrics such as employed by Schwartz and colleagues (31). A recent systematic review by de Vries and colleagues (32) has considered the available frailty instruments that could be predictive of outcomes in clinical situations or for observational and experimental studies. These researchers highlight the need to consider the eight major domains of frailty: nutritional status, physical activity, mobility, energy, strength, cognition, mood, and social relations/support (32). The systematic review by de Vries and colleagues concluded that the Frailty Index (proposed by Mitnitski and colleagues 33) was the preferred metric for

assessing frailty as it was most comprehensive. Recent pharmacological studies have utilized the Edmonton Frail scale (34) or modified and validated versions of this scale (35) to investigate the impact of frailty on determinants of medicine response (36–38).

There is a clear association between inflammation and frailty (30). Inflammation has the potential to downregulate drug metabolism and transporter pathways (30,39) reducing the systemic clearance of some medicines. The landmark study of drug metabolism in frail older people by Schwartz (31) used the erythromycin breath test as a marker of CYP3A4 metabolic activity. The study concluded that old and very old (>80 years) people maintain the ability to metabolize CYP3A4 substrates and that frail older people do not universally display reduced drug clearance. However, it was subsequently reported that erythromycin is an imperfect probe for CYP3A4 activity as it is also a substrate for the drug efflux transporter, p-glycoprotein (40) further complicating the interpretation of these data. Wynne and colleagues (21) studied metoclopramide metabolism in frail older people to investigate sulfation conjugative metabolism and found that, while the activity of this pathway is preserved in fit older subjects, it is significantly decreased in frail older subjects. As discussed previously, the same investigators demonstrated a similar impact on paracetamol glucuronidation (20). Taken together with the observations of Hubbard and colleagues (30), who investigated the effect of frailty on esterase activity, these studies support the finding that frailty has an effect on reducing the activity of a number of drug-metabolizing pathways that in turn may result in a reduction in hepatic clearance.

CONCOMITANT MEDICINES AND THE IMPACT ON HEPATIC CLEARANCE

Polypharmacy in older people is a significant risk factor for drug–drug interactions (41) that have the potential to affect CL_H . This contributes to a high prevalence of potentially significant drug–drug interactions (related inhibition or induction of drug metabolism) in older people (42,43). The pharmacokinetic changes that occur in older people typically lead to higher systemic exposure to drugs and metabolites when compared with younger people taking the same doses. This poses a significant risk for metabolic interactions by substrate inhibition, the clinical significance of which are concentration-dependent (1). The impact of age-related changes in the liver on the potential for and significance of interactions has not been widely studied. However, there have been a number of rigorously designed pharmacokinetic studies (44,45) designed to specifically address this issue. These studies support the conclusion that the extent of inhibition and induction of drug–drug interactions in young and older people is not significantly different, despite the fact that the clinical significance might be different due to pharmacodynamic changes in older people (2).

PHARMACOGENOMICS, DRUG METABOLISM, AND OLDER PEOPLE

Pharmacogenomics is recognized as a major determinant of hepatic drug metabolism enzyme activity (3); however, disentangling the impact on genotype- and age-related differences in drug metabolism has remained a challenge (16). Ishizawa and colleagues (46) investigated the effect of aging on the pharmacokinetics of omeprazole, a proton pump inhibitor, after intravenous dosing in people with three different *CYP2C19* phenotypes (poor [PM], intermediate [IM], and extensive [EM] metabolizers). These researchers reported a larger increase (twofold) in the area under the concentration–time curve of omeprazole in older people who were EMs and IMs but not in older PMs. In this case, it seems that the impact of *CYP2C19* genotype has a more significant effect on hepatic clearance than age-related changes in the liver for drugs metabolized by this enzyme.

On the other hand, Brenner and colleagues (47) investigated exposure to diclofenac and celecoxib, both of which are *CYP2C9* substrates in healthy young and old people of known *CYP2C9* genotype and found no impact of aging in the systemic exposure of these drugs at steady state. The anticoagulant warfarin has also been widely studied to understand the relative impact of age, weight, and genotype of pharmacokinetic (*CYP2C9*) and pharmacodynamic (*VKORC1*) determinants on warfarin dose requirements (48). Together these factors accounted for more than 60% of the variability in dose requirements for warfarin. *VKORC1* genotype (up to 49%) accounted for the greatest portion of the variability in younger patients, but interestingly age remained an influential factor on warfarin dose with requirements decreasing by 0.2 mg per decade (from the ages of 10–90 years) irrespective of genotype and patient weight (48). A major area of research interest is the possible impact of epigenetics on drug metabolism (49). In this context, epigenetics refers to the inherited differences in drug metabolism phenotype (or the expression of genes encoding drug metabolizing enzymes) as a consequence of factors other than changes in DNA sequence (eg, DNA methylation). Epigenetic changes are likely to be highly prevalent in older people and has potentially important implications for hepatic clearance and variability in response to medicines in older people (49).

Taken together, these studies support the general conclusion that further research is needed in this area and recognizes that (epi)genotype is an important determinant of hepatic drug metabolism for many drugs; however, age-related changes in the liver have a greater impact on hepatic clearance and the overall interpatient variability in older people (1).

CONCLUSIONS

Age-related changes in the liver have a major impact on CL_H that in turn influences variability in response to medicines in older people. Chronological age is a relatively poor predictor of hepatic clearance, and hence a detailed under-

standing of the factors that regulate drug clearance is needed. The impact of aging on drug metabolism also needs to be considered in the context of comorbid disease, frailty status, concomitant medicines, and (epi)genetics. Clearly, further research is needed into the pharmacokinetic and pharmacodynamic properties of commonly used medicines in older people, especially those that are frail and most vulnerable to the harms (and benefits) of medicines. A systematic understanding of hepatic clearance of drugs and metabolites in older people and the factors that influence the clearance of unbound drug by the liver is critical to informing the optimal use of medicines in older people based on the sound principles of clinical pharmacology. In general terms, the pharmacologically guided approach to optimizing the outcomes from medicines requires a detailed understanding of the pharmacokinetics and pharmacodynamics in the relevant patient population to inform drug and dose regimen selection.

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