Clinical implications of changes in hepatic drug metabolism in older people

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Abstract: Prescribing for older people is challenging because of the paucity of clinical trial evidence of therapeutic benefit in this population and the presence of evidence that older people are at increased risk of adverse drug reactions. The outcomes of pharmacotherapies in older people depend on age-related changes in both pharmacokinetics and pharmacodynamics. Of the pharmacokinetic changes, those in hepatic metabolism are the most significant. Recent advances in biogerontology have improved our understanding of changes that occur in hepatic pharmacokinetics in older people. Knowledge of age-related changes in hepatic metabolism can guide prescribing and help reduce the risk–benefit ratio of using medications in older people.

Keywords: aging, pharmacokinetics, liver, adverse drug reactions, prescribing

Medication use by older people

Older people are major users of medications because of the increased prevalence of chronic diseases and increased susceptibility to acute illness with age. On average, older people use two to five regular prescription medications, and 15%–40% use five or more medications (polypharmacy) (Table 1) (Helling et al 1987; Stewart and Cooper 1994; Anderson and Kerluke 1996; Barat et al 2000; Chen et al 2001; Jorgensen et al 2001; Linjakumpu et al 2002; Byles et al 2003). Use of medications by older people has continued to increase over the past two decades (Stewart et al 1991; Linjakumpu et al 2002) and because of the increased risk of disease, older people should benefit from medications (Ebrahim 2002). However, the evidence base for prescribing to older people is limited with regard to both efficacy and safety (Bugeja et al 1997).

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Table 1 Prevalence of polypharmacy in community-dwelling older people

Age group	Mean or median number of medications	Polypharmacy (%)	Definition of polypharmacy	Place	Reference
>64	3.1 (1990–1991) 3.8 (1998–1999)	19 (1990–1991) 25 (1998–1999)	5 or more	Finland	Linjakumpu et al 2002
65–74	2.03	11	5 or more	UK	Chen et al 2001
>75	2.47	15			
>64	4	53	4 or more including OTC	Australia	Byles et al 2003
65–74	2.2	24	6 or more	Canada	Anderson et al 1996
>75	3.8	37			
>75	4.2	34	5 or more	Denmark	Barat et al 2000
>65	4.8 (female) 3.8 (male)	39	5 or more	Sweden	Jorgensen et al 2001

Abbreviations: OTC, over the counter.

Increasing age is correlated with increasing incidence of adverse drug reactions both in hospital and in the community (Hurwitz and Wade 1969; Kellaway and McCrae 1973; Carbonin et al 1991; Atkin and Shenfield 1995; Martin et al 1998; Gholami and Shalviri 1999; Pouyanne et al 2000; Bordet et al 2001). Susceptibility of older people to adverse drug reactions is considered to be secondary both to extrinsic factors (prescribing and medication management) and intrinsic factors (pharmacokinetics and pharmacodynamics) (Nolan and O'Malley 1988). This review will describe the pharmacokinetic changes that occur as a result of aging changes in the liver. It will highlight clinical implications of these changes and guide prescribing to maximize therapeutic effects and reduce the subset of adverse reactions due to altered pharmacokinetics in older people.

Pharmacokinetic considerations related to the aging liver

Hepatic clearance (Cl_{liver}) is illustrated by the formula:

$$Cl_{liver} = \frac{Q[C_a - C_v]}{[C_a]} = QE \qquad (1)$$

where, C_a=concentration of drug in portal vein and hepatic artery, C_v=concentration of drug in hepatic vein, Q=sum of hepatic portal and arterial blood flow, and E=steady state extraction ratio. The clearance of medications by the liver depends on hepatic blood flow and intrinsic clearance (enzyme activity and mass). The clearance of highly extracted substrates is predominantly determined by hepatic blood flow (flow limited), while that of poorly extracted substrates is influenced by intrinsic clearance (capacity limited) and in some cases, protein binding. Aging is associated with a reduction of approximately 40% in hepatic blood flow and 30% in liver mass (McLean and Le Couteur 2004). Impaired hepatic drug clearance in older people has been attributed to these changes (Woodhouse and Wynne 1988).

The clearance of flow-limited drugs is reduced to a greater extent than that of capacity-limited drugs in older people (Table 2). The metabolism of flow-limited drugs is reduced by approximately 40%, consistent with the reduction in blood flow in older people. The in vitro metabolism of many capacity-limited drugs is relatively preserved, consistent with preservation of the content, activity, and gene expression of phase I and II drug metabolizing enzymes with age (Le Couteur and McLean 1998; Kinirons and O'Mahony 2004) (Table 2).

Table 2 The influence of old age in humans on the metabolism of drugs and other compounds that undergo phase I, phase II, capacity-limited, and flow-limited metabolism

Hepatic metabolism	Reduced	Unchanged
Flow-limited	pethidine morphine propranolol verapamil amitryptiline lignocaine	
Capacity-limited	theophylline	diazepam phenytoin salicylic acid valproic acid warfarin
Phase I	ibuprofen lignocaine diltiazem propranolol theophylline impramine amitryptiline verapamil	warfarin caffeine phenytoin
Phase II	morphine	isoniazid oxazepam paracetamol salicylic acid temazepam

Source: Adapted from Le Couteur DG, McLean AJ. 1998. The aging liver: drug clearance and an oxygen diffusion barrier hypothesis. *Clin Pharmacokinet*, 34: 359–73. Reproduced with permission from Adis International.

Even so, there seems to be an age-associated selective impairment of phase I drug metabolism with no significant reduction in phase II metabolism (Le Couteur and McLean 1998) (Table 2). Even though there is no change in in vitro activity of phase I enzymes with age (no reduction in enzyme expression [Schmucker et al 1990] or activity [Hunt et al 1992]), most drugs metabolized by phase I pathways have reduced clearance in older people (Le Couteur and McLean 1998). The paradox of reduced phase I drug metabolism in older people (Schmucker 2001) has been explained by the oxygen delivery hypothesis (Le Couteur and McLean 1998). Phase I enzymes are more oxygen dependent than phase II enzymes. The normal endothelium of the hepatic sinusoid is attenuated and fenestrated and does not impair oxygen transfer. However, in aged rats (Le Couteur et al 2001), baboons (Cogger et al 2003), and humans (McLean et al 2003) the sinusoidal endothelium is thickened and defenestrated and there is associated deposition of collagen and basal lamina formation. These structural changes could

reduce oxygen or even drug transfer to the hepatocytes (Le Couteur et al 2005). We recently demonstrated the importance of the hepatic sinusoidal endothelium as a barrier to drug transfer in a study of the hepatic disposition of liposomal doxorubicin. The liposomes were restricted to the sinusoidal lumen, presumably secondary to steric exclusion by fenestrations in the sinusoidal endothelium, explaining the longer half-life and reduced hepatic extraction of liposomal doxorubicin compared with doxorubicin (Hilmer et al 2004).

Phase II metabolism generally is not affected by normal aging. However, it may be impaired in frail older people. This is seen with paracetamol conjugation, which is preserved in healthy older people (Miners et al 1988) but impaired in frail, hospitalized older people (Wynne et al 1990).

The reduction in hepatic metabolism with age is also important in first-pass metabolism and therefore oral bioavailability of medications. In older people, drugs undergoing extensive first-pass metabolism, such as propranolol and verapamil (Wilkinson 1997) have increased bioavailability. However, prodrugs, such as perindopril (Todd and Fitton 1991) may have slower first-pass activation in the aged liver.

The phase III hepatic pathway is the transport of drugs into the bile, predominantly by P-glycoprotein and other transporters in bile canaliculi (Yamazaki et al 1996; Marzolini et al 2004). Transporters including P-glycoprotein are also involved in efflux of compounds (including drugs) from the intestines (Chan et al 2004). There are no human studies on phase III hepatic metabolism in aging. Expression and activity of P-glycoprotein in lymphocytes are increased with age in rodents in some studies (Gupta 1995). Other studies in young and old people have demonstrated a decrease in the activity of P-glycoprotein in T lymphocytes (Machado et al 2003) with age, with no change in its function in natural killer cells (Machado et al 2003; Brenner and Klotz 2004). In each subject, the expression of P-glycoprotein in different organs is not clearly associated (von Richter et al 2004). There is wide (40x) genetically determined inter-individual variation in expression of P-glycoprotein (Kim et al 1999) and this variability would be expected to be even greater as heterogeneity increases with age. Surprisingly, the function of P-glycoprotein in natural killer cells differs between the CC and TT genotypes in young but not elderly subjects (Brenner and Klotz 2004). This is probably because the increasing heterogeneity with

age is not due to genetic factors. Recently, P-glycoprotein expression and function has been described in young, intermediate, and old rats in a range of tissues important for drug disposition. P-glycoprotein expression increased with age in lymphocytes and the liver, decreased in the kidneys, and did not change significantly and was very variable in intestinal microsomes and blood brain barriers (Warrington et al 2004). If there is a similar trend in aging humans, then changes in P-glycoprotein may increase the biliary excretion and decrease renal excretion of drugs with variable effects on intestinal absorption.

Implications of hepatic pharmacokinetic changes when prescribing for older people

Hepatic changes must be considered in the context of other pharmacokinetic changes and pharmacodynamic changes in older people. However, of the pharmacokinetic changes with age, changes in hepatic metabolism are the most significant (McLean and Le Couteur 2004). Age-related changes in drug absorption (Mangoni and Jackson 2004), distribution (higher fat: muscle ratio) (Turnheim 1998), and protein binding (Benet and Hoener 2002) are not usually clinically significant. Renal elimination of drugs is reduced with age to a lesser extent than was previously believed (McLean and Le Couteur 2004) but remains important for renally excreted drugs with narrow therapeutic-toxic windows. This is especially true with the onset of acute renal failure, eg, contrast nephropathy. Consequently, impaired hepatic metabolism, which affects both bioavailability and hepatic clearance, is a major pharmacokinetic factor to consider when prescribing for older people.

Dose adjustment for older people

Aging changes in hepatic pharmacokinetics suggest that initial doses of most drugs with high hepatic extraction ratios and particularly those that undergo phase I metabolism should be reduced by approximately 40% in older people to achieve similar pharmacokinetic profiles to young people (Table 2). The adjustment in maintenance dose, D'_m, required to correct for a decline in metabolic clearance can be calculated from the formula:

$$D'_m = D_m \frac{fCL'}{f'CL} \qquad (2)$$

Where, D_m is the maintenance dose in a young adult, f is the drug bioavailability, and CL the clearance (Turnheim

Table 3 Pharmacokinetic data for HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitor	Simvastatin	Pravastatin	Atorvastatin
Prodrug	Yes	No	No
Hepatic extraction (% absorbed dose)	78–87	66	>70
Active metabolites	Yes	No	Yes

Source: Adapted from Igel M, Sudhop T, von Bergmann K. 2002. Pharmacology of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), including rosuvastatin and pitavastatin. *J Clin Pharmacol*, 42:835–45. Reproduced with permission from Sage Publications.

2003). In contrast, intravenous loading doses do not require adjustment for age, and should be adjusted only to the patient's volume of distribution, which can be estimated using their weight.

It is important to consider whether the drug is a prodrug and whether it has active or toxic metabolites in selecting a starting dose. For example, HMG-CoA reductase inhibitors (Table 3) have high hepatic extraction ratios and are processed by phase I, II, and III pathways in the liver (Igel et al 2002). Their therapeutic effects are related to their actions in the liver, but toxic effects are related to drug concentrations in both the liver and the periphery. Simvastatin is a prodrug and conversion to its active metabolites by phase I metabolism will be less efficient in older people. The dose may need to be maintained in older people for therapeutic effect but patients may be at increased risk of toxic effects from the accumulated prodrug. Pravastatin and atorvastatin are not prodrugs. Pravastatin is metabolized to inactive metabolites while atorvastatin has active metabolites, which undergo biliary excretion. In older people, lowering the dose of pravastatin and atorvastatin by about 40% should correct for the decreased phase I metabolism to give a similar pharmacokinetic profile to a standard dose in a younger person. This is supported by clinical trial evidence. A 20-mg dose of pravastatin gives a larger AUC for pravastatin in older than younger people, but the pharmacokinetics of the metabolite SQ 31 906 are similar in both age groups (Pan et al 1993). A 20-mg dose of atorvastatin has a C_{max} 42.5% higher, AUC 27.3% greater, and elimination half-life 36.2% longer in older than younger people. Phase III metabolism of HMG-CoA reductase inhibitors depends on P-glycoprotein, and if the expression and activity of this protein is increased in the livers of older people as it is in the livers of older rats (Warrington et al 2004), then biliary excretion of the metabolites may be more efficient in older people.

Adverse drug reactions

There is a strong association between the risk of adverse drug reactions and old age (Beyth and Shorr 1999). Some evidence suggests that rather than being an independent risk factor, age may simply be a marker for comorbidities, altered pharmacokinetics, and polypharmacy (Figure 1) (Williamson and Chopin 1980; Leach and Roy 1986; Carbonin et al 1991; Gurwitz and Avorn 1991; Atkin and Shenfield 1995; Cooper 1999; Mannesse et al 2000).

Polypharmacy increases the risk of adverse events (Figure 1), secondary to both cumulation of adverse reactions to each drug and drug–drug interactions (Rosholm et al 1998; du Souich 2001). Many predictable drug–drug interactions occur through induction or inhibition of the cytochrome P450 pathways of hepatic metabolism (Tanaka 1998). More recently drug–drug interactions have been recognized in phase III metabolism. One study found digoxin levels correlated with the number of inhibitors of P-glycoprotein patients were taking, eg, amiodarone, atorvastatin, quinine, spironolactone, verapamil (Englund et al 2004). However, this is more likely to be related to P-glycoprotein inhibition in the intestines than in the liver.

One of the strongest independent risk factors for polypharmacy is the prescriber, so attempts to reduce polypharmacy focus on educating the prescribing doctors. Inappropriate prescribing can be reduced using "academic detailing" (Soumerai and Avorn 1990). This includes assessment of baseline knowledge and motivations for current prescribing, focusing programs on specific categories of physicians and on their opinion leaders, defining clear educational and behavioral objectives, establishing credibility through a respected organizational identity, referencing authoritative and unbiased sources of information, presenting both sides of controversial issues, stimulating active physician participation in educational
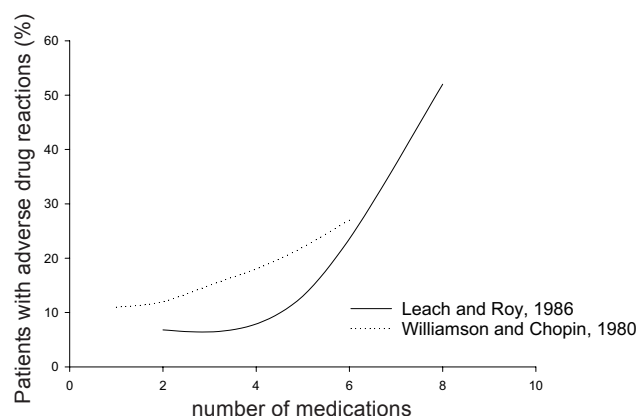
Figure 1 The relationship between polypharmacy and adverse drug reactions.

interactions, using concise graphic educational materials, highlighting and repeating the essential messages, and providing positive reinforcement of improved practices in follow-up visits. However, we found attempts to reduce polypharmacy with "academic detailing" and a patient-held medication card were less effective than introduction of a government co-payment for prescriptions (Atkin et al 1996). The introduction of co-payments may decrease the use of both necessary and unnecessary medications.

Stopping medications can be associated with adverse drug effects related to withdrawal (Woodward 2000), recurrence of the underlying condition (Nelson et al 2002), or alterations in the pharmacokinetics and pharmaco-dynamics of the patient's other medications.

Over 80% of adverse drug reactions that require admission or occur in hospital are the type A, dose-related kind (Shenfield 2001; Routledge et al 2004). Consideration of aging pharmacology should be able to reduce those adverse drug reactions due to high drug concentration at the site(s) of action.

Many adverse reactions in older people are due to pharmacodynamic changes (with normal aging and disease) and loss of compensatory homeostatic mechanisms with aging. Such adverse drug reactions occur with drug concentrations in the therapeutic range at the target receptors. For example, therapeutic serum levels of digoxin result in adverse drug reactions in older people.

Even type B, idiosyncratic adverse drug reactions, such as interstitial nephritis and hepatitis with H2-receptor antagonists appear to be commoner in older people (Fisher and Le Couteur 2001), and these are not preventable with our current understanding of aging pharmacology.

Broad implications of age-associated changes in hepatic pharmacokinetics

Age-associated changes in the liver affect the metabolism not only of drugs, but also of other substrates. The associations between age and neurodegenerative disease, and age and atherosclerosis may be related to altered hepatic metabolism of neurotoxins and lipids (Le Couteur et al 2002), respectively.

Conclusions

Unfortunately, there is little clinical trial evidence to guide prescribing in older people (McLean and Le Couteur 2004). In addition, older people are a very heterogeneous group.

Therefore, clinical decisions must be made for each individual with vigilant monitoring for efficacy and adverse drug reactions. An understanding of impaired hepatic metabolism of drugs in older people can guide the clinician in selecting starting doses of medications. Medications that are prodrugs requiring activation through hepatic metabolism may be less effective in older people, and medications that are metabolized for biliary or renal excretion may require lower or less frequent doses in older people.

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