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Dose optimisation—the effect of age

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Abstract

Although the absolute and relative size of the pensionable population is not currently rising, that population is ageing. As a result, prescriptions for elderly patients continue to increase. People over the age of 60 represent around 22% of the many western European populations, yet receive nearly 54% of the medication prescribed. Over the age of 75, the proportion of the population is around 14%, yet 33% of prescriptions are written for this group. Depending on the age group, between 20% and 30% are taking at least three drugs. A number of problems complicate the process of prescribing for elderly patients. Pharmacokinetic changes consequent upon the physiological changes associated with ageing result in a fall in the renal clearance of drugs. Similarly, the reduced proportion of body water seen in old age results in an increased volume of distribution, and hence elimination half-life of lipid-soluble drugs. Liver volume falls with increasing age, although in vitro studies demonstrate enzyme activity is normal. As a result of this, the clearance of hepatically metabolised drugs tends to fall with age. Over and above the effects of ageing, changes associated with frailty are also seen. These result additionally in a reduction in plasma albumin protein binding—clinically relevant only for acidic drugs very extensively bound-leading to a reduction in volume of distribution. In addition, reduced hepatic enzyme activity further reduces the hepatic clearance of drugs which undergo hepatic metabolism. In addition to age-related pharmacokinetic changes, changes in pharmacodynamics also occur. A change in pharmacodynamics implies a change in drug effect per unit concentration or change in sensitivity. The characterisation of such effects often requires formal concentration effect analysis to separate kinetic from dynamic effects. Increased sensitivity to benzodiazepines, warfarin, hypertensives, anaesthetics, neuroleptics are well described, as is the reduced sensitivity to the hypotensive effect of β -blockers and dystonic effects of neuroleptics. The higher prevalence of dose-related adverse drug reactions seen in elderly patients relates not only to age-associated pharmacokinetic and pharmacodynamic changes, but also to the increased prevalence of disease states and use of concomitant drug therapy. Indeed, numbers of drugs prescribed is probably the most important factor. Although age is only one determinant, these changes are clearly

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important determinants of the optimal dosage for older patients. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Although the absolute and relative size of the pensionable population is not currently rising in many western societies, that population is ageing. As a result, prescriptions for elderly patients continue to increase. People over the age of 60 represent around 22% of the many western European populations, yet receive nearly 54% of the medication prescribed. Over the age of 75, the proportion of the population is around 14%, yet 33% of prescriptions are written for this group. Depending on the age group, between 60% and 80% of elderly people are taking some form of medication, and between 20% and 30% are taking at least three drugs. The special needs of elderly patients are thus ever more important. An important aspect of these special needs is the different approach to prescribing. Rational prescribing in elderly patients can only be achieved with an understanding of the relationship between age and both pharmacokinetics and pharmacodynamics, thus minimising adverse drug reactions and clinically significant adverse drug interactions. Reference will also be made to the relevance to dose optimisation in the early years of life.

2. Pharmacokinetics

For many years, regulatory authorities did not require data on the effect of age on the pharmacokinetics of new chemical entities when the drug would be used in elderly patients. Most pharmacokinetic studies were performed on young healthy white males, but paradoxically, the drugs were subsequently largely consumed by elderly females of varying ethnic groups [1]. European and North American regulatory bodies now insist on recruitment of appropriate volunteers and patients into clinical trials. Despite the limited evidence base, few drugs are not licensed for use in elderly patients and many drugs in current use in paediatrics are used off-licence. It is important that age should be seen as just one of many determinants of pharmacokinetics and, thus, dose. Many of these determinants are considered elsewhere in these proceedings.

2.1. Absorption

Following enteral administration of a drug, there are a number of factors that determine its entry into the systemic circulation. These include the drug's physico-chemical properties (molecular size, particle size, charge, solubility and pK_a), local pH (stomach vs. intestine), rate of gastric emptying, extent of the absorptive surface and first pass metabolism (intestine and

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liver). The first four of these determine rate and extent of absorption. Most drug absorption takes place in the upper small intestine. Some absorption takes place in the stomach, depending on the pK_a of the drug and the pH of the stomach. Newborn infants have relative achlorhydria, reduced gastric emptying and slower intestinal transit times than older children.

Although early studies with often frail or institutionalised elderly people suggested gastric emptying was reduced [2], more recent studies with healthy older people have not confirmed this [3,4]. Similarly, small bowel transit times were also well preserved [4]. The large absorptive area of the intestinal villi accounts for the small intestine's large contribution to absorption. It does not decline with age [5]. In addition to the measurement of paracetamol absorption kinetics as a surrogate of gastric emptying, many other drugs have been studied including a number of benzodiazepines [6–8] and β -blockers [9]. An age-related reduction in the rate, but not extent, of absorption of digoxin has, however, been demonstrated [10]. It is not clear whether this is a genuine effect of age rather than a chance finding.

2.2. Bioavailability and first pass metabolism

Once a drug has been absorbed, it may undergo presystemic metabolism in the wall of the small bowel prior to entering the hepatic portal vein and passing to the liver, where presystemic hepatic metabolism may occur. The estimation of a drug's bioavailability (F) is a reflection of the extent of absorption and first pass metabolism. It can be measured by comparing the AUC extrapolated to infinity after a single oral dose and a single i.v. dose.

The physiological changes in neonates result in enhanced bioavailability of drugs that are partially acid labile, such as ampicillin [11], but no change in the bioavailability of many drugs, for example diazepam [12]. In old age, studies using digoxin [10], paracetamol [13], lorazapem [6,14], theophylline [15], bumetanide [16] and flumazanil [17] have not shown significant differences in systemic bioavailability with age. Clearly, for drugs with little presystemic metabolism leading to high bioavailability, little change would be expected. In contrast, the bioavailability of ondansetron is increased with age [18] and similar findings have been described for nifedipine [19].

2.3. Distribution

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The distribution of drugs throughout the body depends on the ability of the drug to pass through lipid membranes. This ability is determined by the lipid solubility of the drug and the extent of plasma protein binding as free, unbound drug in the plasma is in equilibrium with free drug in the tissues.

2.3.1. Volume of distribution

Volume of distribution (V_d) can be defined as the volume into which a drug appears to be distributed based on its plasma concentration. Like clearance, it is a primary determinant of elimination half-life (t1/2z), which is the clinically relevant parameter from the point of view of dose optimisation:

$$t1/2z = \frac{0.693V_{\rm d}}{\rm Cl}$$

Therefore, $t1/2z \propto V_d/CL$, where CL=plasma clearance of drug; 0.693 = natural logarithm of 2.

For lipid soluble drugs, V_d is substantially larger than the total volume of the individual, e.g. 3–60 l/kg, whereas for water soluble drugs, V_d is similar to total body water, e.g. less than 1 l/kg. Age-related falls in both total body water [20] and lean body mass result in an increased proportion of body fat and reduced proportion of body water [21]. For water soluble drugs, this results in a fall in V_d with increasing age, leading to higher plasma concentrations, e.g. ethanol [22] and cimetidine [23]. The effect on V_d , however, tends to be offset by a reduction in renal clearance (see below) resulting in a neutral effect on t1/2z.

For lipid soluble drugs, these changes can result in a significant rise in V_d with increasing age, for example diazepam [24], lorazepam [14], chlormethiazole [25], and barbiturates [26]. In view of the relationship between V_d and t1/2z, the rise in V_d results in prolongation in t1/2z. For some other drugs, the findings are conflicting suggesting the magnitude of any effect is small and not clinically significant, e.g. lignocaine [27,28].

2.3.2. Plasma protein binding

Drugs tend to bind to either serum albumin, in the case of acidic drugs such as warfarin and diazepam, or $\alpha 1$ acid glycoprotein, in the case of basic drugs such as lignocaine and tricyclic antidepressants. Only unbound drug is free to cross plasma membranes, enter tissues or bind to receptors. Only for drugs that are highly protein-bound will small changes in protein binding result in significant changes in the active free drug concentration. For a drug which is 95% protein-bound, a small decline in serum albumin, resulting in a 1% reduction in protein binding to 94%, will result in a rise in free drug of 20% (from 5% to 6%). In contrast, a drug which is 30% protein-bound would show a rise in free drug under the same circumstances of around 1.5%—not sufficient to produce any clinically relevant change. Therefore, changes with age will only be important for highly protein-bound drugs. Even if there are significant changes in free concentrations of drugs, they will only be clinically relevant if the drug has a narrow therapeutic ratio. The therapeutic ratio is a measure of the relationship between the concentrations necessary to produce therapeutic and toxic effects for a particular drug. Only drugs whose plasma protein binding is greater than 90% with a narrow therapeutic index and a high hepatic extraction ratio (ER) are likely to lead to important protein binding interactions [29]. Plasma protein binding is lower in infants than in adults, resulting in significantly higher free fractions [30], hence expanding the distribution volume and prolonging t1/2z.

Although serum albumin falls in the presence of both acute and chronic disease, recent studies have demonstrated that serum albumin does not fall significantly with age in adult life [31,32]. Earlier studies, for example from the Boston Collaborative Drug Surveillance Program [33] which found an age effect, failed to resolve the confounding effect of disease on the relationship between age and serum albumin. Alpha 1 acid glycoprotein is an acute phase protein rising with illness [34]. Not surprisingly a spurious, but opposite, effect of ageing on α 1 acid glycoprotein was reported [35] for similar reasons to those accounting for changes in serum albumin. The fall in serum albumin and rise in α 1 acid glycoprotein seen in elderly patients in the presence of disease results in reduced binding of acidic drugs to albumin, e.g. warfarin [36] and increased binding of basic drugs to α 1 acid glycoprotein. e.g. lignocaine [28].

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2.4. Clearance

Plasma clearance is the volume of plasma that appears to be cleared of a drug per unit time and has the units of volume/time, e.g. l/min. Any process that leads to removal of parent drug from the plasma contributes to clearance whether this be the removal of volatile drugs from the lung or metabolism in the skin. In the main, however, hepatic metabolism and renal excretion are the key processes. Lipid-soluble drugs are metabolised in the liver, whereas water-soluble drugs and metabolites are cleared via the kidney, hence even for drugs metabolised in the liver, this is the final path of removal from the body.

2.4.1. Metabolism

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Drug metabolism is arbitrarily divided into two phases. Phase 1 reactions, for example oxidation reactions metabolised by the cytochrome *P*450 system, and phase 2 reactions which involve synthetic pathways such as glucuronidation or acetylation. Both phases result in metabolites with enhanced hydrophilicity, which facilitates excretion in the urine. Although the principal organ for drug metabolism is the liver, the intestine is emerging as an additional important organ for drug metabolism [37]. There is a large body of evidence demonstrating reduced phase 1 and phase 2 metabolism in newborn infants [38], with maximal values being reached by 1 year [12]. Newborn infants receiving twice the adult dose of diphenylhydantoin per kilogram had lower plasma values than adults [39].

The cytochrome P450s are series of super families of enzymes which play a central role in all metabolism. They metabolise many drugs and there is significant interindividual variation in functional expression of these enzymes. CYP3A, for example, is known to vary 10-fold between individuals [40]. Such differences in drug metabolising ability can lead to substantial differences in drug concentration. The consequences for the patient are anything from lack of effect to toxicity. Antipyrine, a widely studied drug used in the past as a non-specific probe for cytochrome P450 metabolism, is an example of a low extraction drug. Wood et al. [1] reported an age-related decline of 19% in clearance of antipyrine. Similar work using propranolol has demonstrated a similar effect of age on its clearance [41]. Similarly, ageing also leads to a decrease in theophylline clearance [42].

Lorazepam is extensively metabolised by glucuronidation. Early studies, which examined the effect of age and liver disease on its metabolism, did not find any significant reduction in the clearance of lorazepam with age following intravenous administration. [14]. Numerous studies have suggested that there is no age-related decline in clearance with oxazepam [43]. A more recent study of very elderly patients (aged 80–94 years), who had been admitted for reasons other than an acute medical problem (e.g. reduced mobility due to progressive osteo-arthritis), found no significant decline in total clearance compared to young volunteers. However, unbound clearance was significantly reduced compared to young volunteers and this led to a measurable increase in drug effect [44].

A reduction in conjugation of paracetamol due to ageing has been reported [45]. Acetylation may also be affected by age with an increase in the incidence of the slow acetylator phenotype suggested by one study [46], although this methodology is affected by changes in renal function.

A recent study examined the effect of age on both CYP2D6 and non-CYP2D6 pathways of propranolol metabolism [40]. Non-CYP2D6 pathways include conjugation

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of propranolol to its glucuronidated metabolite. No selective loss in capacity of either pathway was seen when comparing young to elderly (65–81 years). However, the reduction in clearance of total propranolol in older patients who are deficient in CYP2D6 pathway was greater than 50% compared to young subjects with functioning CYP2D6 (Kinirons et al., personal communication). This suggests that elderly subjects who are deficient in CYP2D6 are at risk of experiencing much higher drug concentrations, and hence at risk of adverse drug reactions. The effect of inducing agents on hepatic drug clearance in old age is not entirely clear. Theophylline clearance was induced to a similar extent in old vs. young smokers [15], yet this was not seen for antipyrine [1]. Whether these and other conflicting findings in the literature represent differences in the individuals studied, differences in the pathways studied or concentration-related differences remains unclear. Enzyme inhibition, on the other hand, is more consistently reported to be unchanged by ageing [47].

Although there are limited data, liver volume corrected for body weight is at its highest at birth and subsequently falls to adult values at puberty. Liver volume declines by approximately 30% [48,49] by late life, with a parallel reduction in liver blood flow (LBF) of 20-35% in healthy elderly compared to young volunteers [1,49,50]. While reductions in liver volume would be expected to be associated with an appropriate reduction in LBF, relative reduction in LBF is only important for drugs that undergo high extraction for example propranolol, triazolam and chlormethiazole.

2.4.2. Renal excretion

Glomerular filtration rate correlates well with gestational age [51] and reaches adult values when corrected for age in the second year of life. Creatinine clearance decreases from around the age of 20 based on cross-sectional studies [52], and such mean population changes in creatinine clearance can be estimated using a multivariate equation [53]:

creatinine clearance (ml/min)

$$=\frac{(140 - \text{age in years}) \text{ weight } (\text{kg}) \times 1.23 \text{ (men) or } 1.04 \text{ (women)}}{\text{serum creatinine } (\mu \text{mol}/1)}$$

The use of the serum creatinine (as opposed to creatinine clearance) as a measure of renal function is unreliable because of the fall in muscle mass, and hence creatinine production with age and disease. The early promise of serum cystatin C as a more useful serum marker of renal function has not materialised. A longitudinal study has demonstrated great variability in the rate of decline of renal function, with some individuals showing small increases, while others show varying rates of decline [54]. Nutritional factors may play a role in this variability. For drugs whose principal route of excretion is renal, creatinine clearance is a good guide to the clearance of the drug. Dosing should therefore be reduced in proportion to the fall in creatinine clearance. Drugs, predominantly renally excreted, include the aminoglycosides, lithium, digoxin, tetracycline and cephalosporins. Of these, the first three have narrow therapeutic ratios and demand much more precise dosing adjustments.

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3. Frailty

Woodhouse et al. [55] have attempted to relate pharmacokinetic changes associated with ageing to the presence of frailty defined in functional terms. They have demonstrated reductions in plasma esterase activity [56] and metoclopramide clearance [45] in frail vs. fit older individuals.

4. Pharmacodynamics

Age-related changes in responsiveness to drugs have been demonstrated in isolated cells and tissues, but from the point of view of dose optimisation, the most relevant changes are those that have been demonstrated in clinical studies. Such changes result from altered responses of organ systems to drug, or from a changed counter regulatory response or a combination of the two. In clinical studies, it may be difficult to separate these components. A variety of changes have been described, which in the main, result in reduced wanted effects or increased unwanted effects (Table 1). Of particular relevance in the light of developments in cardiovascular medicine are the emerging changes in vascular responsiveness.

The response of the dorsal hand vein to noradrenaline is reduced in old age [67]. Similar reductions in sensitivity have been seen for the β_2 receptor [68], neuropeptide Y receptor [69] and the H₂ receptor [70]. Lack of an age effect has been noted for the H₁, adenosine, bradykinin, PGE1 receptors and the NO donor GTN. Using forearm plethysmography to study the local effects of infused substances on resistance rather than capacitance vessels, a slightly different pattern emerges. Reduced sensitivity of the β_2 receptor and α_1 receptor [71], and equivocally of the acetylcholine receptor [72,73], has been demonstrated. Impaired endothelium-dependent vasodilatation has also been demonstrated using infusions of a nitric oxide synthase inhibitor [74] compatible with reduced sensitivity to acetyl choline, which requires intact endothelial function for its full effect. More recently, the absence of an age-related change in endothelium-independent relaxation has been demonstrated in the presence of an age-related change in endothelium-independent relaxation has been demonstrated in the presence of an age-related change in endothelium-independent relaxation has been demonstrated in the presence of an age-related change in endothelium-independent relaxation has been demonstrated in the presence of an age-related change in endothelium-independent relaxation has been demonstrated in the presence of an age-related change in endothelium-independent relaxation has been demonstrated in the presence of an age-related change in endothelium-independent relaxation [75]. These authors also demonstrated the absence of an age effect on angiotensin II mediated vasoconstriction.

Drug	Effect
Warfaun	\uparrow sensitivity [57], although pK changes are probably also relevant
Benzodonzepines	t postural sway, sedation, confusion, falls [58–60]
β-blockers	↓ hypotensive effect [61]
β-agonists	sensitivity in lung and cardiovascular system [50,62]
Calcium channel blockers	hypotensive effect [19,63]
Neuroleptics	↑ risk of tardive dyskinesia and Parkinsonism [64,65]
Anticholinergics	Urinary retention in men and light headedness/dizziness
Anaesthetic agents	† sensitivity [66]

 Table 1

 Pharmacodynamic changes associated with ageing

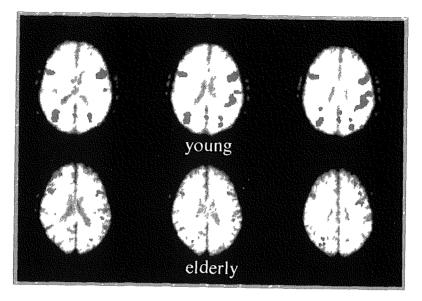


Fig 1 Functional magnetic resonance imaging during a spatial working memory task in six young and six elderly volunteers showing reduced activation in old vs young volunteers

Of interest, newer tools to study drug responsiveness in the brain have been developed. Functional magnetic resonance imaging is one such technique, which, unlike positron emission tomography, does not expose the subject to ionising radiation. We have recently demonstrated substantially reduced blood-oxygen dependent contrast during both

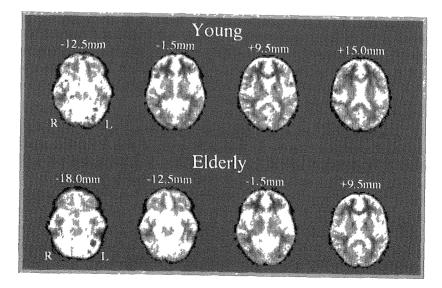


Fig 2 Functional magnetic resonance imaging during olfactory stimulation via an olfactometer showing

cognitive (Fig. 1) and sensory (Fig. 2) paradigms (unpublished observations). This technique has also been used in the study of drug effects, but not yet in the study of the effects of age.

5. Conclusions

Changes in pharmacokinetics and pharmacodynamics do result in a requirement to modify doses downwards and certainly account for some interindividual variabilities in dose. A much greater source of interindividual variability relates to unexplained differences, although many other known sources exist, particularly the presence of concurrent medications and the underlying disease processes for which they are being taken. The differentiation of age and disease is sometimes difficult both in the context of screening elderly volunteers for research studies and the clinical setting. Further, the interaction of age and disease can also result in the need to reduce dose. For example, the enhanced toxicity of anticholinergics in patients with benign prostatic hypertrophy or Alzheimer's disease can substantially enhance toxicity above levels expected on the basis of age alone. Avoidance of such agents is usually possible.

Appendix A. Discussion 20

J. Lötsch: When I saw your ibuprofen picture, it came into my mind to ask you whether there is any information about the inversion clearance affected in the same proportion as your overall clearance of ibuprofen.

S. Jackson: You are basically asking whether there is any effect on the endogenous conversion from the inactive R to the active S form. What I can say at this stage, is that about 60% in both old and young is inverted from the inactive R to the active S. If one were to swallow 100 mg of racemate, in fact 80 mg effectively becomes available as S. There is no difference in that between old and young. What we are in the process of doing is looking at modelling that inversion, to see whether there are changes with time, perhaps concentration-related, but I don't have data on that now.

M. Ingelman-Sundberg: If you look at *P*450 enzyme induction, it declines quite drastically in magnitude in your first slide. It really implicates that the over 100 thousand deaths that we have in adverse drug reaction in the US annually might largely be caused by drug-drug interactions, and we don't take these factors into account.

S. Jackson: There are conflicting data on this equation. We've all included the wrong sort of people in studies in retrospect, and it may well be that some of the individuals you got into some of the studies were people who had other confounding factors present. As opposed to inhibition, which is much more consistent, one can inhibit enzymes easily and equivalently in old and young.

W. Deakin: I was interested in the fMRI studies, and in two specific things. Firstly, what was the auditory stimulus that caused the visual cortex to be activated?; and secondly, do you think that the failure in the elderly to see that activation is a neuronal thing, or do you think it's something about the linkage between neuronal activity and

increased flow? Particularly in view of what you were saying about nitric oxide, because that is critical in linking the two. Is it more of a vascular problem for imaging, or neuronal?

S. Jackson: The on-state was a talking book and the off-state was non-meaningful words: 30 s on, then 30 s off, I think it was the meaning that produced the visual activation. As far as what the mechanism of the age-related change is, it might well be neuro-vascular coupling; there has been some PET work giving GTN infusions as a nitric oxide donor (Hugh Markus et al., at St. George's Hospital, London), but they didn't really find very much. I suspect that is part of it, and of relevance is the endotheliopathy associated with ageing, even in the absence of traditional cardio-vascular disease. What we cannot say at this stage is that there is no BOLD effect of ageing, and it's obviously important to try and work that one out, but it's a difficult one to solve.

L. Sheiner: I just wanted to make a chairman's comment on the last two talks. I think we've heard that there are a great many potential influences of liver disease and age on both pharmacokinetics and pharmacodynamics. Unlike some of the other problems we've discussed here, where it seemed clear what one ought to do about them, there haven't been many suggestions as to what kind of optimisation ought to occur for liver disease and age, in the light of emerging knowledge. It strikes me that Marcus Reidenberg's earlier point applies here as well: there are now a myriad of drugs which interact in complex ways with other drugs and liver enzymes, and these interactions further interact with age and liver disease. Unfortunately, we cannot—like grapefruit juice—outlaw ageing or liver disease. If we want to take this seriously and imagine that we should undertake drug dose optimisation and individualisation accounting for the effects of these and other variables, we are inevitably looking towards some kind of a computer-aided system, whether it be an automated system such as those that work for warfarin, or whether it be something else. But it will require, at a minimum, that the physician find it easy to consult databases that indicate what they should do. The point is that physicians cannot be expected to carry the relevant information around in their heads: they are already burdened enough with the many things that they have to know.

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