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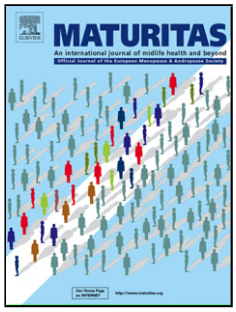

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Drug metabolism in the elderly: a multifactorial problem?

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Highlights

- Drug metabolism in healthy old age is similar to that found in young adults.
- Drug metabolism may be reduced in elderly subjects who are frail and/or ill.
- Adverse drug reactions in elderly patients are not predictable on current models.

Abstract

Whether or not an individual's drug metabolising capacity declines with advancing age is a vexing question. There is no clear evidence that drug metabolism itself ('the biologically-assisted chemical alteration of the administered parent molecule') is less efficient in healthy old age than at younger ages, whereas a decreased capacity may be associated with ill-health and frailty. However, elderly individuals do show a reduced enzyme induction capability and are less able to tolerate overdoses. It appears that the majority of deleterious clinical outcomes related to drug therapy in an elderly (usually ill or frail) population may be ascribed to various anatomical and physiological age-related changes. These may affect both pharmacodynamics and pharmacokinetics, but not necessarily drug metabolism. Information gleaned from animal studies undertaken mainly in rodents does not seem to be of relevance to humans and studies in healthy aged human populations may not highlight possible problems. However, certain circumstances may influence metabolic competence, and phenotyping rather than genotyping is of more value in identifying those susceptible to adverse drug reactions. This short review discusses the potential contributions of four factors (inflammation, circadian rhythm, gut microbes, epigenetic aspects) which may lead to alterations in drug metabolism with increasing age.

Keywords: age effect; xenobiosis; inflammation; circadian rhythm; gut microbiota; epigenetic factors

Introduction

Many interacting factors influence the journey of a drug through the human body and age-related changes may lead to differences in an older subject's ability to process and respond to drugs when compared to a younger cohort. As time passes, anatomical and physiological changes take place within several body organs and a general alteration of body composition occurs, all aspects which may influence drug pharmacokinetics and pharmacodynamics, potentially leading to a variety of clinical outcomes (Table 1).

This short review concerns itself with one of these aspects, namely drug metabolism, the 'biologically-assisted chemical alteration of the administered parent drug molecule'. It should be appreciated that although there may be general trends, many factors (both genetic and environmental) will influence a particular individual's situation and that knowledge of a subject's chronological age may not be a true indicator of their functional biological age. This

is certainly true if they have been exposed to a previous chemical background, are of poor nutritional status or have suffered ill health [1-4].

Drug metabolism in the elderly (more than 65 years old) is of particular interest since this group is forming an increasingly larger part of the population. People are living longer thanks to modern drug discoveries and to 'polypharmacy' where individuals have multiple prescriptions increasing the potential for drug-drug interactions. However, although the aged are prescribed more drugs than other sections of the population, it is rare to find that therapies are trialled in this age-group during the drug development process. In most Western countries, adverse drug reactions (ADRs) account for *c.*10% of hospital admissions and the elderly are over-represented in this category. The question therefore arises as to whether or not they have specific patterns of drug metabolism which reduce their ability for detoxification and if so, what circumstances might be involved.

Drug metabolism

Absorption of a compound is more readily achieved if it is lipid-soluble whereas excretion is facilitated by water-solubility. Hence the body, with a quest for maintaining the status quo, being 'assaulted' by a lipid-soluble molecule, strives to increase its water solubility via chemical modification and, perhaps by default, also reduce its pharmacological interaction. The pathways of drug, or xenobiotic metabolism, have been assigned traditionally to one of two categories or phases. In Phase I metabolism, the drug is generally made more water-soluble, usually by modifications such as hydrolysis or hydroxylation via the cytochrome P-450–linked family of enzymes (CYP450). Phase II typically involves masking chemically reactive groups and increasing polarity by linking the parent drug or its metabolite from Phase I with some large water-soluble anion from endogenous metabolism such as sulfate or glucuronic acid (Figure 1).

Phase I metabolism and age

Animal models

That age may affect drug metabolism was demonstrated over fifty years ago [5] and since that time many studies, mainly in rodents, have confirmed these initial observations [6]. It is widely accepted that the overall trend is for a decrease in metabolism as the animals move from maturity into senescence [7]. For those reactions involving the mixed function oxidases, mainly CYP450, this is generally correct for the male rat although increases have been reported for some compounds. In the female rat, most activities remained constant except for decreases in some dealkylation reactions including aminopyrine [8], though other workers reported an increase for this compound [9]. A more confused situation exists for the mouse where increases, decreases and no changes have been reported with these results sometimes varying between different studies [7]. Probable animal strain differences are undoubtedly important here.

Human studies

Following drug administration, the majority of studies in man have measured blood and sometimes urine levels of the unchanged compound and then calculated various pharmacokinetic parameters, such as the maximum plasma concentration (C_{max}), plasma elimination half-life ($t_{½}$), area under the concentration/time curve (AUC) or clearance (CL). These values are composites that reflect the many processes influencing the passage of a drug through the body and where drug metabolism may only play a minor role. The use of test compounds of previously known high hepatic clearance (extraction) may offset some of these difficulties but the results are still not necessarily indicative of drug metabolism. For example, pharmacokinetic studies employing the 'model drug' antipyrine as a global measure of Phase I drug metabolism (metabolic pathways involving CYP3A4, CYP1A2, CYPC8/9) have shown both increases and decreases in its clearance with advancing age [10,11].

Early studies using human liver biopsies found no significant correlation between age and overall cytochrome P450 content, or any decrease in aldrin epoxidation or 7-ethoxycoumarin-*O*-deethylation [12,13]. Similarly, no age related declines in drug microsomal enzyme activity

were detected in primates [14,15]. Other investigations have shown that total microsomal P450 levels were not particularly reduced with age [16,17] and that the activities of various CYP450 isozymes including 1A2, 2A6, 2B6, 2C, 2D6, 2E1 and 3A4, in human hepatic microsomes showed no marked differences in older subjects [16,18-20]. The hydrolysis enzymes, benzoyl, butyryl and acetylcholine esterases also show no decline in activity with age [21]. This implies that Phase I metabolism itself is unimpaired in the healthy elderly population [22-24].

Phase II metabolism and age

Animal models

Amongst the conjugation reactions, glucuronic acid condensation appears little changed in rodents and only minor perturbations were observed with glutathione conjugation whereas several groups reported that sulfation (sulfonation) of paracetamol decreased. The sulfation of nitrophenol also decreased in the male rat [25] but increased in the mouse [26]. Again, there were no overarching patterns.

Human studies

Investigations in humans suggest that Phase II metabolism is relatively well-preserved in aging populations. A study employing paracetamol demonstrated that no correlation existed between old age and glucuronidation or sulfation reactions, indicating that age itself does not lead to a decrease in these activities in man [27]. The present authors compared the metabolism of paracetamol in a small healthy student population (age 18-22 years) with two geriatric populations (age 75-85 years). The excretion of glucuronide and sulfate metabolites in the elderly cohort taking no other medications was not significantly different from values in the student population whilst there were reductions of 30-35% in glucuronide and sulfate excretion for the elderly cohort who were in ill health and taking an average of 5.2 prescription drugs each. This may reflect either the polypharmacy or the underlying physiological dysfunction in the latter group. In the healthy aged there is no evidence of any effects on the pathway of glutathione conjugation and there appears to be no reduction of hepatic reduced glutathione [13].

Factors potentially affecting drug metabolism with age

As well as the previously mentioned anatomical and physiological features that alter with increasing age (Table 1), there are a few other aspects, less well recognised, that should be considered with regard to drug metabolism. However, this is not meant to imply that they may not have influence at any of the other stages of a compound's progress through the body, namely; absorption, distribution, metabolism and excretion (ADME).

Inflammation

Inflammatory states become more common as individuals age, with many maladies having distinct inflammatory components that signal the development and progression of the disease [28]. Upsurges in inflammatory activity have been observed in the earliest phases of dementia including Alzheimer's disease, and also in type 2 diabetes and Metabolic Syndrome as well as with chronic obstructive pulmonary disease and during bouts of rheumatoid and osteoarthritis. Such situations may compromise the ADME enzymes and inflammation has been shown both *in vivo* and *in vitro* to regulate the CYP isoforms which carry out Phase I metabolism [29]. Phase II metabolism may also be affected; the sulfation pathway is known to be reduced in inflammation, probably by the release of cytokines [30] whilst *in vitro* studies suggest that formation of glucuronide and glutathione metabolites may be reduced [31]. Frailty is associated with higher inflammatory markers and lower esterase activity [32] so these findings may be a partial explanation of the increased rate of ADRs in elderly patients.

Circadian rhythms

Circadian regulation is mediated through the suprachiasmatic nucleus (SCN) which acts as the master controller, combining environmental cues from light and food intake to entrain internal clocks [33]. Drug absorption is known to have a circadian variation; lipophilic drugs are absorbed faster when taken in the morning although there is no circadian variation in absorption of water-soluble compounds. Drug metabolism also varies with the time of day and expression of the cytochrome P450 gene family is regulated by the biological clock. In turn, in a feedback loop with a period of about 24 hours, these monooxygenases metabolise melatonin, the pineal hormone which resets the biological clock. This potential variation is particularly important if

the parent drug or metabolites are toxic and there are clinical guide lines on the optimum timing of drug dosing for many compounds including anti-cancer, cardiovascular, anti-inflammatory, antiepileptic and immuno-suppressive agents [34,35]. However, disturbed circadian rhythms are more common in elderly populations in general and less stable patterns are linked with increased mortality. Dysregulation of the biological clock is associated with depression and anxiety and also with neurological disorders and cancer [36,37]. The elderly may therefore not respond to the standard recommended timings for medication and are potentially more at risk from ADRs.

Gut microbiota

The microbial ecosystem that exists within the human gastrointestinal tract is of great interest and known to be important in the maintenance of human health, since it appears to modulate innate immunity and probably cognitive function as well as assisting in nutritive processes. These microbes are thought to account for up to 90% of the cells present in a human organism and, although rapid advances are now being made, relatively little is understood about the composition of the gut microbiome with only about 30% being identified. However, it is appreciated that gut bacteria do play a part in drug metabolism and, as they are largely anaerobic, they usually participate in reactions involving chemical reduction or fission of molecules. For instance, the metabolism of epacadostat, a potential immunomodulatory and antineoplastic agent, in humans involves formation of an amidine metabolite by gut bacteria (N-OH to N-H) which is then absorbed and further metabolised via side-chain dealkylation by CYP450 [38]. Many other clinically-relevant drugs are known to be co-metabolized by host and gut microflora [39]. Clearly, if composition of the gut microbiome changes, and this is known to occur with aging (particularly *Bifidobacterum* spp.), particularly amongst frail individuals and long-stay residents in care homes, then drug metabolism may be altered also with ensuing consequences [40,41].

Epigenetics

Perturbations encompassing the hereditary material deoxyribonucleic acid (DNA) that do not involve actual sequence changes, but affect gene expression and cellular phenotypes, are termed ‘epigenetic’. Many modifications are known to occur, including the addition of methyl groups to the cytosine or guanine residues (CpG islands) within the DNA molecule and histone acetylation and methylation, potentially leading to an overall remodelling of the chromatin package (histone/DNA complex). Also, the production of non-coding ribonucleic acid molecules (ncRNAs) which are functional, but not translated directly into a protein, is able to modulate the transcriptional and post-transcriptional regulation of gene expression in a variety of ways. Studies on older populations (>75 years) confirmed that there were age-related changes in DNA methylation patterns at specific CpG islands and that high methylation levels were linked to a subsequent diagnosis of cancer [42]. Specific epigenetic changes in DNA methylation in brain and peripheral blood leukocytes have also been noted in patients with Parkinson’s disease [43] in line with abnormal patterns of drug methylation.

Epigenetic regulation of ADME genes is an area of great interest. Much of the work has been undertaken in tumour cell lines which obviously may not be representative of the normal healthy *in vivo* situation. Nevertheless, it is clear that both Phase I and II reactions are affected [44] although the research has generally focused on the CYP450 isoforms. The human CYP2C9 gene is involved in metabolism of many pharmaceuticals and endogenous substrates and its activity has been shown to be easily inducible and also regulated by epigenetic mechanisms. The expression of both CYP1A1 and CYP1B1 genes is similarly highly inducible, especially by dioxins and polycyclic hydrocarbons. Regulation of CYP3A4 is also epigenetic in man and its silencing in human foetal liver has been linked with the DNA hypermethylation of certain CpG sites close to key gene regulatory elements. During development demethylation occurs with a consequent increase in activity and once adult levels are attained there appears to be no significant variation in CYP3A4 expression [45]. Nevertheless, it may be appreciated that subsequent methylation in the elderly (like the foetal situation) could be a mechanism to reduce activity.

It has been appreciated for some time that elderly individuals have a reduced enzyme induction capability and are less able to tolerate overdoses [46]. This may reflect increased epigenetic

gene silencing with age since DNA methylation was shown to inhibit subsequent attempts at dioxin-mediated induction of the CYP 1B1 gene activity. Environmental contaminants are known to be involved in alterations to gene expression (common pollutants such as bisphenol A can have epigenetic effects) and, as elderly patients will have had more potential exposure to such chemicals, there may be a general phenomenon of altered methylation patterns with time. Such changes have been reported as reflecting differential biological aging [47,48].

Conclusion

Much work on drug metabolism in elderly mammalian populations has been undertaken on rodents and there is relatively little available information for humans. Unfortunately, gender differences in metabolism are pronounced in rats and mice and any attempt at extrapolation to man is fraught with difficulties, if not meaningless. This problem has been subtly stated in an alliterative manner, the "*effect of senescence seems to depend upon species, strain, sex and substrate*" [49]. Seemingly, the only true model for man is man.

The literature, understandably, has relatively few examples where drugs are administered to healthy but elderly populations. However, it is clear that any changes in drug metabolism with age are less obvious in such populations but are important potentially in those who are already frail or ill, in other words, the targets for drug therapy. This is reasonable since the metabolic pathways of both xenobiotics such as drugs and environmental contaminants and endogenous compounds such as steroids are essentially inter-related. Factors affecting health will potentially also affect the therapeutic agents which are prescribed. Epigenetic regulation of ADME-related genes is obviously more likely in an aging population with an increased exposure to environmental factors affecting gene expression; this area is currently of considerable interest and future work will certainly clarify the situation. A further complication is that drug testing in elderly rodents is unlikely to give useful information on human responses and even testing in elderly but healthy humans will not mirror the situation for the target group for therapy, the frail hospitalised patient. It may never be possible to predict ADRs.

Generally, decreased drug metabolism as such is not the major causative factor in the differing clinical responses observed in elderly subjects. However, frail and ill individuals do have increased susceptibility and their overall responses reflect the complex interplay existing between many genetic and environmental influences.

Contributors

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure Legend
Figure 1

The major routes of absorption, distribution, metabolism and excretion available to a drug following oral administration.

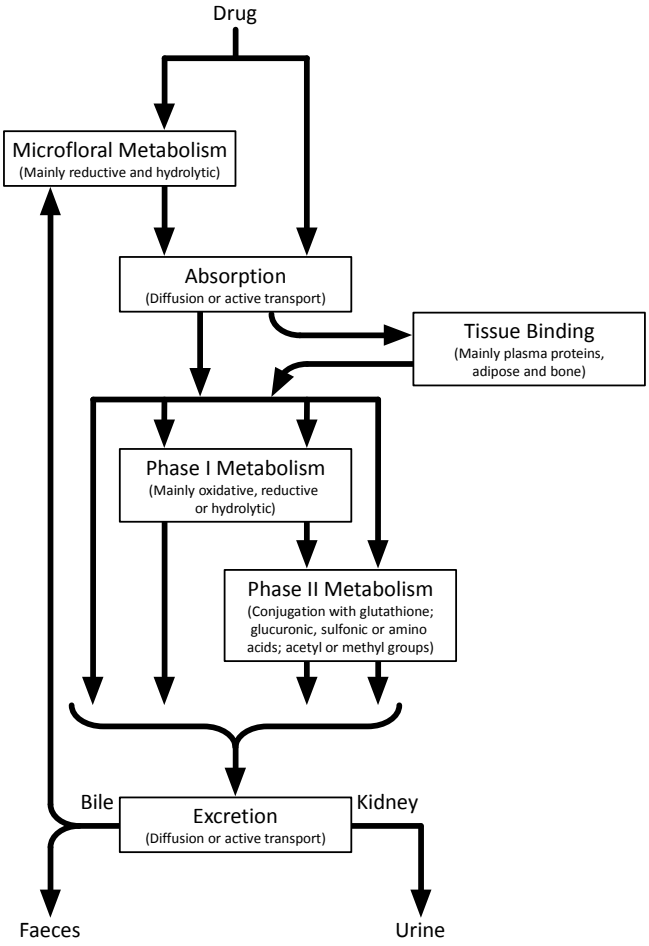

Table 1. Factors that may influence drug pharmacokinetics and pharmacodynamics in an elderly population

Absorption
Alteration in gastric and intestinal motility *
Variable rate of gastric emptying, lower gastric acid secretion *
Decreased absorptive surface of small intestine *
Decreased splanchnic blood flow*
Distribution
Lowering of total body water content
Reduced lean body mass, increase in adipose tissue
Altered plasma-protein binding *
Metabolism
Decrease in hepatic blood flow
Decrease in liver size and number of functional hepatic cells

Changes in enzyme activity
Changes in gut microbiome

Excretion
Decrease in renal mass
Reduction in renal perfusion
Glomerular filtration rate falls
Tubular excretory/secretory function falls
Alteration in biliary secretion efficiency*

Organ sensitivity
Changes in receptor sensitivity
Adaptive response to previous exposure
Alteration in blood-brain barrier shield, increased CNS sensitivity
Accumulated damage to cellular functions

Other factors
General nutritional status
Chronic disease states
Life-style habits, physical exercise and general fitness
Previous chemical exposure
Compliance: overdose / underdose

* The literature contains conflicting reports as to the significance of these effects in the elderly [1].