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Review article

Drug metabolism in the elderly: A multifactorial problem?

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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.

Contents

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1. 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.

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

Absorption
Alteration in gastric and intestinal motility[a]
Variable rate of gastric emptying, lower gastric acid secretion[a]
Decreased absorptive surface of small intestine[a]
Decreased splanchnic blood flow[a]
Distribution
Lowering of total body water content
Reduced lean body mass, increase in adipose tissue
Altered plasma-protein binding[a]
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[a]
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

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

2. 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 (Fig. 1).

3. Phase I metabolism and age

3.1. 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.

3.2. 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