PHARMACOTHERAPY IN OLD AGE

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Older people are prone to increased risks of adverse drug reactions (ADRs). Whilst part of this excess may be due to increased drug usage, other factors such as increased incidence of disease, multiple prescribing and age-related changes in pharmacokinetics and pharmacodynamics also play a part. Most studies about altered age-related drug action have been cross-sectional rather than longitudinal, and so assist in explaining more about age differences in drug action than about changes in drug action with age. Knowledge of the different ways in which older people handle and respond to drugs is an essential first step towards reducing ADRs. Most of the adverse reactions in older people are dose-related (Type A) rather than idiosyncratic (Type B). This review will concentrate on the age-related pharmacokinetic and pharmacodynamic changes.

PHARMACOKINETICS

Drug absorption

Many changes in the gut occur with age. These include reduction in gastric acidity, decreased gastric emptying, increased intestinal transit time, decreased absorptive surface, reduced gut blood flow, and reduction in liver size and blood flow. Despite these changes, absorption of drugs is largely unaffected in older people.[1] There are two exceptions to this. L-dopa is subject to acid-catalysed decarboxylation in the gastrointestinal tract, which then restricts its bioavailability; higher serum levels of L-dopa, due to a decrease in the presystemic gastrointestinal clearance at the higher gastric pH, are observed in older people.[2] Clorazepate is a benzodiazepine that requires acid hydrolysis in the gastrointestinal tract to be converted to its active metabolite, desmethyldiazepam. The plasma levels of desmethyldiazepam are lower in older people, presumably due to decreased conversion from the parent drug.[3]

Drug distribution

Drug distribution in older people may be altered by changes in body composition with age. The relative lipid content increases markedly with age. Male body fat increases from 19% at age 25 to 35% at age 70. The female body fat increases from 33–49% over the same age range.[4] This results from atrophy of muscle tissue, with a decline in total body water and intracellular water.[5] The increase in body fat and decrease in body water with age may lead to changes in the apparent volumes of distribution of highly lipid or water-soluble drugs. For example, the apparent volume of distribution for digoxin, which is highly water-soluble, is reduced in older people as a consequence of reduction in body water and a smaller loading dose is required to digitalise the patient.[6] Similarly, ethanol, cimetidine, antipyrine and morphine demonstrate smaller volumes of distribution and greater serum levels in older people, following the administration of comparable weight-adjusted doses.[7, 8] In contrast, for lipid-soluble drugs such as diazepam, nitrazepam, lignocaine and thiopentone, the volume of distribution rises because of increased body fat.[9–11] This may lead to an increased half-life of the drug if plasma clearance remains constant. Lorazepam is an exception, with a reduced volume of distribution. Short-acting benzodiazepines, such as triazolam and oxazepam, are preferred in older people because they are less likely to produce accumulation and progressive toxicity.

Since women generally have a larger proportion of adipose tissue, drug distribution may differ as a function of sex, regardless of age.[12]

Protein binding

Alterations in plasma protein-binding that occur in older people are not attributable to age, but to physiological and pathophysiological changes that may occur more frequently in older people. Many factors can significantly alter the plasma protein binding of drugs, e.g. gender, nutritional status.

Serum albumin decreases from 4% in young adults to 3·5% in patients over the age of 80.[13] The fall in plasma albumin with age leads to an increased free (and hence active) concentration of some drugs: e.g. increased free concentrations of warfarin (a highly protein-bound anticoagulant) may lead to over-anticoagulation and potentially serious bleeding; tolbutamide has an increased incidence of hypoglycaemic events in older people;[14, 15] the mean free plasma concentration of naproxen in older people is twice that in young people.[16] Protein binding in older people is also reduced for meperidine, phenytoin, acetazolamide, etomidate, valproate, diflunisal and salicylates.[17–19]

Many basic drugs have a higher affinity for α1-acid glycoprotein, the concentration of which tends to increase with age.[20] The binding of some basic drugs, such as lignocaine and disopyramide, is increased in older people.[21]

Hepatic clearance

A decline in liver mass[22] and hepatic blood flow,[23] decreased microsomal oxidation,[24] and a decline in liver enzyme induction[25] with age affects drugs with a high hepatic extraction (first-pass metabolism). Thus drugs with high rates of hepatic extraction, such as most major tranquilisers, tricyclic antidepressants and anti-arrhythmic agents, should be administered cautiously in older people. Reduced hepatic blood flow, in particular, may result in an increase in the systemic availability of drugs subject to high extraction ratios in the liver, such as propranolol and chlormethiazole.[26] Although plasma concentration of propranolol are increased in elderly individuals following oral administration, the reduced sensitivity of the β-blocking action of the drug may result in a similar magnitude of β-blockade effect to that in young patients.

The function of hepatic microsomal enzymes responsible for Phase I oxidative drug metabolism (hydroxylation, N-dealkylation, sulfoxidation) may be impaired in old age, leading to reduced total drug clearance. On the other hand, ageing has a much smaller effect on glucuronide-conjugation capacity (Phase II reaction). Thus barbiturates, antipyrine, diazepam, chlordiazepoxide, alprazolam, propranolol, nortriptyline, clorazepate and phenylbutazone have a reduced metabolic clearance in older people, possibly reflecting reduced oxidative drug-metabolising enzyme activity.[27–30] However, metabolism of drugs biotransformed by conjugative pathways, such as acetaminophen, lorazepam, temazepam and oxazepam, do not greatly change in older patients.[31–3] There is a lack of agreement regarding the effect of ageing on the distribution of acetylator phenotype.[34, 35]

Renal clearance

Glomerular filtration rate falls with age, with a mean 35% reduction in older people as compared with young.[36, 37] Renal tubular function also deteriorates with age, and may affect the elimination of drugs, which are actively secreted in the nephron. The ageing kidney also shows a decreased mass and a reduction in the number and size of nephrons,[38] and this may lead to accumulation of drugs whose total clearance is accomplished partly or entirely by renal excretion of the intact drug. Examples of such drugs include digoxin, cimetidine, lithium, procainamide, chlorpropamide and most antimicrobial agents. With drugs like penicillins, which have a high therapeutic index, accumulation is relatively unimportant, but for digoxin, moderate accumulation may lead to potentially serious toxicity.

Serum creatinine is inadequate alone as a measure of renal function in older people, but the rate of creatinine clearance is a useful guide to the rate of renal drug elimination. Creatinine clearance can be estimated by using the following formula.[39]

$$Cl_{cr} = \frac{(140 - \text{age}) \times \text{weight in kilograms}}{6{,}365 \times \text{plasma creatinine level in micromoles per litre}}$$

Thus, drugs that are excreted substantially by renal excretion should be given in reduced doses or less frequently to avoid accumulation and untoward pharmacological effects. Frusemide, however, is an exception; although it accumulates as renal function declines, its efficacy is reduced because it acts on the luminal side of the renal tubule, and its access to this site of action is reduced with declining renal function, with more frusemide being required to produce the desired diuretic response.[40]

PHARMACODYNAMICS

Altered drug action in older people is not simply correlated with pharmacokinetic changes; pharmacodynamic changes, such as a reduced reserve capacity, altered homeostasis and changes in almost all individual systems, play a major role. For example, there is a decrease in concentrating and diluting abilities of the kidneys[41] and the homeostatic mechanisms for electrolytes and acid-base balance in older people. Lower plasma renin activity and urinary aldosterone secretion may be the cause for the inefficient handling of sodium. Older people have a greater rise in osmolality and antidiuretic hormone (ADH) on water restriction. They also fail to drink sufficiently once water restriction is lifted because of impaired thirst mechanism.[42] Another example of age-related impairment of homeostatic mechanisms is the accentuated effect of drugs that lower blood pressure, causing postural hypotension[43] due to impairment of baroreflex mechanisms in older subjects.

Pharmacodynamic changes are less well studied in older people because of the difficulty in measuring pharmacodynamic response data; such age-related changes may lie at a number of points between the drug/receptor interaction and the final pharmacological effect.

Autonomic nervous system

Older people have significant changes in cardiovascular autonomic reflexes,[44] such as decreased β-adrenergic responses, decreased ventricular α-receptors and increased atrial muscarinic receptors. All these changes probably contribute to a decrease in the cardiovascular function with exercise. Five percent of older people have postural hypotension, possible factors being a diminished baroreceptor reflex, reduced compensatory tachycardia and impaired sodium conservation.[45, 46] Older people have a higher peripheral resistance, intrinsic heart rate and lower vagal restraint. The sinoatrial (SA) node and atrioventricular (AV) node dysfunction increase with age; maximum heart rate and

peak cardiac output at exercise decrease. The lower heart rate response is due to changes in response to β-adrenergic stimulation.[47] Increase in left ventricular mass results in a lower maximum coronary flow. A delayed and reduced response of the sympathetic nervous system causes a decline in adaptation of the ageing heart to stress.[48] Reduced performance and oxygen consumption at stress is associated with a lesser capacity to increase heart rate, cardiac output and ejection fraction. There is marked reduction in α2-adrenoceptor responsiveness, but little change in α1-adrenoceptor responsiveness with age.[49] The maximal response of the myocardium to catecholamines is reduced with ageing.[50] In older subjects, plasma levels of noradrenaline are often higher than in younger people, suggesting a defect in responsiveness to catecholamines.

Beta-receptor sensitivity declines with age.[51] The findings have been most consistent in the case of chronotropic and inotropic myocardial responses. The chronotropic response to isoprenaline decreases linearly with age.[52] A decrease in high-affinity binding sites, rather than a change in total receptor number, and changes in post-receptor transduction mechanisms underlie this reduced β-receptor sensitivity.[53] This may also result in age-associated decline in sensitivity to hypotensive effects of β-antagonists.[54] Age-related decrease also occurs in β2-adrenergic functions, including that of peripheral vasodilatation.[55] Interestingly, hepatic β2-receptors show increased sensitivity whilst lung, muscle and neutrophil β2-receptors show no change. Bronchodilatation effect of β-agonists is reduced in older people.[56]

Actions of β-blockers are related to renin-angiotensin-aldosterone system. Plasma renin activity decreases with age and β-blockers are less effective in low-renin hypertension.[57] Lower levels of cAMP, reduced adenylate cyclase activity[58] and functional post-receptor defect[59] are the possible factors for altered action of β-blocker in elderly patients.

Calcium channel blockers and nitrates

When corrected for plasma concentrations, age has no effect on the blood pressure reduction in response to verapamil.[60] However, the effects of verapamil on cardiac conduction in older people are less clear. The EC_{50} (the plasma concentration required for half-maximal effect) of verapamil for PR-interval prolongation is increased in older patients after short-term intravenous dosage. Thus, older patients appear to be less sensitive to the short-term effects of verapamil on cardiac conduction.[61] On the other hand, the short-term administration of diltiazem results in PR-interval prolongation of greater duration in older people than in younger people.[62] Intravenous diltiazem, when given to younger and older hypertensives, caused a greater drop in blood pressure and suppressed the heart rate more in the older patient group.[63] Nitric oxide production and nitric-oxide-mediated vasodilatation is diminished in old age.[64]

Cholinergics and anticholinergics

Pre- and post-synaptic neurochemical markers of the brain cholinergic system decline with age[65] and decreases in muscarinic receptors are found in brains of humans during ageing. The muscarinic receptor number declines by 50–60% in the caudate nucleus, putamen, hippocampus and frontal cortex.[66] Cholinergic-receptor responsiveness decreases with age. Atropine-induced tachycardia is attenuated with increasing age,[67] probably due to post-receptor changes. In contrast, there is anticholinergic hypersensitivity, consistent with neurochemical reductions in cholinergic system.[68] Older subjects are therefore more prone to the side-effects of anticholinergic drugs. Anticholinergic drugs increase body temperature by anhydrosis and peripheral vasoconstriction, and can cause hyperthermia. Selective cholinergic deficit may be relevant to the patho-physiology of Alzheimer's disease. Anticholinergic drugs have a tendency to cause urinary retention in old age possibly due to deficient detrusor strength in the ageing bladder.

Neuroleptics

Dopamine receptors can be divided into two major subtypes, D-1 and D-2. Age-related decreases in D-2 receptor subtypes occur in both rodents and humans,[69] especially in the caudate nucleus, putamen, substantia nigra and globus pallidus. In contrast, D-1 receptors have been reported to increase or show no change with age,[70] in humans there is a steady decline in dopaminergic cells in the substantia nigra with age. The number of dopaminergic neurones in each substantia nigra declines from 400,000 at birth to 250,000 at age 60. Specific dopamine D-2 receptor binding is reduced in human studies.[71] Increased activity of MAO-B may reduce the synaptic concentration of dopamine with age and exacerbate the functional consequences of age-related loss of dopamine neurones. The age-related loss of D-2 receptors may underlie the increasing incidence of tardive dyskinesia with ageing due to neuroleptic dopamine blocking drugs.[72] Older patients demonstrate increased sensitivity to both autonomic and extrapyramidal side-effects of neuroleptics. The dose of neuroleptics should be one-third to one-half the amount given to young adults, and dose increments should be small since the age-related pharmacodynamic changes lower the therapeutic ratio, resulting in increased postural sway and an increased incidence of confusion and falls.

Neuromuscular blocking drugs

Neuromuscular blockade is more intense and prolonged with advancing age, and it is more difficult to antagonise,[73] probably due to increased sensitivity of neuromuscular junction to these agents. Ganglion

blockade results in decreased gastrointestinal tone and motility.

Tricyclic antidepressants and SSRIs

Noradrenaline concentrations decline with increasing age in the hypothalamus.[74] The largest group of noradrenergic neurones is located in the locus caeruleus, where marked age-related loss of neurones has been observed.[75] The serotonin (5-HT) responses to increasing age are variable: total brain 5-HT levels decrease with age,[76] but hindbrain 5-HT levels do not change.[7] A significant reduction in the number of 5-HT (1D) and 5-HT2 sites, together with a decrease in the 5-HT2 binding affinity, has been found in the frontal cortex.[77]

Reduced noradrenaline, as well as serotonin, receptor function may make older patients more sensitive to the effects of tricyclic antidepressants. Tricyclic antidepressants at 'subtherapeutic' plasma drug concentrations have produced positive clinical responses in depressed elderly women, perhaps indicating that the substrate for drug activity may be changed in older people.[78] Among tricyclic antidepressants, the tertiary amine subgroup (imipramine, doxepin, amitriptyline, and trimipramine) tends to produce the most frequent side-effects. The secondary amines (desipramine and nortriptyline) are therefore the cyclic antidepressants of choice in older patients.[79]

Benzodiazepines and opiates

The activity of glutamic acid decarboxylase (GAD) and GABA concentrations fall with age in a number of cerebral cortical areas,[80] whereas GABA receptor binding sites are increased or unchanged.[81] These alterations in GABA-benzodiazepine receptor complex function may make older patients more sensitive to benzodiazepines, barbiturates and alcohol. The precise mechanism of this accentuated response to benzodiazepines is unclear as there are no age-related changes in human benzodiazepine receptor binding.[82] Older patients developed confusion, ataxia, immobility and incontinence at normal adult doses of some benzodiazepines.[83]

Increased receptor response, resulting in augmented drug effect, has also been noted with use of opiates.[84] The increased intensity of action of fentanyl and alfentanil in older patients is due to age-related pharmacodynamic, rather than pharmacokinetic, changes.[85] Uniform levels of metoclopramide have a greater antiemetic effect in preventing cisplatin-induced emesis in older people than in younger people.[86] Older people are less responsive to pain stimulus than younger people,[87] and are more sensitive to barbiturates and their side-effects.[88]

Warfarin

Older patients are more sensitive to warfarin, but the precise mechanism for this increased sensitivity to warfarin amongst elderly patients is uncertain, one possibility being an increased sensitivity to enzyme inhibition. Greater inhibition of vitamin K-dependent clotting factor synthesis at similar plasma warfarin concentrations in older patients has been described.[89]

Aspirin

The efficiency of thermoregulatory mechanisms decreases with advancing age.[90] Impaired shivering, defective vasoconstriction and poor appreciation of low temperatures occur more frequently in the older subjects.[91] Hypothermia is more pronounced and prolonged in older patients.[92] Hypothermia can be induced in older patients if aspirin is added to a regimen containing other drugs (psychotropics) that can adversely affect the thermoregulatory mechanisms.[93]

CONCLUSION

Drug therapy in older people remains one of the most significant challenges in clinical medicine. Age-related changes in drug metabolism are a complicated interplay between genetics, ageing, disease and environment. Although altered pharmacodynamics modifies therapeutic efficacy, age-related changes in average pharmacokinetic and pharmacodynamic parameters do not predict the older person's individual dose requirement or response. Drug dose requirements for individual patients are best determined by careful dose titration against clinical response or therapeutic drug monitoring.

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