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Pharmacology and the Elderly

Abstract: This paper describes the impact of ageing on an individual's ability to process drugs. It considers adverse drug reactions in the elderly and discusses prescribing for the older dental patient.

Clinical Relevance: Many older dental patients will be suffering from medical conditions or taking prescribed or non-prescribed drugs. These can influence the impact of drugs prescribed by dentists.

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Elderly patients often suffer from multiple medical conditions and take many prescription and non-prescription medications. With improved medical health and dental care, patients are not only living longer, but significant proportions are now maintaining a full or partial dentition throughout their life. The General Dental Practitioner will increasingly be faced with elderly patients requiring the administration of a variety of drugs. These patients require a cautious approach as a result of the physical and physiological alterations that occur during ageing. These changes may influence the patient's ability to process drugs and can affect the adverse reactions that may occur.

Physiological changes in the elderly

There are significant physiological changes that occur in old age. These can affect both the pharmacokinetics and pharmacodynamics of any drug taken.

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A description of the pharmacodynamic and pharmacokinetic changes that occur in the elderly will illustrate those principles that should be borne in mind when prescribing medication for this group in the population.

Pharmacokinetics

Pharmacokinetics refers to the mechanisms by which a drug is absorbed, transported, distributed, metabolized and then excreted from the body. Changes that occur with age can influence many of these processes and have a direct effect on the pharmacokinetics of drugs.

Absorption

Most drugs that dentists prescribe or administer are given orally or by injection. The former involves absorption via the gastro-intestinal tract. The gastro-intestinal system undergoes many changes throughout life, which can lead to a significantly altered absorption environment. Such changes include the reduced production of hydrochloric acid by the stomach,[1] decreased cardiac output with a parallel fall in gastro-intestinal blood flow, a reduction in gastro-intestinal emptying and lowered gastro-intestinal motility. Changes in the local vasculature will affect the absorption of drugs that are given by injection in older patients. Surfaces other than the gastro-intestinal tract may be involved in absorption of some drugs. These include skin, nasal mucosa and the alveoli of the lungs. Ageing effects on the lungs include reduced alveolar surface areas, chest wall compliance and lower effective lung volumes. Whilst the effect of these phenomena on the absorption of inhaled drugs is largely unknown, it has been shown that reduced cognitive and motor function in frail elderly patients can result in an ineffective inhalation technique,[2] potentially reducing the absorption of aerosols such as GTN spray or salbutamol.

Age-related changes to the nasal mucosa have not been widely investigated. Alterations in skin with age include a thinning epidermis and increased dryness.[3] Whether these changes would be mirrored in the nasal mucosa is debatable and potential changes in nasal absorption in the elderly should be considered unknown.

Distribution

Once a drug is absorbed into the body, it is transported via the circulation and is distributed throughout plasma, lean muscle mass or fat tissue. The compartment to which the drug is distributed is decided by the individual characteristics of the drug in question. Age-related changes to the body composition affect the proportions of these different tissues. Changes that occur during normal ageing include a decrease in total body water, a decrease in lean muscle mass and an increase in fat tissue.[4,5]

The reduction in total body fluid in elderly patients means that there is

a decreased volume in which hydrophilic drugs preferentially distribute.[6] Therefore, the plasma concentration of these drugs is increased in elderly patients. This increases the risk of adverse drug reactions and problems with overdose, which is further exacerbated by the loss of lean muscle mass commonly observed in the elderly. Examples of hydrophilic drugs include alcohol, warfarin, propranolol and a number of hypnotics and sedatives.[1,7] For drugs of this nature, it is recommended that clinicians should reduce the dose administered to the elderly patient to compensate for this decreased volume of distribution.

The increase in the percentage of fat tissue observed during the ageing process favours the deposition of lipophilic drugs which, as a result, are more heavily distributed throughout the adipose tissue. This increases the half life of these drugs, so they remain in the body for a longer time.[1] Examples include midazolam and diazepam, lidocaine and some synthetic steroids. It may be that this phenomenon is partially responsible for the increased sensitivity of elderly patients to benzodiazepines. When prescribing or administering these drugs, the dentist should consider dose reduction to take this into account.

A significant proportion of the transport of many drugs occurs when bound to plasma proteins, such as albumin. Albumin levels decrease with age.[8] This reduction in albumin levels occurs at a faster rate as age increases. It can have the effect of increasing the effects of drugs that are highly plasma-bound. Any drug that is bound to plasma proteins is unavailable for receptor-binding and therefore cannot exert a pharmacodynamic effect. When albumin levels decrease, a greater proportion of the drug remains unbound and will be free to bind to receptors and be pharmacologically active. This can lead to an increased risk of toxicity with drugs that are very highly protein-bound. Whilst amoxicillin is weakly bound in plasma (17–23%), flucloxacillin is very highly bound (93%)[9] and therefore caution should be exercised when prescribing flucloxacillin. Warfarin is another drug that is highly protein-bound and the reduction in protein available for binding that occurs in the elderly can make its clinical effect unpredictable. This makes daily fluctuations in INR values more likely, particularly if a patient is placed on any medication, such as an antibiotic, that competes with warfarin for protein-binding. If a surgical procedure, such as an extraction, is to be performed on an elderly patient taking warfarin in combination with other drugs, such as antibiotics, it is advisable to obtain an INR value on the day of surgery to ensure competitive plasma binding has not increased the levels of free warfarin.

Hepatic metabolism

The liver normally metabolizes drugs in a bi-phasic manner. Phase 1 reactions typically consist of oxidations, reductions and hydrolysis. Phase 2 processes consist of conjugation reactions. Whilst these effects normally inactivate drugs, they can sometimes serve to activate agents by the production of pharmacologically active metabolites. Hepatic blood flow parallels the decrease in cardiac output that occurs with age. This is responsible for the reduced liver clearance of some drugs.[10] Another factor that influences the hepatic metabolism of drugs is the decrease in liver enzymes responsible for drug metabolism.[11]

The changes that occur in elderly patients appear to impair the efficiency of phase I metabolism. This affects the half life of drugs that have high hepatic extraction ratios. Such agents include lidocaine.[12] Drugs that are heavily dependent on phase I metabolism include diazepam and midazolam. These exhibit a reduction in hepatic clearance in the elderly.[12,13] Therefore, the dentist should be careful to limit the dose of such medication to avoid overdose, or adverse reactions.

In contrast, phase II metabolism in the liver does not appear to be significantly affected in the ageing patient.

Renal clearance

The ageing kidney undergoes changes in function, size and anatomy. In addition, there is a reduction in renal perfusion. These alterations combine to cause an overall reduction of between 35–50% in renal function in patients over the age of 65 years.[5] Renal function is measured using creatinine clearance

Mechanism of Pharmacokinetics	Alterations in the Elderly
Absorption	- Reduced hydrochloric acid in stomach - Reduction in gastrointestinal blood flow - Decreased gastric motility and emptying - Reduced lung alveolar surface area
Distribution	- Reduced cardiac output - Decreased total body water leading to increased concentration of hydrophilic drugs - Decrease in lean muscle mass further reducing volume of distribution for hydrophilic drugs - Increase in adipose tissue increasing distribution and half life of lipophilic drugs - Decrease in albumin plasma concentrations leading to increased free-plasma concentrations of drugs
Hepatic metabolism	- Reduction in hepatic blood flow - Reduction in hepatic enzymes affecting phase 1 metabolism
Renal clearance	- Reduction in renal blood flow - 35–50% reduction in renal function

Table 1. The effect of ageing on pharmacokinetics.

and this test is often used to inform dose adjustments. This can lead to an overestimation of renal clearance in elderly patients as muscle mass, which is the main source of serum creatinine, and urinary creatinine excretion decrease at roughly the same rate as renal function,[14] so serum creatinine levels can remain relatively unchanged.

In addition, a reduction in cardiac output and changes in vascular anatomy can lead to an average decrease in renal perfusion of roughly 10% per decade.[15] In practical terms, this decrease in renal clearance should be taken into account as a significant factor if the drug prescribed undergoes 60% or more renal excretion.[6]

When prescribing a drug for the elderly dental patient, it is prudent to start with a low dose and slowly increase it in a step-wise manner to avoid physiological, or renal, toxicity caused by a decrease in kidney function and a toxic increase in metabolites. This is particularly the case for drugs that are eliminated by the kidney. Such medicines include penicillins and aminoglycosides.[16] Drugs which have metabolites that are eliminated by the kidney include diazepam and flurazepam.[17] If prescribing penicillin, or a benzodiazepine for more than a one-off dose, the dentist should take into account a reduction in renal function in the elderly by adjusting the drug dose downwards. This degree of caution will help avoid drug toxicity, or other adverse drug reactions with normal doses in the elderly.

Table 1 summarizes the pharmacokinetic changes that occur in the older patient.

Pharmacodynamics

Pharmacodynamics is the mechanism by which a drug achieves its actions. The size of the response to any drug is affected by the concentration of the drug in question and the affinity of this drug for the relevant receptors. In other words, it is determined by the number of drug-receptor complexes that are achieved.

Whilst most studies tend to be carried out in younger patients, there is evidence that pharmacodynamic reactions can change with increasing age. These commonly result in an increased sensitivity to an administered drug, which may result from either a rise in the number of the drug receptors, or an increased receptor response following activation. Such reactions that occur with age can be produced by commonly used drugs. The benzodiazepines and non-steroidal anti-inflammatory drugs are two such agents often administered in a dental setting and, as such, warrant further discussion.

Benzodiazepines

The pharmacodyamics of the benzodiazepines changes with age. Elderly patients have an increased sensitivity to agents affecting the central nervous system.[1] It has been demonstrated that the pharmacodynamics of midazolam differs when administered to older patients.[18,19] The elderly show decreased reaction times, and increased dose-response with midazolam compared to younger individuals, despite no change in the distribution of the drug. This means that oversedation may be more likely in the older patient, so the use of lower doses of midazolam in elderly patients is more appropriate.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are frequently prescribed for the relief of dental pain, particularly following minor oral surgical procedures. Drugs of this class most commonly prescribed include aspirin, ibuprofen and diclofenac. It is estimated that between 40–60% of patients who use NSAIDs are over the age of 60 years old.[20]

NSAIDs have been shown to lead to an increased risk of peptic ulcer disease, with drug prescriptions for peptic ulcer disease increasing from 10.5%, in elderly patients not taking regular NSAIDs, to 25.8% in those elderly patients regularly prescribed NSAIDs.[21] As a result, advanced age combined with NSAID-induced peptic ulceration has been shown to lead to an increased risk of serious or fatal upper gastro-intestinal tract bleeding.[22] Thus it is contra-indicated to prescribe NSAIDs to a patient already taking oral anti-coagulants.

NSAID therapy has been associated with confusion in elderly patients.[23] Avoiding prescribing NSAIDs for those with existing cognitive impairment may help reduce the risk of increasing confusion and exacerbation of existing neurological disorders.

Other frequently occurring side-effects with NSAIDs include renal impairment and, less commonly, hepatotoxicity.[24,25] Thus administering NSAIDs to patients with pre-existing renal, or hepatic impairment, is also contra-indicated.

Adverse drug reactions (ADRs)

The chances of unwanted effects arising from drugs are increased approximately 10-fold in the elderly patient. In fact, about 40% of all adverse drug reactions occur in older people.[26] In addition, the physiological changes that affect the pharmacodynamics in the elderly can lead to many of the common ADRs. The risk factors for ADRs are listed in Table 2.

The elderly population are heavy consumers of drugs. They receive some 40% of all drugs supplied.[27] Some will

Risk Factors for Adverse Drug Reactions
Patients over the age of 85 years
Female gender
Low body weight
Renal impairment
Dementia
Use of multiple prescribing healthcare workers/pharmacies
Use of six or more medications

Table 2. Risk factors for adverse drug reactions.

be consuming 4–5 different medications daily. Roughly 20% of patients admitted to geriatric departments suffer from side-effects related to drug administration. Community-based studies have shown that the prevalence of side-effects can be as high as 80% in those taking six medications or more, and 18% in those taking less than six medications.[28] This means that ADRs represent significant morbidity in the elderly population. Often, polypharmacy can lead to ADRs through prescription from multiple health providers with little or no knowledge of current drug history or poor clinician understanding of drug interactions. In addition, confusion of the patient may lead to misunderstandings over drug regimens or misidentification of the prescribed drugs. It is important that as simple a regimen as possible is followed when prescribing medication to older patients. Very clear instructions about dosing should be provided. This can be complicated by over-the-counter drugs that the patient may be taking. An example of a readily available over the counter drug responsible for many ADRs is a NSAID. As mentioned above, these are responsible for a high proportion of hospital admissions, for example NSAIDs increase lithium toxicity.[29,30]

Expected drug side-effects often occur in increased severity and incidence in elderly patients. An example of this is pseudomembranous colitis, which is a well-known side-effect of clindamycin. This potentially fatal condition increases in incidence in patients over the age of 60.[31] The increased sensitivity of older people to benzodiazepines was discussed above. Xerostomia, a side-effect of many medications, impacts on oral health and the effects should not be underestimated in the elderly patient. These include oral discomfort, problems with denture wearing, eating and speech and an increased occurrence of caries and periodontal problems. Sometimes ADRs occur that are unexpected, or unpredictable, and the dental practitioner should remain alert to the potential for such reactions.

Summary of geriatric administration of commonly used drugs in dentistry

Local anaesthetics

Local anaesthetics are very safe drugs as long as they are injected into the correct site and appropriate doses are used. Factors that may affect the blood concentration of local anaesthetics in the elderly include systemic illness, age, body weight, drug composition and dosage.[16] Good clinical technique, with routine use of aspirating syringes and careful administration, can reduce the likelihood of depositing local anaesthetics directly into the bloodstream. The importance of aspiration is highlighted by the results of some studies[32] that have demonstrated positive aspiration of blood in over 20% of inferior alveolar nerve blocks. Pharmacodynamic and pharmacokinetic changes can affect both the blood concentration and the clearance of local anaesthetic solutions. Most amide local anaesthetics, such as lidocaine, are metabolized by hepatic enzymes, which were discussed above. Reduced kidney function may also lead to an increase in the blood concentration of these drugs. The effect of these natural changes can be compounded when a systemic illness, such as liver disease, is present. When considering the total dosage that can be administered to an elderly patient, systemic illness should be taken into consideration.

As the maximum recommended safe doses (such as 4.4 mg/kg for lidocaine) have been calculated for the average adult patient, it may be prudent to modify these doses for the elderly patient (for example, a maximum of 2.2 mg/kg for those over 65). Fortunately, dental local anaesthesia can be more effective in older compared to younger patients. This is probably the result of a reduced blood supply impairing absorption of the drug and decreased bone density allowing better infiltration.

Sedative drugs

The elderly are much more sensitive to benzodiazepines than those of younger age. Therefore an increased rate of ADRs and over sedation in the elderly should be expected. The drugs lorazepam, oxazepam and temazepam all undergo phase II metabolism and, as such, are not metabolized significantly differently in the elderly patient.[13] They can therefore be considered as a safe alternative if required.

Diazepam must undergo oxidation before conjugation and has a half life of 100–200 hours in the elderly patient.[6] This prolonged clinical effect should be considered to be greatly in excess of that required for routine dental treatment. Therefore the use of diazepam by the dental practitioner on an elderly patient can rarely be justified.

Analgesics

The problems with administering long-term pain relief in the form of NSAIDs in elderly patients can be significant and can include peptic ulceration, confusion, renal impairment and, less rarely, hepatotoxicity. The use of NSAIDs in the elderly patient should therefore proceed with caution and the potential for ADRs must be balanced against the clinical benefit achievable.

Paracetamol should be considered the analgesic of choice in the elderly patient owing to its relative lack of side-effects and adverse reactions.[28] Whilst the metabolic clearance of paracetamol has been shown to be roughly 23% lower and renal clearance up to 43% lower in the elderly patient,[33] dose adjustment will not usually be required for short-term use. It may be advisable to avoid longer term, high dose paracetamol therapy, however, to minimize the risk of liver toxicity, especially in those patients with chronic liver disease.

Antibiotics

Dose adjustment is not often required for the commonly prescribed antibiotics owing to their relatively short half life. The reduction in renal function means that caution should be exercised where an antibiotic is eliminated via the kidney, with routine dose reduction deemed sensible with vancomycin and gentamicin to prevent nephrotoxicity.[34] Penicillin has been shown to have a half life increase from 23.7 hours to 55.5 hours between the ages of 50 and 70 years[6] and, when the creatinine clearance falls below 30ml/min, the dose of renally cleared drugs should be halved.[28] Therefore, in the presence of renal failure, penicillins, cephalosporins and tetracyclines should be reduced in dose, whilst routine dose reduction in antibiotic therapy lasting 1–2 weeks has been shown to reduce the incidence of ADRs and nephrotoxicity.[16]

Generally, if the treating dentist

Guidelines for Prescribing to the Elderly
Take a thorough medical history
Take an accurate drug history, including non-prescription drugs
Take a thorough social history
Take into account physiological effects of ageing, such as reduced renal function, kidney function, body composition
For long-term drug treatment start dosing low and increase slowly
Communicate with other healthcare workers to eliminate conflicting treatment or advice
Simplify drug regimens – try to comply dose timings with other current therapies if possible – consider pill organizers
Consider practical implications of drug storage containers and measurement of liquid volumes
Refer to a publication such as the British National Formulary to check for possible drug interactions and the impact of renal and hepatic disease

Table 3. Practical guidelines when prescribing to the elderly.

Figure 1. A pill organizer can be useful to aid correct dosing of medication.

Figure 2. Older patients with impaired manual dexterity may find it difficult to use a spoon to measure the correct dosage.

has a concern about the renal function of an elderly patient, specialist advice should be sought before prescribing renally-excreted drugs, including many commonly used antibiotics.

Practical points

Table 3 outlines the points that should be considered when prescribing to an elderly patient. One of the reasons why drug therapy may fail is due to a lack of compliance. This is not always deliberate and may occur with older people for a number of reasons. Some of these are worth considering when prescribing. If the patient is taking a number of medications at set times of the day it is worthwhile choosing the timing of doses for any new prescribed medication that fits in with the current schedule. This can be aided by the use of pill organizers such as that shown in Figure 1.

Other problems that interfere with compliance include the inability to take the medication itself or take the appropriate dose. This can be the result of decreased manual ability with ageing or a concurrent condition such as Parkinson's disease. This can make it difficult to open child-proof containers. In addition, if a liquid formulation is used it may be difficult to control the amount placed in a dosing spoon (Figure 2). In the latter instance, the use of a syringe may be preferred for more accurate dosing. In any event, the taking of a good social history is important to ensure that help is available for proper drug administration.

Finally, in order to reduce the chances of drug interactions the dental practitioner should consult a publication such as the *British National Formulary*, which lists drug interactions in Appendix 1. An online version is available at **http://www.bnf.org**. In addition, this publication gives advice on the impact of renal and hepatic disease on the drugs that dentists may prescribe. A little time spent consulting such publications to increase the safety of prescribing is highly recommended.

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Abstracts

WILL DIGITAL RADIOGRAPHY REALLY IMPROVE YOUR PRACTICE EFFICIENCY?

Work flow with digital intra-oral radiography: a systematic review. Wenzel A and Møystad A. *Acta Odont Scand* 2010; **68**: 106–114.

I was told recently that intra-oral digital radiography is one of the fastest growing developments in general dental practice. This paper reports a systematic review of the six most frequently stated advantages of this modality; less working time, lower radiation dose for the patient, fewer retakes and errors, wider dynamic range, easier access to patient information and easier image storage and communication.

The results were somewhat surprising. There is indeed a saving in time when the switch is made from conventional to digital imaging. However, other unexpected problems than those under initial consideration were found which adversely affected the outcome. These were patient discomfort, damage to the digital receptor, degradation of the image, cross-contamination and viewing conditions. These seem to lead to an increased number of retakes which then counters the anticipated reduction in patient dose.

Interestingly, patients reported that there was no improvement in information and understanding whether the image was a digital display or a conventional film. Patients also reported that there was a significant increase in discomfort when the image sensors were compared to conventional film. Concern was expressed over the storage of digital images, which may not be as accurate as anticipated. Furthermore, digital images may be 'enhanced' or manipulated, which may involve a loss of accuracy or even legitimacy. Concerns were also expressed with regard to cross-infection risks, particularly when the phosphor plate system is transferred to the digital processor.

The authors' conclusion that not all the anticipated advantages were found to be supported by the literature may be of considerable interest to practitioners considering changing their radiographic practice.

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