ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS - THE LESSON TO LEARN

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Summary
Elderly people are at an increased risk of adverse drug reactions (ADRs) due to the changes in pharmacokinetics and pharmacodynamics as a result of ageing. We report two patients who developed adverse drug reactions to commonly prescribed medications. Indapamide, a commonly prescribed anti-hypertensive, caused severe hyponatraemia, which was reversible on suspending the drug and providing supportive treatment. Enalapril unexpectedly led to hepatotoxicity which was also reversible on cessation of therapy. Although both patients recovered, it is not uncommon to find mortality and morbidity associated with ADRs. A thorough understanding of the pharmacology of the drugs we are prescribing and careful monitoring of the patients are essential to reduce ADRs.

Introduction
Elderly patients are at an increased risk of adverse drug reactions (ADRs). The overall effects of a drug depend on the handling of the drug by the body (pharmacokinetics) and the target organ sensitivity to the drug (pharmacodynamics). With ageing, both of these factors may be changed by a variety of mechanisms. In general, there will be longer duration of activity, a greater or lesser drug effect and an increase in incidence of drug toxicity and ADR.

The majority of ADRs occur with drugs that are commonly prescribed in clinical practice. ADRs have an important influence on inpatient management. Mean duration of hospital stay is prolonged for patients who have an ADRs\(^1\) and the morbidity and mortality are higher than in those without ADRs.

As illustrated by the following cases, simple commonly prescribed drugs can cause adverse effects and morbidity in elderly.

Case reports
Case 1
A 75-year-old man who was previously living alone and walked unaided was admitted for confusion for 2 days. He had history of hypertension and was on indapamide, nifedipine and propanolol. On examination, he was totally disorientated in time, place and person. There was generalized hypotonia and hyper-reflexia with power at grade 4/5. Blood pressure was 170/100 mmHg. He remained afebrile. Blood results showed Na 111 mmol/l (normal 135-145), K 3.0 mmol/l (normal 3.5-5.3), urea 9.2 mmol/l (normal 2.5-7.5), creatinine 97 µmol/l (normal 50-140), glucose 7.5 mmol/l, serum osmolality 257 mOsm/kg (normal 275-295) and urine osmolality 456 mOsm/kg. White cell count was 11x10\(^9\) per dL. His arterial blood gas while breathing room air was: pH 7.385 (normal 7.35-7.45), pCO\(_2\) 2.85 kPa (normal 4.7-6), pO\(_2\) 8.9 kPa (normal 10.0-13.0) and total HCO\(_3\) 12.9 mmol/l (normal 24-26). Total T\(_4\) was 113 nmol/l (normal 62-154) and TSH 0.80 mIU/l (normal 0.29-4.0). Cortisol level at 9am was 2816 nmol/l (normal 133-690) and at 9pm was 3535 nmol/l (normal 69-345). ECG was in sinus rhythm with ventricular rate at 100 beats/min. The differential diagnoses were stroke, electrolyte disturbances and central nervous system infection. Urgent CT brain showed normal findings and septic workup was negative. A presumptive diagnosis of metabolic encephalopathy was made. Indapamide-induced hyponatraemia was suspected. All current medications were stopped immediately on admission. After correction of the hyponatraemia with normal saline and potassium supplement, a gradual improvement of the sodium level and conscious state was seen. His blood pressure remained stable at 150/80mmHg without any anti-hypertensive drugs. He stayed in the hospital for 2 weeks and was discharged home without any anti-hypertensives. Seven similar cases of...
indapamide-induced hyponatraemia have been reported in our hospital in the preceding year and we have reported them to our hospital chief pharmacist for record.

**Case 2**

A 71-year-old man was admitted for orthopnoea and ankle edema. He had a history of chronic obstructive airway disease and was not on regular medications. On examination, he was tachypnoeic with elevated jugular venous pressure. His apex beat was displaced and there were bilateral basal crepitations in the chest. Blood pressure was normal and he was afebrile. ECG showed sinus rhythm of 120/min and right bundle branch block pattern. A diagnosis of congestive heart failure was made. He was then put on frusemide 40 mg daily, enalapril 5 mg bd and amoxycillin 500 mg tds. On day 3 of admission, he developed impaired conscious state with hypoglycaemia (spot glucose 2.4 mmol/l). No focal neurological sign was detected. He had not received any hypoglycaemic agent before. There was no history of alcohol consumption. Liver function test showed hepatic picture with bilirubin 79 µmol/L (normal 1-17), albumin 32 g/l (normal 35-50), globulin 22 g/l (normal 20-35), alkaline phosphatase 80 IU/l (normal 39-117), AST 3790 IU/l (normal 1-37) and ALT 1330 IU/l (normal 1-40). Electroencephalogram showed diffuse slow activities and bursts of moderate to high amplitude of triphasic waves predominantly in the frontal region compatible with hepatic encephalopathy. He was put on anti-liver failure regimen with lactulose and neomycin. Ultrasound of the liver was normal. CT scan revealed a cyst in the right lobe of the liver. Serological tests for hepatitis A, B and C were all negative. Viral studies were negative. Enalapril-induced hepatotoxicity was suspected. Enalapril has been taken off and the liver function test and conscious state improved. The patient was finally discharged after one month of hospital stay with full recovery of his liver function.

**Discussion**

The use of prescribed medications in general is higher in elderly patients than in the young. The overall incidence of adverse drug reaction in elderly patients is two to three times that found in young adults\(^2\). Age is an important variable affecting the pharmacokinetics of drugs. It has been recognized that elderly patients are disproportionate consumers of prescribed medications. Ninety-six percent of the overall increase in annual prescription items dispensed in the United States are attributed to elderly patients\(^3\) and more than 3 million Hongkong dollars are spent on drug expenditure in geriatric patients in our hospital. Numerous factors contribute to the high prevalence of drug use in the elderly population. The longer a person lives, the more chronic medical conditions he will accumulate and therefore more medications are needed to manage them.

**Pharmacokinetic changes with old age**

The change in pharmacokinetics with advancing age is important and well documented for the development of adverse drug reactions. Various physiological and anatomical changes that occur with normal ageing can affect drug absorption. There is a reduction in rate of gastric acid output and gastric emptying. The intragastric pH will be raised. There will also be a decline of blood flow to small intestines by 40%. However, studies on the absorption of orally administered drugs showed no change in the absorption rate\(^4\) in old people. There is a net increase of adipose tissue in elderly people, thus the volume of distribution of lipid soluble drugs is larger\(^4\). This implies that the half life of lipid soluble agents will be prolonged which is especially important for drugs that affect central nervous system. Total body water decreases by 15% when one grows old. Therefore the volume of distribution of water soluble drugs is decreased. When diuretics are also used, the extracellular fluid volume can be reduced further. All these lead to an increase in the serum concentration of water soluble drugs\(^5\). The fall of plasma protein concentration such as albumin in an elderly person will lead to a reduction in the protein bound (inactive) form of many drugs and a greater concentration of free (active) drugs\(^5\). Therefore caution should be made in the use of highly protein bound medications.

The rate of drug metabolism by the liver is determined by hepatic function and blood flow. Hepatic mass decreases with ageing and the number of functioning hepatocytes is also reduced\(^6\). This will produce a reduction of metabolic clearance of a large number of compounds which are metabolised via microsomal oxidative pathway with a major reduction of first pass metabolism. The renal size, number of functioning glomeruli, glomerular filtration rate and renal blood flow also decrease with age\(^7\). Therefore chronological age is a good predictor of the rate of elimination of drugs excreted unchanged in the kidney\(^7\).
Pharmacodynamic changes with old age

Changes also occur in end-organ responsiveness to medications with ageing. These may be due to a change in receptor binding, decrease in receptor number or altered transplantation of a receptor-initiated cellular response into a biochemical reaction.

Because of these differences in pharmacodynamics and pharmacokinetics, elderly people become more susceptible to ADRs. This will result in a longer duration of hospital stay. As illustrated by the above two cases, the majority of ADRs are pharmacologically predictable and occur with well established drugs. A knowledge of the pharmacology of a prescribed drug is essential and the usage of drugs whose ADR profile is minor should be employed where possible.

Indapamide

Indapamide is a non-thiazide indole derivative of chlorosulphonamide. It differs from thiazide by the presence of a methylindoline ring system linked via an amide group to the chlorobenesulphonamide ring rather than by the presence of a thiazide ring. This methylindoline moiety increases the lipid solubility of indapamide compared with thiazide diuretics. Indapamide acts in the cortical diluting segment of the distal convoluted tubule. It increases the activity of the renin-angiotensin-aldosterone system and increases sodium delivery to the distal renal tubules which results in a dose-related increase in urinary potassium excretion and decrease in serum potassium concentration. The mechanism for diuretic-induced hyponatraemia is multifactorial and may be complicated by underlying conditions. It can cause sodium and volume depletion, stimulating ADH secretion and leads to dilutional hyponatraemia. Other factors may include excessive urinary sodium loss in the presence of a low salt intake, a shift in sodium from extracellular to intracellular compartments, impaired free water excretion caused by diuretics and reduced renal blood flow, unrestricted intake of hypotonic fluid and concomitant drug therapy. We have already collected seven cases of indapamide-induced hyponatraemia which is in contrast to literature reported by Chaffman that serum sodium concentrations are not altered following long term treatment with indapamide. Severe hyponatraemia caused by diuretics may cause weakness, confusion, postural hypotension, postural dizziness, falls and seizures as illustrated in our patient. Old age appears to be an important risk factor for diuretic-induced severe hyponatraemia. The unusual high lipid solubility of indapamide may help to explain the relatively higher incidence of hyponatraemia when compared to those taking thiazide diuretics. Since indapamide is commonly prescribed in our elderly population, cautious use and regular monitoring is essential to avoid development of ADR.

Angiotensin converting enzyme inhibitor (ACEI)

ACEIs have become increasingly popular for managing hypertension and congestive heart failure. As experience with ACEI has grown, potential toxicity has become more widely reported. Hepatotoxicity is one of the major toxicities seen. Signs and symptoms of hepatotoxicity are frequently present. Jaundice is the most common finding as cholestasis is the most common hepatotoxic pattern of injury. Pure hepatocellular injury and mixed hepatocellular and cholestatic components are also seen. The duration of therapy prior to detection of hepatotoxicity varies from 5 days to 12 months with a mean time of 14 weeks and a median time of 1 month. Doses employed are variable and the time for recovery varies from approximately 2 weeks to 9 months. The mechanism by which ACEIs produce hepatotoxicity is not known. Proposed mechanisms include a hypersensitivity reaction and altered hepatic eicosanoid metabolism related to antagonism of kininase II and consequent failure to metabolize bradykinin. A selective increased concentration of specific prostaglandins could mediate ACEI-associated cholestasis while leukotrienes are associated with hepatocellular and biliary tract toxicity. Thus the early phase of ACEI-associated hepatotoxicity may be mediated by an increased concentration of prostaglandins that reduce bile flow causing cholestasis. Continued exposure to ACEI results in an elevation of hepatotoxic leukotrienes and hepatic injury. ACEI-induced hepatotoxicity is usually reversible on cessation of therapy, but it may be severe and potentially fatal if continued. Therefore, it is essential to recognize this problem and quickly discontinue the agent involved.

Conclusion

As a result of age related physiological changes and the high frequency of comorbid conditions in elderly people group, the appropriate prescribing of medications for elderly patients can be challenging. An enhanced quality of life is the primary goal of drug therapy in the elderly. The cure of chronic disease is not often possible and the alleviation of symptoms can involve simple measures even without the use of drugs. However when medical therapy is required, the physician should be aware of the potential effects of age and disease in altering drug disposition and drug response. By increasing our knowledge of the actions of drugs in elderly people and improving the communication between patient and physician, we can improve the overall care of our elderly patients greatly.
Direction of Geriatrics in the eyes of Geriatricians in Hong Kong

In preparation for a meeting with Mr. Yiu-Chung Tam in May 1997, I have conducted a survey to find out in what direction local geriatricians wanted geriatrics in Hong Kong to go to. The survey was in the form of a rather hectic questionnaire and there were altogether 13 returns. Here, I try to summarize the rather hectic remarks in the questionnaire which I hope, may provoke some thoughts:

About Acute Care

Several respondents suggested that we should establish Geriatric Evaluation and Management (GEM) in acute setting to cover for patients not under geriatricians’ care. One suggested GEM with 20 acute assessment beds should be set up in every acute hospital. Many treasured the input of organ specialist in the management of acute illness in elderly patients, but were concerned about too much focusing on disease and on ageism that may erode the welfare of elderly patients. One respondent commented that geriatrics may develop their own organ specialist. One respondent suggested that we have to define geriatrics care in acute setting and set up standards and protocols.

About Extended Care

Two respondents emphasized the importance of monitoring performance and outcome in extended care. One respondent suggested that special programs (such as dementia, bedsore, pain relief, osteoporosis, fall, etc.) and even acute care (such as cardiorespiratory care) should be set up in extended care setting. Many showed concern on the coordination of extended care service (rehabilitation and infirmary) and community service. Some suggested all these should be under one umbrella and run by geriatricians. One respondent suggested that only geriatricians are equipped with the skill and training for the job. One respondent commented that young disabled patients should be managed by rehabilitation specialists as these patients have different needs.

About Community Care

Many suggested that we should improve the current coverage of community service to include all institutes caring for elderly people. The need for continuity of care and a coordinated service was highlighted. Two respondents suggested that the Department of Health should utilize geriatricians in directing their health care project for elderly people. A term “residential geriatrics” was suggested.

Additional Comments

Two respondents commented physician training should include geriatrics and extended care. One respondent suggested that we should establish base in extended care by “bed power”; status in acute/teaching setting by “profession”; and credential in the community by “involvement”.

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References