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Drug-Associated Diarrhoea and Constipation in Older People

1. Diarrhoea

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ABSTRACT

Diarrhoea and constipation are common side effects of many drugs. In the elderly, such drug-related iatrogenic conditions compound the increased prevalence of acute and chronic illness. In older persons, an awareness of diarrhoea and constipation as complications of drug therapy and the use of preventative measures wherever practical may significantly increase the quality of life of the patient. It is important to understand the mechanisms whereby medications may cause diarrhoea and constipation and to periodically review drug use in the elderly.

The first part of this review explains the mechanisms involved in drug-induced diarrhoea and gives examples of drugs commonly involved.

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INTRODUCTION

In our rapidly ageing society, increased drug consumption and drug-related side effects, such as diarrhoea, affect the quality of life of older persons. Globally, the proportion of persons aged 60 or over was 10 per cent in 1998 and is projected to reach 22 per cent in 2050.¹ In Australia, it has been estimated that approximately 25 per cent of the population will be aged 65 years or over by the year 2051, compared with 12 per cent in 1997.² This increase in our ageing population will inevitably impact on health services, as ageing is associated with an increased incidence and prevalence of acute and chronic illnesses, and increased drug consumption and polypharmacy. The elderly are amongst the highest users of medication. Drug consumption increases with age and it is documented that about 85 per cent of older persons are treated for single or multiple disease processes.³

In the elderly the increased prevalence of acute and chronic, often multisystem, illnesses is compounded by the problem of drug-related iatrogenic illness such as diarrhoea. Diarrhoea is a potential cause of morbidity

and mortality. In older persons limited physiological reserves and coexisting diseases increase the frequency and severity of complications such as dehydration and electrolyte loss which may be fatal.⁴ Malnutrition and undernutrition are other important consequences of diarrhoea in older persons, especially those in nursing homes and acute care facilities.⁵

Diarrhoea, Ageing and the Gastrointestinal System

Diarrhoea, irrespective of aetiology, occurs due to an imbalance between absorption and secretion. When the absorptive capacity of the intestine is exceeded and net secretion is greater than absorption, diarrhoea occurs. Ageing is not associated with significant changes in gastrointestinal absorption or secretion.

Ageing and Drug Handling

Ageing affects both drug pharmacodynamics and pharmacokinetics. The elderly are more susceptible to drug side effects due to increases in drug sensitivity and alterations in drug handling. The major organs of drug clearance, the kidney and the liver, are affected by age. Decreases of up to 50 per cent in the glomerular filtration rate and renal clearance of drugs occur between the ages of 25 and 85 years with an average decrease of about 1 per cent per year after 40 years.⁶ Diarrhoea as a side effect of renally cleared drugs, such as digoxin and lithium, is therefore more likely.⁷ Diseases that may aggravate renal function in their own right, such as diabetes mellitus, hypertension and heart failure, compound the effects of ageing on renal function.

Both liver mass and blood flow decrease in older persons: a 24 per cent decrease in liver volume and a 35 per cent reduction in hepatic blood flow is reported in persons aged above 65 years of age.⁸ Therefore drugs such as propranolol that rely primarily upon hepatic blood flow for their metabolism (i.e. high hepatic extraction) may have lowered metabolism and increased risk of side effects including diarrhoea.⁹ Thus normal ageing may diminish physiological reserves and the responsiveness of compensatory mechanisms, and may result in increased drug side effects such as diarrhoea in the elderly.

DEFINITIONS

Diarrhoea is an increase in the frequency, fluidity, or volume (weight) of bowel movements, relative to the usual

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habit for that individual. The World Health Organization defines diarrhoea as three or more unformed bowel actions in 24 hours.¹⁰ Acute diarrhoea is defined as an episode of diarrhoea that lasts less than two weeks, while persistent diarrhoea is an episode that lasts for two weeks or longer.¹⁰ Chronic diarrhoea is defined as diarrhoea for at least three to six weeks.¹¹

Drug therapy is one of the most common causes of diarrhoea in the elderly (Table 1).¹² Diarrhoea is more often dose-related than due to idiosyncratic drug reactions.¹³ For this reason, considering and eliminating a drug-related aetiology is essential in older persons with diarrhoea.³ This simple measure would obviate unnecessary investigations, expense and inconvenience.

Table 1. Drugs associated with diarrhoea

Cardiovascular drugs	
<ul style="list-style-type: none"> • methyldopa, digoxin, quinidine, propranolol, hydralazine, ACE inhibitors, procainamide 	
Gastrointestinal drugs	
<ul style="list-style-type: none"> • laxatives, lactulose, antacids (magnesium salts), H₂-receptor antagonists, proton pump inhibitors, cholestyramine, chenodeoxycholic acid, olsalazine, misoprostol, enprostil, cisapride 	
Musculoskeletal drugs	
<ul style="list-style-type: none"> • colchicine, indomethacin, auranofin, naproxen, phenylbutazone, mefenamic acid 	
Central nervous system drugs	
<ul style="list-style-type: none"> • anticholinergic agents, levodopa, alprazolam, lithium, fluoxetine, donepezil, tacrine 	
Endocrine system drugs	
<ul style="list-style-type: none"> • oral hypoglycaemic agents, clofibrate, thyroxine 	
Miscellaneous	
• Antibiotics	clindamycin, amoxicillin, ampicillin, cephalosporins, neomycin, erythromycin
• Antimetabolites	5-fluorouracil, methotrexate
• Osmotic cathartics	magnesium containing antacids, lactulose, sorbitol, acarbose, propranolol

MECHANISMS OF DRUG-RELATED DIARRHOEA

Drugs may directly affect the gastrointestinal tract by damaging the mucosa of the small intestine or colon, or by altering the physiological processes of fluid absorption and/or secretion. Diarrhoea may also be caused indirectly by drugs that interfere adversely with gastrointestinal defence mechanisms, promoting infections that cause diarrhoea. Multiple drug-induced mechanisms may also be responsible for diarrhoea.

Direct Causes

Drugs directly cause diarrhoea via several mechanisms of action.

Mucosal Damage

In the small intestine drug-induced mucosal damage can lead to malabsorption and diarrhoea. Neomycin therapy causes histological changes ranging from loss of only microvilli to severe villous atrophy.¹⁴ Large doses of colchicine in the treatment of acute gout lead to villous atrophy, malabsorption and diarrhoea.¹⁵ This side effect is commonly used as a dosing guide in acute gout. Recently colchicine has been advocated in the treatment of

constipation.¹⁶ Antineoplastic drugs damage immature epithelial cells compromising the absorptive function of these enterocytes when they mature, leading to diarrhoea.

In the large intestine, drug-induced mucosal damage results in colitis that causes diarrhoea. Gold administered parenterally may result in serious enterocolitis within three months of therapy and occurs more often in females. The diarrhoea is severe and unrelated to dosage.¹⁷ Colitis is also associated with cancer chemotherapeutic agents (especially antimetabolites), penicillamine, methyldopa, antibiotics, flucytosine and the non-steroidal anti-inflammatory agents.¹⁸

Increased Motility

Drugs with cholinergic activity, cholinomimetics, mimic the parasympathetic effects of acetylcholine either by acting directly upon acetylcholine receptors, or by inhibiting the enzyme acetylcholinesterase. The accumulated acetylcholine in the parasympathetic nerve synapses excites the muscles of the gastrointestinal tract causing increased motility and hence diarrhoea. Tacrine hydrochloride¹⁹ and donepezil²⁰ in Alzheimer's disease reversibly bind with and inactivate acetylcholinesterase, resulting in diarrhoea. Irinotecan hydrochloride also inhibits the action of acetylcholinesterase, causing a cholinergic like syndrome.²¹ In this case, diarrhoea may be of sudden onset and severe enough to be life threatening. Cisapride is extensively used in the management of gastro-oesophageal reflux disease. The drug induces diarrhoea by increasing interdigestive and post-prandial small bowel motor activity.²² However, diarrhoea is usually mild and in most patients requires no intervention.

Disruption of Fluid and Electrolyte Absorption and Secretion

Drugs may affect the physiological mechanisms that regulate water and electrolyte absorption and secretion.

Secretory diarrhoea

Secretory diarrhoea is a specific entity. Drugs act as secretagogues to cause net fluid secretion. The cellular mechanisms involve the binding to a specific receptor on the epithelial cell surface of the small intestine (and less often in the colon) which activates adenylate cyclase in the cytoplasm of the cell. Adenylate cyclase reacts with ATP to generate cyclic AMP, which in turn activates a protein kinase that phosphorylates membrane proteins involved in active ion transport. This results in the active secretion of anions (Cl⁻ and HCO₃⁻), the passive efflux of Na⁺, K⁺ and H₂O, and the inhibition of Na⁺ and Cl⁻ entry into cells.²³ Net fluid loss occurs.

Drugs associated with secretory diarrhoea include ricinoleic acid (formed by the hydrolysis of castor oil by colonic bacteria), and common laxatives such as dioctyl sodium sulfosuccinate (docusate sodium) and bisacodyl.²⁴ Secretory diarrhoea is the predominant side effect of misoprostol, especially during the first two weeks of treatment, with a prevalence ranging from 5-13 per cent to 40 per cent.²⁵ Misoprostol specifically stimulates Cl⁻ secretion.²⁶ Ursodeoxycholic acid used in cholestatic liver disease causes diarrhoea as a side effect in about three per cent of subjects. The drug acts as a secretagogue to stimulate cyclic AMP in the colonocytes and cause net fluid secretion.²⁷

Na⁺-K⁺ exchange pump

The Na⁺-K⁺ exchange pump is a second mechanism that regulates water and electrolyte transport. Its efficiency is vulnerable to drug therapy, leading to diarrhoea. The Na⁺-K⁺ exchange pump regulates secretory activity and in the intestine is located in the basolateral membrane of the epithelial cells. This exchange pump moves three Na⁺ ions out of the cell in exchange for two K⁺ ions. The potential difference across the epithelial cell membrane provides an electrochemical gradient for the (electrogenic) entry of sodium and water from the intestinal lumen into the cell. The hydrolysis of one molecule of ATP by ATPase provides the energy for the activity of the pump. Diarrhoea results when some drugs cause a concentration-dependent inhibition of ATPase and 'pump malfunction' occurs.

Digoxin decreases Na⁺-K⁺-ATPase activity, and was second only to antibiotics as the commonest cause of diarrhoea in a study of 100 elderly inpatients.²⁸ In older persons it is important to adjust digoxin therapy and monitor blood levels since renal function, and hence drug clearance, declines with age.²⁹ Drugs that may increase digoxin levels include amiodarone, quinidine and verapamil. Hypokalaemia, common in older persons due to the use of thiazide and loop diuretics, also predisposes to digoxin toxicity.

Diarrhoea due to oral gold (auranofin) is also due to inhibition of Na⁺-K⁺-ATPase activity.³⁰ Although diarrhoea declines with time, in 8-14 per cent of patients the severity requires the drug to be discontinued.³¹ In the first six months diarrhoea reportedly occurs in 30-40 per cent of patients and at 18-24 months in about 10 per cent; at least one episode of diarrhoea was reported by 74 per cent of patients.³¹ Diarrhoea resolved in about half the patients spontaneously and in the others with antidiarrhoeal medication or dosage reduction or both. Auranofin-induced diarrhoea can cause enterocolitis and may persist despite drug withdrawal.³²

Colchicine is another example of a drug that may cause diarrhoea by inhibiting Na⁺-K⁺-ATPase activity.

Osmotic diarrhoea

The mechanism in osmotic diarrhoea is physiological. In the lumen of the intestine osmotic agents create a high osmolality disrupting the normal water gradient. Drugs associated with osmotic diarrhoea are included in Table 1. Lactulose, a synthetic disaccharide that reaches the colon unchanged, is metabolised by colonic bacteria to lactic, acetic and formic acids and exerts an osmotic action leading to diarrhoea. Sorbitol also induces diarrhoea because of its osmotic potential. Other osmotic agents that may cause diarrhoea are antacids containing magnesium trisilicate or magnesium hydroxide.

Acarbose, an alpha-glucosidase inhibitor, is also associated with osmotic diarrhoea. The drug acts locally in the gastrointestinal tract to inhibit small intestine enzymes that digest disaccharides, oligosaccharides, and polysaccharides. The slow digestion and release of glucose reduces postprandial hyperglycaemia.³³ The fermentation of the accumulated undigested, non-absorbed carbohydrates can result in osmotic diarrhoea, flatulence and colic.³⁴ The diarrhoea can be minimised by starting on a low dose and gradually titrating upwards. Persistent diarrhoea warrants a reduction in dose or, rarely, cessation.

Though the occurrence is infrequent, propranolol also has the potential to cause osmotic diarrhoea.³⁵ Antibiotics may alter the colonic bacterial flora and decrease the colonic fermentation of carbohydrates resulting in osmotic diarrhoea.³⁶

Indirect Causes

Drugs can predispose to diarrhoea by affecting the immune and non-immune host defences of the gastrointestinal tract, increasing the risk of infective diarrhoea.

Immune Defences

The human gastrointestinal tract is continuously in contact with literally thousands of antigens of immense diversity. In the gut the primary immune response is the production of secretory IgA which is highly dependent upon T cells, especially T₄. Agents such as immunosuppressive drugs that decrease T cell numbers affect secretory IgA production. Older persons may experience a decreased primary immune response, since the quality and proportion of T-helper and T-suppressor subpopulations decrease with age³⁷ and there is a higher prevalence of malignant disease that may require immunosuppressive therapy which affects T cell numbers.

Non-Immune Defences

The non-immunological defences are the gastric acid barrier, the motility of the stomach and the small intestine, and the commensal bacteria of the large intestine.³⁸ Drugs may seriously impair these defences.

Gastric acid has a strong bactericidal activity, due to the low pH rather than the other components of gastric juice.³⁹ Decreased acid production and the increase in gastric pH significantly increase the risk of diarrhoea due to enteric infections.⁴⁰ The management of diseases such as peptic ulcer disease, gastro-oesophageal reflux disease and the Zollinger-Ellison syndrome requires a substantial and prolonged reduction in gastric acidity and the drugs used in these conditions may lead to diarrhoea. H₂-receptor blockers cause diarrhoea in 3 to 12 per cent of patients.⁴¹ Cimetidine and antacids in combination resulted in the growth of Gram-negative rods in a majority of patients.⁴² Bacterial overgrowth is reported in up to 53 per cent of patients on omeprazole.⁴³ In normal volunteers, a transient increase in gastric colony count occurs with omeprazole and resolves on discontinuing the drug.⁴⁴ In addition to gastric 'contamination', drugs causing decreased acid production lead to small bowel bacterial overgrowth; this results in the bacterial deconjugation of bile salts and a subsequent secretagogue action on the colon.⁴⁵

Gastric motility also contributes to the defences of the gastrointestinal tract by mixing gastric contents (which may contain pathogens) with gastric juice. Increased gastric emptying by prokinetic agents such as metoclopramide, domperidone, cisapride or erythromycin decreases contact of ingested pathogens with gastric acid, reducing its effectiveness.⁴⁶

Small bowel motility is an important defence mechanism that prevents bacterial invasion, reduces mucosal adherence of pathogens and decreases contact time between the mucosa and toxic substances. Although the most frequent side effect of anticholinergic agents is constipation, these agents can also cause diarrhoea via their ability to decrease intestinal motility and hence pro-

mote bacterial overgrowth.⁴⁷

The intestinal flora of the colon provides a powerful non-immune defence mechanism. The commensal bacteria form a complex, well-balanced ecological system, unique to each individual, which defends the host from harmful pathogens.⁴⁸ This protection occurs by modification of bile acids, stimulation of peristalsis, induction of immunologic responses, depletion of essential substrates from the environment, competition for adhesion sites, creation of restrictive metabolic environments, and elaboration of antibiotic-like substances.⁴⁹

Antibiotics, which breach this colonic line of defence, are probably the most common iatrogenic cause of diarrhoea in older persons. The temporary alteration of the commensal colonic bacteria causes antibiotic diarrhoea and is usually mild and self-limiting. Superinfections occur most frequently with *Clostridium difficile*, and rarely with *C. perfringens*, salmonella and shigella. The most serious consequence of antibiotic-associated diarrhoea is pseudomembranous colitis due to *C. difficile*.⁵⁰ The commonly implicated antibiotics are clindamycin, lincomycin, ciprofloxacin and due to their widespread use, amoxycillin, ampicillin and cephalosporins.⁵¹

Multiple Mechanisms

Some drugs cause diarrhoea by more than one mechanism. Diarrhoea is a side effect in 12-25 per cent of patients with ulcerative colitis treated with olsalazine. Olsalazine inhibits sodium-dependent bile acid transport into the ileum and bile acids that remain in the lumen reach the colon to act as powerful secretagogues that cause a secretory type of diarrhoea.⁵² Another mechanism may involve the inhibition of Na⁺-K⁺-ATPase activity.⁵³ Colchicine causes diarrhoea by villous atrophy leading to malabsorption and also by diminishing the activity of the Na⁺-K⁺-ATPase pump. Misoprostol acts by increasing motor activity to cause diarrhoea⁵⁴ and also acts as a secretagogue.²⁶ Ricinoleic acid, a metabolite of castor oil, acts as a secretagogue while castor oil increases intestinal motility to cause diarrhoea.

Spurious Diarrhoea

Spurious diarrhoea, also known as overflow diarrhoea, is a consequence of faecal impaction, predominantly a problem in the elderly.⁵⁵ Constipation is the single most common cause of spurious diarrhoea in the institutionalised elderly,⁵⁵ and may be related to drug therapy. Spurious diarrhoea may be the presenting complaint, masking constipation,⁵⁶ and patients with spurious diarrhoea may unfortunately therefore be investigated vigorously for diarrhoea. In some instances, these patients may even be treated for diarrhoea.

MANAGEMENT

Diarrhoea due to drug therapy is preventable. The information given to patients by health professionals that diarrhoea may be a side effect of their therapy is often inadequate. Verbal and even written instructions may not be understood due to difficulty in hearing and/or poor eyesight or cognitive impairment. Some elderly patients may continue to take drugs that cause significant adverse effects such as diarrhoea because they do not associate the adverse effect with the drug.

A comprehensive drug history is essential, including that of over-the-counter medications, in older per-

sons presenting with diarrhoea. In patients who are unreliable historians, or from whom a history cannot be obtained, information on all medications taken should be obtained from carers and/or the patient's physician or pharmacist. Determining a drug-related cause of diarrhoea ideally includes sighting all drugs consumed, over-the-counter medications and other health products. Withdrawal of the drug resulting in the cessation of diarrhoea should confirm a drug-related cause, obviating expensive and tiresome investigations. However, drug-induced morphological damage to the small intestine can result in diarrhoea that would resolve only when villous architecture returns to normal and absorptive function is restored. Diarrhoea due to colonic damage would resolve more rapidly. In most instances, diarrhoea can be controlled with drugs such as loperamide, which has significant advantages over diphenoxylate and atropine.

The commonest complication of diarrhoea, depending on severity, is dehydration. The presentation of dehydration in older persons is different to that in younger patients.⁵⁷ The prevention of dehydration and electrolyte loss should be the primary management objective. The treatment of dehydration should centre on oral rehydration in the first instance, though this may be difficult in some older patients who may require intravenous therapy. In almost all cases of dehydration, oral rehydration alone effectively replaces fluid and electrolyte loss. A large (fluid) osmotic load should be avoided, for example Coca-Cola (680 mOsm per kg), apple juice (870 mOsm per kg), orange juice (935 mOsm per kg) and grape juice (1170 mOsm per kg). Commercially available oral rehydration solutions in adequate quantities replenish fluid and electrolyte loss. The duration of a diarrhoeal episode is reduced if nutrients, fluids and electrolytes are available for epithelial cell regeneration when mucosal damage has occurred.⁵⁸

CONCLUSION

Alterations in gastrointestinal function, especially diarrhoea, can significantly affect the quality of life of both an older person and carer. Diarrhoea is a common side effect of many drugs. Given the ever increasing ageing population and the high rates of polypharmacy and altered drug handling in older people, it is important that use of medication in the elderly is constantly reviewed. Pharmacists can play a crucial role, by providing advice regarding the judicious choice and review of medications in older persons and as a valuable source of information on agents that cause diarrhoea.

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Further Reading

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