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Drug-Associated Diarrhoea and Constipation in Older People

2. Constipation

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ABSTRACT

Diarrhoea and constipation are common side effects of many drugs. In older persons, these iatrogenic consequences compound the increased prevalence of acute and chronic illness. An awareness of diarrhoea and constipation as complications of drug therapy in this age group and the use of preventative measures wherever practical may significantly improve 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.

This second part of the review explains the mechanisms of drug-induced constipation and presents examples of drugs commonly associated with this abnormality of bowel function.

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INTRODUCTION

Constipation, perhaps more so than diarrhoea, is a significant problem in older persons. Both constipation and a troublesome consequence, spurious or overflow diarrhoea due to faecal impaction, can seriously affect the quality of life of patients and carers. Unrecognised spurious diarrhoea can result in unnecessary investigations that are both expensive and uncomfortable to the patient.

Most instances of constipation in older persons are secondary to drug side effects, rather than an illness altering gastrointestinal tract motility or age-related changes of the gastrointestinal tract.

There is no strict definition of constipation. This reflects the considerable variation in normal bowel habit. Constipation may be described as a chronic condition of over six weeks duration with the passage of hard stools and/or a frequency of bowel action less than three times a week.¹ Some patients may use the term constipation to refer to straining during the passage of stools or a sense of incomplete evacuation (real or imagined). A US study of 209 elderly persons living at home showed that 30 per cent of men and 29 per cent of women reported that they

experienced constipation at least once a month.² This however was not related to frequency of bowel actions but to straining during defecation.

Constipation, Ageing and the Gastrointestinal Tract

The prevalence of constipation is high among the elderly compared with younger people, dramatically increasing after the age of 65 and is a problem in about 60-70 per cent of older persons in long-term care facilities. The increased occurrence of constipation among older persons is not due to a dysfunction of the gastrointestinal tract due to ageing. The human gastrointestinal tract shows no significant or persistent changes in regard to morphology or function due to age.³ There is no conclusive evidence that colonic transit time is altered in older people compared with younger age groups.^{4,5} However, in elderly unwell persons, and particularly in those bed-bound, colonic transit time is prolonged.^{1,5}

The process of stool formation is primarily a colonic function. Digested food in liquid form enters the terminal ileum and the conversion of liquid digested material to solid faeces occurs. Distinct embryological origins reflect the different function between the proximal two-thirds of the transverse colon and the rest of the large intestine in stool formation. The region up to the junction of the proximal two-thirds of the transverse colon develops from the mid-gut and has the primary function of absorbing fluids and electrolytes by non-propulsive contractions between the colonic haustra. These movements are up and down (rather than forward and propulsive). Throughout this area of the colon, continuous fluid absorption results in the progressive formation of solid faeces. In the rest of the large intestine forward propulsive contractions push the now solid faecal mass to the rectum, lubricated by mucus from goblet cells.

Ageing and Drug Handling

As discussed in the first part of this review,⁶ the pharmacodynamics and pharmacokinetics of drug handling in older persons are altered. This reflects the effects of ageing on the kidney and the liver, the major organs of drug clearance. The reduction in glomerular filtration rate,⁷ for example, affects the clearance of morphine-6-glucuronide, the active metabolite of morphine: constipation is a side effect, unless the dose is reduced.⁸ Other diseases common in the elderly, including heart disease, com-

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pound the effects of ageing on renal function. Liver mass and blood flow are decreased with age.⁹ Thus, drugs that rely principally upon hepatic blood flow for their metabolism (i.e. with a high hepatic extraction ratio) like morphine and some tricyclic antidepressants (e.g. desipramine and nortriptyline) have a lowered metabolism and therefore an increased risk of side effects such as constipation.⁸

Aetiology

The aetiology of constipation is extensive. The aetiological factors range from dietary causes to systemic illnesses, metabolic disturbances, cerebrovascular accidents, malignancy and, especially in an ageing population, drug therapy.¹ Chronic laxative use is also associated with constipation.

Idiopathic or simple constipation is the term used when a medical cause cannot be identified. Common remediable causes of idiopathic constipation are insufficient intake of dietary fibre (a predominant cause), inadequate fluid intake, lack of exercise and poor toilet habits. Important and inadequately addressed causes of constipation are habits such as not setting aside a regular and adequate time for going to the toilet and ignoring 'the call to stools'. The high prevalence of constipation in patients newly admitted to hospitals is attributed to having to use toilets in an unfamiliar environment.

Depression, dementia and confusional states are important causes of constipation. In those with cognitive impairment, finding the toilet, especially in unfamiliar surroundings, may be a problem and patients may suppress the urge to defecate. However, the most likely cause in depressed or confused patients is drug related. Confusion is a recognised side effect of many medications, especially benzodiazepines, tricyclic antidepressants, antipsychotics and opioids, and may thus indirectly contribute to constipation in the elderly.¹⁰

In cerebrovascular accidents, depending on the site of the lesion, weakness of the abdominal and pelvic muscles and hypomotility of the large bowel may result in constipation. Constipation may also be due to ignoring the urge to defecate. A variety of spinal cord lesions can lead to an adynamic bowel. These include trauma (e.g. secondary to osteoporotic vertebral crush fractures), malignancy, ischaemia and spinal cord stenosis. In Parkinson's disease, constipation results from prolonged colonic transit and may be worsened by drug side effects. Constipation alternating with diarrhoea should raise suspicion of a malignancy.

DRUG-RELATED CONSTIPATION

While constipation is associated with many illnesses that are common in the elderly, due to the increased use of medications in this population, it may often be drug related. Precise mechanisms by which drugs cause constipation are unknown in many instances, but may occur through direct or indirect effects, discussed below in the context of some commonly implicated agents. Examples of therapeutic agents associated with constipation are shown in Table 1.

Opioid-Induced Constipation

Opioid analgesia is associated with constipation in most patients. It is thought to be dose related and due to significantly extended gut transit times. In long-term

Table 1. Examples of therapeutic agents that cause constipation

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- Opioids e.g. codeine, pethidine, morphine, fentanyl, oxycodone
 - Antacids e.g. calcium and aluminium compounds
 - Antispasmodics e.g. dicyclomine
 - Antidepressants e.g. imipramine, amitriptyline
 - Antipsychotics e.g. clozapine, thioridazine
 - Antiparkinsonian medications e.g. benzotropine
 - Antidiarrhoeal agents
 - Antihypertensives e.g. methyl dopa, clonidine, propranolol, verapamil
 - Anticonvulsants e.g. phenytoin, clonazepam
 - Minerals
 - aluminium e.g. antacids, sucralfate
 - calcium compounds
 - iron compounds
 - lead, arsenic (poisoning)
 - barium sulfate
 - Miscellaneous compounds
 - octreotide
 - polystyrene resins
 - cholestyramine
 - oral contraceptives
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methadone therapy, 58 per cent of patients experience constipation, of varying severity, and some patients may require the use of enemas.¹¹

Opioid-related constipation should be anticipated and preventive measures, dose reduction and laxative therapy considered. Although the exact mechanism of opioid-induced constipation is not fully understood, the mechanisms may be a reduction in motility, a reduction in gastrointestinal secretions, and an increase in intestinal fluid absorption.¹² Some, if not all, of these effects may be mediated by a local effect on the opioid receptors in the gastrointestinal tract, since the use of oral naloxone (an opioid antagonist) alleviates opioid-induced constipation without loss of analgesic effects.¹³

Anticholinergic Effects

Drugs with inherent anticholinergic effects are commonly implicated in causing constipation. Included in this category are some antiparkinsonian drugs (e.g. benzotropine), tricyclic antidepressants and antipsychotic agents. These drugs antagonise acetylcholine resulting in decreased intestinal tone and motility. Of the tricyclic antidepressants, the tertiary amines (e.g. imipramine, amitriptyline, clomipramine) may have the greatest anticholinergic effects, while the phenothiazines (predominantly thioridazine) have the most potent anticholinergic effect of the antipsychotics.¹⁴ Clozapine, a newer generation antipsychotic is increasingly recognised as a prominent cause of constipation.^{15,16}

Fluid Balance

Diuretics can vicariously cause constipation due to fluid loss. Restriction in fluid intake in patients with cardiac failure, ascites or undergoing dialysis can cause constipation. Bulking agents in the absence of sufficient oral fluids may also promote constipation. A judicious balance between fluid intake and output is crucial to prevent constipation.

Other Mechanisms

Verapamil, a calcium channel blocker, commonly causes constipation. The exact mechanism is unknown. Some evidence suggests verapamil increases transit time in the colon, resulting in an increase in fluid absorption due to the increase in mucosal contact time, causing constipation.¹⁷

Vincristine, a cytotoxic vinca alkaloid, is invariably associated with constipation. Other gastrointestinal side effects are an adynamic ileus, megacolon and abdominal pain.¹⁸ Vincristine may damage the autonomic nervous system and/or the enteric nervous system (the myenteric plexus or Auerbach's plexus, a nerve plexus located between the longitudinal and circular muscular layers of the intestine) resulting in disordered gastrointestinal function.¹⁹

Aluminium containing antacids may cause constipation, via the astringent effect of aluminium, and can result in intestinal obstruction in high doses.²⁰ Stimulant laxative abuse (via loss of smooth muscle tone and contractility),²¹ and overuse of antidiarrhoeal agents may also cause constipation.

COMPLICATIONS

An important consequence of constipation is continued fluid absorption from stools which then leads to faecal impaction. Faecal impaction in turn can result in overflow diarrhoea, also known as spurious diarrhoea. Spurious diarrhoea is caused by faecal impaction, but may be the presenting complaint masking constipation.²² It is a common problem in the elderly and amongst elderly persons in institutional care, approximately 10 per cent experience this problem at least once a week.²³ The prevalence is 42 per cent in geriatric wards.²⁴

Another consequence of faecal impaction is distension of the rectum and pelvic floor that may cause parasympathetic inhibition of the bladder resulting in urinary retention. Appropriate measures should be taken to treat this and also prevent its recurrence.

MANAGEMENT

In the management of constipation, simple measures to initially follow are increased fibre and adequate fluid intake, exercise and eliminating a drug-associated cause. At least 1.5 L of fluid a day should be consumed. Ensuring adequate intake of fluid is especially important in older people because the efficiency of thirst mechanisms decreases with age.²⁵ Laxatives should be introduced if these simple measures fail. Bulk-forming laxatives should be the mainstay of treatment. If these compounds are not effective, an osmotic agent such as sorbitol, 20-30 mL up to four times a day could be used. If constipation is still not resolved, the aetiology should be carefully reviewed. It is important to determine if faecal impaction is present. Appropriate additional agents are suppositories in the first instance, and if they are ineffective, then enemas should be considered.

Recent approaches to treat constipation are the use of drugs in which diarrhoea is a prominent side effect. Colchicine, in an oral dose of 0.5 mg three times daily, has been effective in treating chronic refractory constipation.²⁶ However, the drug is associated with significant side effects, and extreme caution would have to be exercised so that patients do not take increasing doses to deal with the refractory constipation. Fatal outcomes

are possible even with colchicine doses less than 0.5 mg/kg.²⁷ Colchicine acts by increasing motility, intestinal secretion and prostaglandin secretion.

Misoprostol has also been advocated for use in constipation.²⁸ The drug acts by increasing intestinal motility and increasing fluid secretion in the lumen of the intestine.^{28,29} The recommended dose is 1200 µg per day. Treatment with cisapride increases stool frequency in patients with chronic constipation.³⁰ This prokinetic agent facilitates or restores motility throughout the length of the gastrointestinal tract.

CONCLUSION

The ever increasing ageing population and the high rates of polypharmacy and altered drug handling in older people increases the potential for drug side effects such as constipation. Exercising drug prescribing vigilance avoids this common problem. Information for patients on the potential side effect of constipation flags to the patient that a beneficial medication could have an inconvenient side effect. Instead of seeking or consuming further treatment for constipation in the first instance, the solution may lie in dose adjustment or an alternative medication.

The promotion of initiatives to prevent constipation is important. Simple factors within the control of the patient are a high fibre diet, adequate fluid intake, exercise and regular toilet habits, and especially not deferring the urge to defecate. Laxatives should be used cautiously and judiciously. Pharmacists have a crucial role to play in educating medical practitioners on appropriate choices to avoid inconvenience to older patients. Patient education is equally essential to avoid constipation, a common problem in older persons.

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