Today's Treatment

Diseases of the alimentary system

Gastrointestinal reactions to drugs

ALEX PATON

British Medical Journal, 1976, 2, 1179-1180

By the nature of things few drugs can be entirely free from gastrointestinal side effects, and a glance at the lists of adverse reactions prepared by the Committee on Safety of Medicines¹ will show the impossibility of producing a comprehensive account. The task is somewhat simplified by the fact that relatively few drugs are constant offenders (see table), but the occurrence of new or unexpected gastrointestinal symptoms during the course of treatment should always be viewed with suspicion. Symptoms such as nausea, anorexia, dyspepsia, and diarrhoea are so common that they are all too easily attributed to the illness rather than to the drug.

Although some side effects are dose-related, most depend on the sensitivity of the host. This may vary from time to time so that the fact that a particular drug may not have caused trouble on a previous occasion does not ensure its safety. As with all side effects the spectrum of gastrointestinal sensitivity ranges from the person who reacts to a single dose of a drug such as paracetamol that is normally well tolerated, to the patient who, for example, never experiences dyspepsia even with large doses of corticosteroids. While, obviously, drugs that are taken by mouth might be expected to cause gastrointestinal side effects, there is no guarantee that the latter will be avoided by using alternative routes of administration.

Pre-existing disease, such as peptic ulceration, ulcerative colitis, and cardiac failure may predispose to side effects, as may intrinsic defects of the gastrointestinal tract such as gastric atrophy, coeliac disease, and changes brought about by aging.

The following selective account is confined to therapeutic substances, but it should not be forgotten that both nicotine and alcohol produce deleterious effects on the gut.

The mouth

Most people know that iron and tetracycline may discolour the teeth, but it may not be generally realised that other antibiotics have

been reported to do so, as has sodium cromoglycate. Similarly, the effect of phenytoin on the gums is familiar to every medical student, but many other drugs—for example, oestrogens—may be associated with gingivitis. Dryness of the mouth, stomatitis, and glossitis are also common, especially with psychotropic drugs, hypotensive agents, beta-blockers, and antibiotics. Ampicillin and co-trimoxazole may cause ulceration, as may phenylbutazone, and metronidazole is particularly apt to produce glossitis.

Nausea and vomiting

Six pages of the Committee on Safety of Medicines report¹ are devoted to records of nausea and vomiting. The well-known propensity of opiates to cause vomiting is shared by the newer analgesic compounds—notably, dihydrocodeine, pentazocine and dextropropoxyphene—and by anti-inflammatory drugs. Other substances that are particularly prone to produce nausea and vomiting are anti-Parkinsonism drugs including levodopa, oestrogens and progestogens, cytotoxic agents, bromhexine, and potassium chloride. Of the chemotherapeutic agents, ampicillin, tetracycline, erythromycin, co-trimoxazole, nitrofurantoin, nalidixic acid, and metronidazole are particular offenders. Nausea is the earliest symptoms of digitalis intoxication.

Dyspepsia

Indigestion may go unremarked because it is so common, and with a new drug the relation may not be immediately appreciated. A causative connection between aspirin and dyspepsia is now generally accepted; less so the possibility of acute gastrointestinal haemorrhage, as opposed to chronic blood loss. The rare gastrostaxis is probably a genuine hypersensitivity reaction. It does not seem possible to answer the question whether aspirin has anything to do with perforated peptic ulcer. Most doctors believe that aspirin compounds are potentially dangerous in people with pre-existing oesophagitis, varices, or peptic ulcer. It is necessary only to hold an aspirin tablet against the buccal mucosa until it dissolves to show the harmful effect it has even on normal mucosa.

All compounds containing aspirin are potentially harmful, and the newer formulations have not completely overcome the hazard. It is not always appreciated how many proprietary preparations contain aspirin,² some promoted for the relief of indigestion. Paracetamol is safer but weaker and not entirely free from causing dyspepsia and gastrointestinal bleeding. The most dangerous of the anti-inflammatory drugs are undoubtedly phenylbutazone and indomethacin, but they are by far the best anti-inflammatory agents. This seems to be a general correlation: ibuprofen, for example, the least potent of the group, is associated with the least side effects. Of the newer drugs, naproxen already has a reputation for causing gastrointestinal haemorrhage and I would expect it to be a powerful pain reliever.

The gastric dangers of corticosteroids are too well known to need detailed description. The giant ulcer on the greater curve of the stomach is the classical lesion, but any syndrome from hyperacidity and oesophageal reflux to duodenal ulceration may be met with. Dyspepsia occurs with all types of corticosteroids; is to some extent dose-related though still dependent on individual sensitivity; is more likely in people with previous ulcer histories (though this is not necessarily a

Drugs commonly associated with gastrointestinal symptoms

Benzodiazepines	Hypotensive agents	Corticosteroids
Antidepressants	Beta blockers	Oestrogens and progestogens
Appetite suppressants	Digitalis	Oral hypoglycaemic agents
Opium derivatives	Diuretics	Antibiotics
Synthetic analgesics	Theophyllin derivatives	Sulphonamides
Aspirin	Bromhexine hydrochloride	Metronidazole
Anti-inflammatory agents	Iron, calcium, and potassium salts	Cytotoxic agents
Anticholinergic drugs		
Anti-Parkinsonism drugs		

Dudley Road Hospital, Birmingham B18 7QH

ALEX PATON, MD, FRCP, consultant physician

contraindication to its use); and is said to be commoner in patients with rheumatoid arthritis. Formulations of corticosteroids with drugs like aspirin and phenylbutazone are particularly dangerous.

Various measures can be taken to avoid dyspepsia with these and other drugs. Paracetamol is widely used as an alternative to aspirin but needs to be given in larger doses. Dextropropoxyphene and ethoheptazine, popular for the relief of moderate pain, may also be safer but are not entirely free from side effects. The routine use of alkalis when the more powerful anti-inflammatory drugs or corticosteroids are being used has been recommended; some drugs—for example, phenylbutazone—can be obtained with alkali incorporated. Enteric-coated preparations of aspirin, phenylbutazone, and prednisolone are available, but are considerably more expensive and may cause trouble in the small bowel where they dissolve; they should be reserved for patients known to be sensitive to the ordinary preparations. Serious confusion has resulted from failure to appreciate that enteric-coated prednisolone tablets are only half the strength of the usual prednisolone. Suppositories of indomethacin are widely used, but even this route does not entirely avoid dyspepsia, and a local proctitis may follow long-continued use. Parenteral administration of corticosteroids or corticotrophin does not prevent gastric side effects, adding weight to the view that their action is not solely a local one. Tablets of all these drugs should, of course, be taken with food.

Alterations in bowel habit

We tend to forget that many commonly used drugs may affect the bowels. Magnesium trisilicate is a powerful laxative, while aluminium salts are constipating. Hypotensive drugs often constipate, though guanethidine and methyldopa may cause diarrhoea. Antibiotics of all sorts are apt to loosen the bowels, and serious forms of enterocolitis (pseudomembranous colitis) often with bacterial superinfection have followed the use of newer drugs such as clindamycin and lincomycin, though they were not unknown with previous broad-spectrum antibiotics. Less threatening forms of diarrhoea probably result from alteration of the bowel flora, and fungal infection may supervene. Purgative abuse, with characteristic appearances on barium enema examination and sometimes an Addisonian-like picture, should always be considered as a cause of unexplained diarrhoea.

Anti-inflammatory agents, especially the fenamic acid derivatives, appetite suppressants, and sex hormones may all cause diarrhoea, as may digitalis and diuretics. Digitalis can also produce a syndrome resembling mesenteric occlusion, with pain and bloody diarrhoea, especially in the elderly, while thiazide diuretics have been reported to induce an allergic vasculitis affecting the small bowel. Salts of iron, calcium, and potassium have an irritant effect on the bowel. Enteric-coated potassium chloride had a predilection for causing ulceration of the small bowel, usually manifest as obstruction, but occasionally as perforation or haemorrhage. This effect is said to have been abolished by the introduction of slow-release tablets, but these may still cause similar lesions—for example, in the oesophagus—as a result of hold-up.

Steatorrhoea has been observed after the use of drugs, some predictable, like neomycin, cholestyramine, and cytotoxic agents, others less so, such as phenindione, para-aminosalicylic acid, and mefenamic acid. Some drugs interfere with the absorption of essential factors such as vitamin B₁₂ and folic acid.³

Constipation may be a problem with opiates, psychotropic drugs, anticholinergic agents, hypotensives, and iron. Ileus has been reported with some of these, especially antidepressants; and perforation is a particularly dangerous complication of corticosteroid treatment, since symptoms are often masked by the drug.

Envoi

A great deal of discomfort and much needless investigation might be avoided if we were always to consider the possibility of drugs being the cause of a patient's gastrointestinal symptoms.

References

- ¹ Committee on Safety of Medicines, *Register of Adverse Reactions*, vol III. London, Department of Health and Social Security, 1974.
- ² Banks, C N, and Baron, J H, *Lancet*, 1964, 1, 1165.
- ³ Clark, F, *Adverse Drug Reaction Bulletin*, 1976, 57, 196.

Letter from . . . Chicago

Trichology needs help

GEORGE DUNEA

British Medical Journal, 1976, 2, 1180-1182

That trichology has come of age as a highly organised medical-surgical specialty is attested by the lady who in a raffle at the school fair won a \$50 certificate for "trichology, analysis, cutting, and blow dry." Ushered into an elegant salon with bright walls and loud music, she noted how the clients were mostly young, very thin and chic, and wearing \$300 slacks and Christian Dior T-shirts; and how the trichologists, mostly men, were also slim and fashionable, with tightly fitting trousers, open neck shirts, and turquoise necklaces. An assistant met her,

brought coffee, explained he would co-ordinate the various phases of the treatment (? primary-care trichologist), and then summoned the analyst, a formidable lady in a black coat followed by a docile looking assistant.

The analysis begins with the history: name, address, How often do you wash your hair? What shampoo do you use?—and the data are carefully entered in the personal record. Then without warning the assistant starts painlessly to break off strands of hair from different areas of the scalp. These she hands to the analyst who inserts them upright into the hair-analysis machine. Lights flash, the machine rumbles, the analyst studies some graphs and looks worried: "I am getting a very bad pH reading," she says. She tries another hair, looks at the graph again, "Oh dear, the reading is still pretty bad. What kind of shampoo are you using?" she asks—obviously it is not the right one. Then comes the elasticity test; and again the readings are bad. "What kind of water do you use; it must have plenty of

Cook County Hospital, Chicago, Illinois
GEORGE DUNEA, MB, MRCP, attending physician