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The Adverse Drug Reaction in the Gastrointestinal Tract: An Overview

[1]Molouk Hadjibabaie, [2]Noushin Rastkari, [2]Ali Rezaie and [2]Mohammad Abdollahi
[1]Department of Clinical Pharmacy, [2]Department of Pharmacology and Toxicology,
Faculty of Pharmacy and Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences, Tehran, Iran

Abstract: Every drug can produce untoward consequences, even when used according to standard or recommended methods of administration. Adverse drug reactions can involve every organ and system of the body and are frequently mistaken for signs of underlying disease. Similarly, gastrointestinal tract can be affected by many drugs or chemicals. Regarding different parts of this system, these reactions can be categorized to colon, esophagus, esophagus-stomach, large intestine, liver, oral cavity, pancreas, peritoneum, rectum, small intestine, stomach, and stomach-duodenum. In this study, the drugs that may cause adverse effects in the gastrointestinal tract are reviewed. The knowledge about drug-induced gastrointestinal adverse effects helps health professionals to conduct a better practice in diagnosis of gastrointestinal tract diseases, drug administration, improvement of patients' compliance during drug therapy and may influence a more rational use of drugs.

Key words: Gastrointestinal tract, adverse drug reactions

INTRODUCTION

Adverse drug reactions in general: Adverse drug reactions (ADRs) remain a major clinical problem. There are differences between populations in the occurrence of ADRs and other drug-related problems. This may be due to differences in drug production, in distribution or use, in genetics, diet and traditions of people, in the composition, excipients or pharmaceutical products and finally traditional local remedies. A meta-analysis suggested that in the USA in 1994, ADRs were responsible for more than 100000 deaths[1], making them the fifth commonest cause of deaths. In addition there is evidence that ADRs account for 5% of all hospital admissions[2] and increase the duration of hospitalization by two days at compelling an additional $ 2500 cost per patients[3]. Different types of ADRs particularly with regard to frequency, manifestations or mechanisms may need different methods of detection[4]. From a clinical perspective, ADRs can be divided into two broad types, type A and type B[5]. Type A reactions are predictable from the known pharmacology of the drug and often represent an exaggeration of the known primary and/or secondary pharmacology of the drugs. By contrast, type BADRs are bizarre reactions that are unpredictable from the known pharmacology of the drug and show no apparent dose-response relationship. Typically, type A ADRs have been labeled as host independent. Clearly, this is an over simplification because there is now increasing evidence for a role for genetics in the determination of drug disposition and drug response and thus, susceptibility to ADRs. Type A effects can usually be produced and studied experimentally, and are often already identified before marketing. With type A effects of low specificity, quantitative and controlled assessment may be needed in order to confirm the relationship and measure the frequency. Type B effects are either immunological or non-immunological and occur in patients with often unidentified, predisposing conditions. Besides type A and B some adverse drug effects may be categorized as type C. Type C effects refer to situations where the use of a drug, often for unknown reasons, increases the frequency of a spontaneous disease. Type C effects may be both serious and common (and include malignant tumors) and may have pronounced effects on public health. Type C effects may be coincidental and often concern long term effects; there is often no suggestive time relationship and the connection may be very difficult to prove[6,7].

Corresponding Author: Professor Mohammad Abdollahi, Department of Toxicology and Pharmacology,
Faculty of Pharmacy and Laboratory of Toxicology, Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences, Tehran, Iran Tel/Fax: +98 21 6959104
E-mail: mohammad.abdollahi@utoronto.ca

Etiology, pathogenesis and clinical features of gastrointestinal adverse drug reactions: Virtually any drug has the potential to cause an untoward reaction, but some have a greater ability to do so than others. The gastrointestinal tract is a common site of adverse drug reactions resulting from the fact that most drugs including prescription and over the counter drugs are administered by this route[8]. In USA, the gastrointestinal tract has been associated with 20 to 40% of the drug-induced adverse effects[9]. Pathogenesis of drug reactions may be related to either immunologic or non-immunologic mechanisms. Most adverse reactions to drugs are mediated by the immune system and are drug allergies. Three mechanisms have been proposed for drug allergies. Firstly, IgE-mediated reactions occur when the drug reacts with IgE antibodies bound to mast cells. Secondly, drug allergies can involve a cytotoxic reaction in which an antibody binds to a drug that is already attached to a cell surface. The third mechanism in a drug allergy involves circulation of the antigen for extended periods allowing sensitization of the patient's immune system and production of a new antibody. Non-immunologic drug reactions are not antibody dependent and may directly affect mast cells causing the release of chemical mediators. Also some non-immunologic drug-induced reactions result from a drug overdose or toxicity. The adverse reactions that cause pathological changes (e.g. mucosal ulceration and stricture) should be differentiated from those that do not. Many gastrointestinal side effects like nausea, vomiting, diarrhea, constipation or abdominal cramps are transient and resolve shortly after the drug is discontinued. Patients should be alerted to the early signs of gastrointestinal disorders, in order to prevent long-term complications. Manifestations of drug reactions are dependent on the type of drug, drug dose, and individual patient differences. These reactions can be seen either rapidly or several days after drug use. They are usually transient and disappear after discontinuation of drug but there are some drugs that induce serious adverse effects[10].

Diagnosis of adverse drug reactions: The diagnosis of drug reactions requires a high index of suspicion and careful history taking.

Recent use of a drug is important. Withdrawal of the suspected drug should result in improvement and reinstitution of the drug should exacerbate the patient's condition. The clinical expression of lesions in drug reactions is generally allergic in nature that can help with the diagnosis[7].

Oral cavity: Drug induced oral cavity disorders include taste disturbance, xerostomia (dry mouth), oral lesions and gingival enlargement[11] (Table 1). The mechanism

Table 1: Drugs with potential to cause adverse reaction in oral cavity[17]

Drug name	Reported adverse effect
Antiarrhythmics	Xerostomia
Anticholinergics	Xerostomia
Antihistamines	Xerostomia
Antihyperlipidemics	Xerostomia
Antiparkinson drugs	Xerostomia
Antispasmodic drugs	Xerostomia
Antiulcer agents	Xerostomia
Calcium channel blockers	Gingival enlargement
Carbamazepine	Oral lesion
Coronary vasodilators	Xerostomia
Cyclosporine	Gingival enlargement
Diuretics	Xerostomia
NSAIDs	Oral lesion
NSAIDs	Xerostomia
Penicillins	Oral lesion
Phenytoin	Gingival enlargement
Psychotropic drugs	Xerostomia
Sulfonamides	Oral lesion
Trimethoprim-sulfamethoxazole	Oral lesion

Table 2: Drugs with potential to cause adverse reaction in the esophagus[19-28]

Drug name	Reported adverse effect
Alendronate	Esophagitis
Anticholinergics	Gastroesophageal reflux disease (GERD)
Anticholinergics	Reflux of acid
Broad-spectrum antibiotics	Fungal infection
Busulphan	Esophageal varices
Calcium channel blockers	GERD
Chlormethiazole	Dysphagia
Clindamycin	Esophageal ulceration
Clorazepate	Esophageal ulceration
Doxycycline	Esophageal ulceration
Emepromium bromide	Esophageal ulceration
Ethanol	GERD
Iron	Esophageal ulcer
Nitrates	GERD
NSAIDs	Esophageal ulceration
Opiates	Reflux of acid
Phenoxymethylpenicillin	Esophageal ulceration
Potassium chloride	Esophageal ulcer
Potassium chloride	Esophageal ulceration
Progesterone	GERD
Propranolol	Esophageal spasm
Quinidine	Esophageal ulcer
Rabeprazole	Dysphagia, esophagitis
Salicylates	Esophageal ulcers
Tetracycline	Esophageal ulcer
Tetracycline	Esophageal ulceration
Theophylline	GERD
Thioguanine	Esophageal varices
Tricyclic antidepressants	GERD
Vitamin C	Esophageal ulcer

Table 3: Drugs with potential to cause adverse reaction in the esophagus-stomach[29]

Drug name	Reported adverse effect
Bromocriptine	Nausea, vomiting
Cisplatin	Vomiting
Digitalis glycosides	Nausea, vomiting
Erythromycin	Nausea
Estrogens	Nausea, vomiting
Iron	Nausea
Levodopa	Nausea, vomiting
Mesalamine (delayed-release)	Nausea, vomiting
Opioids	Nausea, vomiting
Potassium	Nausea
Rabeprazole	Nausea, vomiting
Serotonin selective reuptake inhibitors (SSRI)	Nausea
Sucralfate	Nausea, vomiting

Table 4: Drugs with potential to cause adverse reaction in the peritoneum[30]

Drug name	Reported adverse effect
Methylperdnisolone	Susceptibility to infective peritonitis
Metoprolol	Peritonitis
Oxprenolol	Peritonitis
Practolol	Peritonitis
Timolol	Peritonitis

Table 5: Drugs with potential to cause adverse reaction in the liver[34-49]

Drug name	Reported adverse effect
Acetaminophen	Acute liver failure
Allopurinol	Mixed cholestatic injury
Amiodarone	Acute hepatitis
Androgenic steroids	Canalicular cholestasis, dilation of sinusoids
Azithromycin	Intrahepatic cholestasis
Balsalazide	Abnormality in hepatic function, SGOT and SGPT increase
ß-carotene	Cholestasis
Bromfenac	Acute liver failure
Carbamazepine	Hepatotoxicity, neonatal (cholestasis, jaundice)
Celecoxib	Acute cholestasis
Chlorpromazine	Cholestasis, scattered focal areas of necrosis
Ciprofloxacin	Prolonged cholestasis
Clarithromycin	Progressive cholestasis
Co-amoxyclav	Cholestasis, hepatocellular or mixed
Erythromycin	Cholestasis, mixed cholestatic-cytotoxic injury
Gatifloxacin	Hepatic injury
Gliclazide	Exacerbation of underlying liver disease
Halothane	Centraxonial necrosis, steatosis, massive necrosis
Isoniazide	Hepatotoxicity
Itraconazole	Hepatic injury
Labetolol	Acute H-cell injury
Lamotrigine	Hepatic injury
Mercaptopurine	Cholestasis with fatty hepatic necrosis
Mesalamine (delayed-release)	Hepatotoxicity (rare)
Methimazole	Cholestasis
Methotrexate	Hepatotoxicity
Methronidazole	Severe H-cell necrosis and cholestasis
Methyldopa	Cytotoxic injury, subacute necrosis, rare cholestasis, chronic active hepatitis
Minocyclidine	Chronic hepatitis
Mirtazapine	Hepatotoxicity
Nefazodone	Hepatotoxicity
Nicotinic acid	Hepatic necrosis, cholestasis
Nitrofurantoin	Mixed cholestatic-cytotoxic injury, chronic active hepatitis
NSAIDs	Cholestasis, cytotoxic or mixed
Octreotide	Hepatitis (rare), fatty liver (rare)
Oxacillin	Anicteric hepatitis
Paroxetine	Reversible hepatic injury
Phenytoin	Submassive necrosis, lobular hepatitis, cholestatic hepatitis, granulomatous hepatitis
Pioglitazone	Jaundice
Propafenone	Acute cholestasis
Rifampin	Hepatotoxicity
Salicylates	Focal necrosis, steatosis
Statins	Hepatic injury
Sulphonamides	Mixed hepatocellular injury, subacute hepatic necrosis with cirrhosis, chronic active hepatitis, granulomatous hepatitis
Terbinafine	Cholestasis, necrosis
Triazolam	Fulminant hepatic failure
Troglitazone	Hepatocelular, cholestasis
Trovafloxacin	Hepatotoxicity
Valproic acid	Microvesicular steatosis, focal or massive

of action of drug-induced taste disorder is not known but in the elderly includes a distorted (dysgeusia) or a reduced (hypogeusia) sense of taste[12]. After discontinuation of the drug, changes in the sense of taste are usually reversible, even though it may take several months to get resolved[13]. Drug-induced xerostomia is reversible and usually do not cause permanent damage to the salivary glands but can affect patient's nutritional status[14]. For example drug-induced oral lesions in erythema multiforme makes eating difficult for the patient. Gingival enlargement is an overgrowth of the periodontal tissue which in severe cases, the gingiva can cover almost the entire tooth. It happens when the drug is not discontinued[15,16].

Esophagus: Drug-induced esophageal changes (Table 2 and 3) is common and result from changes in motility, changes in mucosal integrity, infection secondary to drugs and obstruction due to formation of a mass of congealed material[18]. The severity of drug-induced esophageal damage can range from mild, asymptomatic inflammation to severe ulceration and stricture formation. Drugs that impair the function of lower esophageal sphincter can produce symptoms of gastroesophageal reflux. The factors that can influence the severity of drug-induced changes to the esophagus include chemical and physical properties of the drug, delay in transit time of the drug and duration the drug is in contact with esophageal mucosa. Almost 100 different drugs can cause esophageal injury. The best management for drug-induced esophageal injury is the discontinuation of the causing drugs.

Peritoneum: The peritoneum is the epithelial lining of the abdominal and pelvic cavities and supports and covers the organs within it. The part of the membrane lining the abdominal cavity is called the parietal peritoneum and the portion lining the internal organs is known as the visceral peritoneum. A serious medical condition called peritonitis occurs when the peritoneum becomes infected. Certain drugs, can cause adverse reaction in the peritoneum (Table 4).

Liver: Many drugs cause liver injury (Table 5). Adverse effects of drugs on the liver can be presented by increasing of serum aspartate and alanine aminotransferases, serum alkaline phosphatase, gamma-glutamyl transferase, or bilirubin to more than double their normal values. Most drug-induced liver disease occurs in adults rather than in children[31-33]. Hepatotoxicity happens more in female gender. Previous history of adverse drug reaction on liver and multiple drug use are other factors that can increase the risk of drug induced liver injury.

Table 6: Drugs with potential to cause adverse reaction in the pancreas[50-59]

Drug name	Reported adverse effect
Amoxapine (overdose)	Pancreatitis
Asparginase	Acute pancreatitis
Azathioprine	Pancreatitis
Balsalazide	Pancreatitis
Carbamazepine	Pancreatitis
Clofibrate	Gallstones, pancreatitis
Cyclophosphamide+doxorubicin+vincristine	Pancreatitis
Didanosine	Pancreatitis
Diuretics (chlorthiazide, furosemide, chlorthalidone)	Pancreatitis
Dolasetron	Pancreas
Ergotamine (overdose)	Ischemic pancreatitis
Erythromycin	Pancreatitis
Gold	Pancreatitis
Lovastatin	Pancreatitis
Mefenamic acid	Pancreatitis
Mesalamine	Pancreatitis
Methyldopa	Pancreatitis
Metronidazole	Pancreatitis
Nitrofurantoin	Pancreatitis
Octreotide	Pancreatitis (rare)
Olsalazine	Pancreatitis
Oral contraceptives	Pancreatitis
Pentamidine	Acute pancreatitis
Piroxicam	Pancreatitis
Procyclidine	Pancreatitis
Rabeprazole	Pancreatitis
Sodium valproate	Pancreatitis
Steroids (large doses)	Pancreatitis
Sulindac	Pancreatitis
Sulphamethizole, sulphasalazine	Pancreatitis
Sulphonamide	Pancreatitis

Table 7: Drugs with potential to cause adverse reaction in the stomach[60-64]

Drug name	Reported adverse effect
Anticholinergics	Delayed gastric emptying
Chemotherapeutic drugs	Vomiting
Chloroquine	Gastric erosion
Dolasetron	Abdominal pain, dyspepsia
Gold	Chronic gastritis
Misoprostol	Abdominal pain
Overdose of sustained release theophylline tab.	Formation of congealed masses
Potassium chloride	Formation of congealed masses
Rabeprazole	Dyspepsia
Steroids (overdose)	Gastric perforation
Sucralfate	Gastric discomfort
Theophylline (overdose)	Gastric perforation

Table 8: Drugs with potential to cause adverse reaction in the stomach-duodenum[29]

Drug name	Reported adverse effect
Anticholinergics	Delay in gastric emptying
Balsalazide	Gastroenteritis
Cisaperide	Increase gastric emptying
Opioids	Delay in gastric emptying
Rabeprazole	Gastroenteritis

Pancreas: Even though drug-induced pancreatic dysfunction is much less than other gastrointestinal adverse effects, but it has been recognized as a complication of many drugs (Table 6). The mechanism of drug-induced pancreatic injury is not always known.

Table 9: Drugs with potential to cause adverse reaction in the small intestine[64-73]

Drug name	Reported adverse effect
5-Fluorouracil	Erosive enteritis
Actinomycin D	Erosive enteritis
Allopurinol	Mucosal damage
Allopurinol	Jejunal mucosal changes, steatorrhea
Anticholinergics	↓small bowel motility, ↓gastric motility
Anticoagulants	Hemorrhage
Anticonvulsants	↓RBC, ↓serum folate
Antiparkinson agents	Dysmotility
Arabinoside	Erosive enteritis
Atropine	Paralytic ileus
Bleomycin	Erosive enteritis
Calcium channel blockers	Dysmotility
Cathartics(large amounts)	Mild steatorrhea
Chlolestyramine	Steatorrhea, malabsorption of fat-soluble vitamins
Colchicine	Mucosal damage
Cytosine	Erosive enteritis
Digitalis glycosides	Haemorrhagic necrosis
Flucytosine	Erosive enteritis
Gold	Panenteritis
Iron tablets	Gangrene of a Meckel's diverticulum
Lithium	Vasculitis
Loperamide	Dysmotility, paralytic ileus
Mesalamine (delayed-release)	Perforated peptic ulcer (rare)
Metformin, phenformin	Impairment of vit. B_{12} absorption, reduction in disaccharidase activity
Methotrexate	Mucosal damage
Methotrexate	Erosive enteritis
Methyldopa	Jejunal mucosal changes, steatorrhea
Neomycin	Mucosal damage
NSAIDs	Ulceration, stricture, perforation
Omeprazole	Enteric infection
Opioids	Dysmotility
Oral contraceptives	Mesentric venous thrombosis
Phenindione	Jejunal mucosal changes, steatorrhea
Phenothiazines	Dysmotility
Potassium tablets	Local lesions, stricture
Purgatives	Steatorrhea
Sodium aminosalicylate	Interference with ileal transport of vit. B_{12}
Sulindac	Diarrhea, abdominal pain
Tetracycline	Impairment the absorption of Ca and Fe, steatorrhea
Tricyclic antidepressants	Dysmotility
Tricyclic antidepressants	Paralytic ileus
Vincristine	Pseudo-obstruction, erosive enteritis
Vincristine	Paralytic ileus
Warfarin	Jejunal hamatomata

Stomach: Nausea and vomiting are common side effects of many drugs that usually happen in the beginning of the therapy. They can be simple adverse effects that would disappear with continuation of use or can be a sign of drug toxicity. Some drugs by affecting the gastric neural and muscular activity can cause the stomach to empty its contents into the duodenum at a slow or fast rate and reduce or increase the rate of gastric emptying. Certain drugs, can cause adverse reaction in the stomach (Table 7).

Table 10: Drugs with potential to cause adverse reaction in the large intestine[74-83]

Drug name	Reported adverse effect
Albendazole	Pseudomembranous colitis
Aluminium hydroxide	Constipation
Anthraquinones (chronic use)	Constipation
Anticholinergics	Constipation
Antimicrobial agents	Diarrhea
Antiparkinson drugs	Constipation
Balsalazide	Aggravation of ulcerative colitis, diarrhea
Broad spectrum penicillins	Clostridium difficile colitis
Calcium carbonate	Constipation
Cephalosporins	Clostridium difficile colitis
Chenodeoxycholic acid	Diarrhea
Cisplatin	Ischemia of colon
Clarithromycin	Pseudomembranous colitis
Clindamycin	Clostridium difficile colitis, vasculitis
Corticosteroids (overdose)	Diarrhea
Danazole	Ischemia of colon
Debrisoquine	Diarrhea
Digitalis (overdose)	Diarrhea
Dolasetron	Constipation
Fluorouracil	Ischemia of colon
Gold	Colitis
Guanethidine	Diarrhea
Isotretinoin	Proctocolitis
Lithium	Constipation
Magnesium	Osmotic diarrhea
Mesalamine (delayed-release)	Diarrhea, colitis flare
Methyldopa	Diarrhea, colitis
Misoprostol	Diarrhea
Nizatidine	Diarrhea
NSAIDs	Colitis
Olsalazine	Diarrhea
Ondansetron	Constipation, diarrhea
Opioids	Constipation
Oral contraceptives	Ischemia of colon
Penicillamine	Colitis
Rabeprazole	Diarrhea, constipation
ß-adrenoceptor blocking agents	Diarrhea
Stimulant laxatives	Cathartic colon
Sucralfate	Diarrhea
Sulphasalazine	Diarrhea
Vasopressin	Ischemia of colon

Table 11: Drugs with potential to cause adverse reaction in the rectum[84-86]

Drug name	Reported adverse effect
Alcohol	Proctitis
Balsalazide	Fecal incontinence, hemorrhoid
Dexamethasone (IV)	Perineal irritation
Ergot suppositories	Anal ulcers
Indomethacin	Proctitis, rectal ulceration
Octreotide	Hemorrhoids
Olsalazine	Rectal discomfort, rectal bleeding
Peppermint oil capsules	Anal burning
Phenybutazone	Proctitis, rectal ulceration
Rabeprazole	Rectal hemorrhage, proctitis

Stomach and duodenum: The adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) have been documented since 1938 and today the toxicity profile of these drugs has been more clear. About 70 million prescriptions have been written each year and 30 billion over the counter (OTC) NSAIDs are sold each year in USA[19]. Elderly patients have increased risk of NSAID-induced gastrointestinal injury due to multiple medical conditions and polypharmacy (Table 8).

Small intestine: Drug induced adverse effects in small intestine (Table 9) include ulceration, hemorrhage, malabsorption, and disordered motility. Drugs that can reduce small bowel motility, as well as gastric motility can cause paralytic ileus. Increased motility throughout the small intestine can lead to diarrhea. Slow release formulations can cause local lesions that may lead to stricture.

Large intestine: Many different drugs can affect colon (Table 10), but the radiographic injury happens in the colon over a longer period of time and the clinical symptoms in compare to upper GI tract are more insidious. Drugs can influence the colon by induction of colitis (antimicrobial colitis, ischemic colitis), ulceration, bleeding and perforation. Drugs that disturb the normal physiologic process which play a role in regulating fluid absorption and secretion and damage the mucosa of the small and large intestine can cause diarrhea[60]. It may be difficult to be precise about the exact site of action in an individual patient. Elderly are susceptible to drug-induced diarrhea because of their age and the number of medications that they use.

Rectum: Some drugs can affect rectum (Table 11) by inducing irritation, ulceration, burning. Proctitis is an inflammatory change of the rectum causing pain, soreness, bleeding, and a discharge of mucus or pus. Proctitis occurs predominantly in adults and males are affected more often than females.

Many drugs can cause gastrointestinal injury and affect patient's nutritional status. Elderly patients need extra attention because of their medical condition and concomitant drug therapy. Since most drug reactions occur within 1 to 2 weeks following initiation of therapy, reactions seen after 2 weeks are less likely to be due to medication use. Some reactions are dependent on dosage or cumulative toxicity. The majority of drug-induced gastrointestinal reactions are moderate in severity. However, severe reactions necessitate rapid withdrawal of the suspected drug. Readministration of the offending drug helps to establish whether the reaction is drug-induced. Reactions after rechallenge may be more severe and therefore, rechallenge should not be performed without medical supervision. The ability to evaluate these issues is necessary to accurately assess client status and prevent situations that compromise client safety. As a final note, rapid progress in pharmacotherapeutics requires clinicians to constantly update their knowledge of drugs used by their patients. Attention must be paid to their toxic and unwanted effects that in many cases may be similar to characteristics of common diseases.

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