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Review Article

Drug-Induced Gastrointestinal Disorders: A Comprehensive Review

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Abstract

Drug-induced gastrointestinal disorders (DIGIDs) present a significant clinical challenge, encompassing a broad range of adverse effects on the gastrointestinal (GI) tract triggered by various medications, such as constipation by anticholinergic drugs. Drugs may also lead to tissue toxicity and damage, as ulcers resulting from non-steroidal anti-inflammatory drugs (NSAIDs). Drugs may disrupt the intestinal microbiota, as seen with antibiotics leading to Clostridium difficile infection. It's worth noting that both the active compound and the additives in the tablet or capsule can contribute to adverse effects. Additionally, symptoms like nausea and vomiting may also be caused by the factors, which are unrelated to the GI tract.

This review also consolidates current insights into the mechanisms, clinical presentations, and management strategies of DIGIDs. The review explores the extensive spectrum of manifestations linked with DIGIDs, spanning from mild symptoms like nausea and dyspepsia to severe complications such as gastrointestinal bleeding, perforation, and pancreatitis. Prompt recognition of these manifestations is essential for timely diagnosis and intervention. Moreover, the significance of identifying risk factors are predisposing individuals to DIGIDs, such as concurrent usage of multiple medications, advanced age, and underlying GI disorders. Approaches to mitigate the gastrointestinal side effects of medications involve strategies such as avoiding or minimizing drug usage, employing the lowest effective doses for the shortest duration possible, considering safer selective COX-2 inhibitors.

Keywords: DIGID; GI; Drug; Diseases; NSAID

Introduction

The gastrointestinal (GI) system consists of two main components: the GI tract and accessory organs. The gastrointestinal (GI) system encompasses a series of interconnected organs responsible for digestion and nutrient absorption, including the mouth, throat, esophagus, stomach, small and large intestines, and anus. Supporting the primary structures of GI, there are additional organs vital for digestion, such as the teeth and tongue, as well as glandular organs like the salivary glands, liver, gallbladder, and pancreas. Together, these components form a complex network that facilitates the processing of food and the extraction of nutrients essential for bodily function. Key functions of the GI system encompass the intake and breakdown of food, absorption of nutrients, secretion of enzymes and fluids, and elimination of waste [1].

No drugs are free from its toxic effects. While some drugs may cause mild side effects, others can lead to more severe consequences. Due to the predominant oral route of medication administration and the intricacies of absorption and metabolism, the gastrointestinal, hepatobiliary, and pancreatic systems are particularly prone to be damaged by drugs [2]. Although the potential gastrointestinal side effects of certain medications are widely acknowledged, others like metformin, antipsychotics, and antidepressants, which are frequently prescribed and can commonly induce gastrointestinal symptoms, may not receive the attention they deserve [3].

Esophagus

Drug-induced esophageal injury often appears as esophagitis, with patients experiencing symptoms like painful swallowing (odynophagia), difficulty swallowing (dysphagia), and chest pain behind the breastbone [4-6]. This condition arises when a drug remains in the esophagus for an extended period, allowing it to dissolve and chemically interact with the mucosal lining [2]. The resulting injury is typically due to a caustic chemical reaction between the drug and the mucosa. For instance, antibiotics such as doxycycline and tetracycline, which are acidic, can cause chemical burns to the esophageal lining [6]. Other medications, like ferrous sulfate and potassium chloride, cause damage through their high osmolarity and effects on local blood flow [5,6]. DIGIDs may involve effects on intestinal microbiota such as the gram-negative bacteria that may lead to the release of toxic bacterial lipopolysaccharides (LPS) that may cause irritable bowel syndrome and various other organ diseases. The use of various medications may need to be assessed to prevent the release of LPS into the gastrointestinal system that may lead to various organ diseases. Plasma LPS levels may need to be monitored with relevance to DIGIDs [7,8].

Stomach

Ulcer mechanism

Drug-induced gastropathy is most caused by nonsteroidal anti-inflammatory drugs (NSAIDs), which are among the most widely prescribed medications globally [2]. The injury mechanism involves a reduction in prostaglandin synthesis. Prostaglandins are crucial for gastric epithelial defense as they promote mucus and bicarbonate secretion and inhibit gastric acid secretion, thus supporting epithelial cell repair and maintaining mucosal blood flow [9-11]. Most conventional NSAIDs inhibit the cyclooxygenase (COX) enzyme responsible for prostaglandin synthesis. COX-1 is a constitutive enzyme essential for maintaining basal mucosal blood flow and pH balance, while COX-2 is an inducible enzyme critical for preserving perfusion during mucosal stress [12]. Inhibition of prostaglandins compromises these defense mechanisms, leading to increased acid and pepsin production, which makes the mucosa more vulnerable to injury [2].

Nausea, being a non-specific symptom, can stem from various sources such as local injury, gastroparesis, or chemical influences on the central nervous system (refer to Box 1). Although drugs that could potentially affect smooth or striated muscle function have been considered to contribute to gastroparesis similarly to their role in dysphagia, there is a notable absence of physiological or clinical substantiation for this theory. This lack of evidence extends to case reports, case series, or drug trials, with the exception being aerosolized atropine, which has demonstrated the ability to prolong gastric emptying [13,14].

Drugs with the potential to trigger nausea and vomiting can be classified based on their proposed mechanisms of action:
Those that lead to tissue damage.
Potassium chloride
Non-steroidal anti-inflammatory drugs (NSAIDs)
Iron supplements.
Chemotherapeutic agents
Those that stimulate chemoreceptors in the central nervous system.
Digoxin
Dopaminergic agents (such as levodopa and bromocriptine)
Opiates

Table a

Small bowel

Mucosal diaphragms

Mechanism

Like the stomach, the proximal duodenum can suffer from the corrosive effects of pepsin and hydrochloric acid when mucosal integrity is compromised, leading to ulceration [15]. NSAIDs are a common cause of drug-induced duodenal ulcers, wall thickening, and inflammation, which can develop into duodenitis and even result in perforation. However, because the rest of the small intestine is not exposed to gastric acid, NSAID-induced gastrointestinal injury involves multiple factors. NSAIDs, being weakly acidic and lipid-soluble, disrupt the phospholipid membranes of enterocytes and interfere with mitochondrial phosphorylation, leading to the breakdown of the mucosal barrier [16-18]. This disruption exposes the epithelium to bile acids, pancreatic secretions, and intestinal bacteria, causing inflammation. Inflamed areas can hemorrhage, develop granulation tissue, and eventually form weblike mucosal strictures. NSAID-induced enteropathy is characterized by thin (typically less than 3 mm) circumferential rings of mucosa that create focal strictures known as mucosal diaphragms [19].

Pneumatosis intestinalis

Mechanism

Pneumatosis intestinalis is a condition where gas accumulates in the wall of the small bowel or colon, with the small bowel being the most affected area. This condition can arise from various causes, ranging from benign to life-threatening. One hypothesis for drug-induced pneumatosis involves the loss of mucosal integrity, which permits intraluminal gas to enter the bowel wall. Certain medications, such as corticosteroids and chemotherapeutic agents, are well-known to be associated with benign pneumatosis. For corticosteroids, the depletion of intramural lymphoid tissue is believed to disrupt the mucosa, allowing gas to dissect into the submucosa. Additionally, the breakdown of the mucosal barrier may permit gas-forming bacteria to infiltrate the bowel wall [20-23]. Intestinal ischemia, a potentially life-threatening cause of pneu-

matosis, can be induced by medications through mechanisms like blood shunting from mesenteric vessels, vasospasm, and thrombogenesis, leading to pneumatosis intestinalis [22].

Colon

Colitis mechanism

Drug-induced injury to the colon most often manifests as colitis. While NSAIDs typically cause damage in the stomach and small bowel, enteric-coated formulations are believed to shift some of this damage further downstream into the colon. A severe form of colitis known as pseudomembranous colitis is characterized by the presence of pseudo membranes on the mucosa, which are visible during endoscopy. This condition frequently arises as a complication of antibiotic therapy, with broad-spectrum antibiotics like cephalosporins, third-generation penicillins, and clindamycin being common culprits. However, all antibiotics, including those used to treat pseudomembranous colitis (metronidazole and vancomycin), can cause it. These antibiotics disrupt the normal intestinal flora, allowing Clostridium difficile, a gram-positive bacterium that forms heat-resistant spores, to colonize the intestine. Once in the colon, these spores activate and produce two exotoxins that cause colonic injury. These enterotoxic and cytotoxic toxins bind to intestinal receptors, compromising mucosal integrity and triggering the release of multiple inflammatory mediators. The resulting inflammation increases capillary permeability, leading to hemorrhage and edema. As the inflammation worsens, ulcers form, accompanied by necrotic debris, resulting in the formation of pseudo membranes, which appear as elevated yellowish-white plaques on the colonic mucosa [2].

Diseases name	Putative mechanisms	Commonly reported drugs
Pill esophagitis	Retention of the pill in the esophagus leading to delayed clearance, localized release of a drug causing caustic injury	Tetracyclines Bisphosphonates Potassium chloride NSAIDs Iron
Gastroesophageal reflux	release of toxic bacterial lipopolysaccharides (LPS)	Intestinal microbiota such as the gram-negative bacteria that may lead to the release of toxic bacterial lipopolysaccharides (LPS) that may cause irritable bowel syndrome and various other organ diseases.
Dysphagia	Restrict the functioning of skeletal muscles	Antipsychotics (dopamine antagonist); often associated with parkinsonism Alcohol
	Prevent the release of LPS into the gastrointestinal system	The use of various medications may need to be assessed to prevent the release of LPS into the gastrointestinal system that may lead to various organ diseases.
	Xerostomia, (commonly known as dry mouth, is a condition characterized by decreased saliva production	Anticholinergics (eg, tricyclic antidepressants, hyoscine, propantheline) Opiates Antipsychotics Antihistamines Clonidine

Table 1: Drugs reported to cause problems in the esophagus, along with their probable mechanisms.

Pancreatitis

Pancreatitis can often be attributed to alcohol consumption, though other drugs can also contribute, albeit less frequently. Among these medications are

- Diuretics such as thiazides, furosemide
- Angiotensin-converting enzyme inhibitors
- Statins
- Sulfonamides
- Azathioprine and 6-mercaptopurine
- Corticosteroids
- NSAIDs
- Sodium valproate
- Exenatide and liraglutide
- L-asparaginase (about 7% of recipients)
- Gliptins
- Immune checkpoint inhibitors (ICI)

Symptom/condition	Medications implicated
Diarrhoea	Metformin Iron supplements Fibrates (less with fenofibrate) Antibiotics (especially amoxicillin-clavulinate) ACE inhibitors β-blockers Angiotensin-2 antagonists Lithium NSAIDs Frusemide Proton pump inhibitors
Constipation	Opiates Anticholinergics Iron Frusemide Levothyroxine Cholestyramine
Inflammatory bowel disease	Antibiotics Oral contraceptives Mycophenolate mofetil Etenercept Ipilimumab Rituximab

Table 2: Substances associated with the development of symptoms or conditions affecting the lower gastrointestinal tract [3].

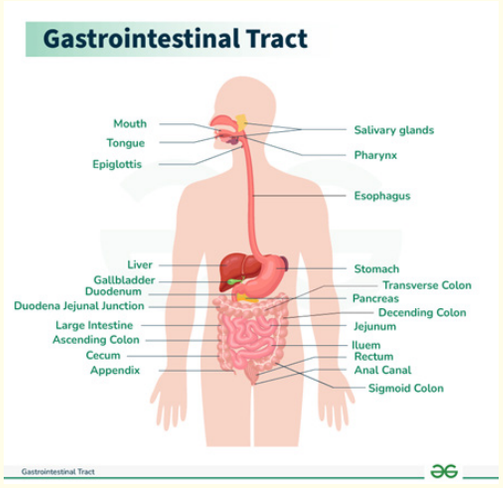

Figure 1: Gastrointestinal system.

Hepatotoxicity

The liver serves a remarkable range of crucial roles in maintaining the body's functions and regulating its internal balance. It participates in nearly all biochemical processes related to growth, immune response, nutrient distribution, energy production, and reproductive functions. Its primary functions encompass carbohydrate, protein, and fat metabolism, detoxification, bile secretion, and storage of vitamins [24]. Hepatotoxicity refers to liver damage caused by chemical substances. Some medicinal drugs, whether taken in excessive doses or even within therapeutic limits, can harm the liver [25]. The drugs which are responsible for hepatotoxicity are

- Anti-tubercular drugs namely, Rifampicin, Isoniazid and Pyrazinamide
- Acetaminophen, Nimesulide, Diclofenac, Ibuprofen are non-steroidal anti-inflammatory drugs (NSAIDs)
- Nucleoside analog reverse transcriptase inhibitors (NRTIs), including Lamivudine (3TC), Tenofovir, Zidovudine, Didanosine, Stavudine, Abacavir (ABC), and Tenofovir (TDF).
- Non-nucleoside reverse transcriptase inhibitors such as Nevirapine, Emtricitabine, and Efavirenz.
- Anti-Hyperlipidemic Drugs such as Statins, Isoflurane, Enflurane, Desflurane
- Anti-Rheumatic Drugs namely, Sulfasalazine and azathioprine
- Anti-Epileptic Drugs (AED) examples, Carbamazepine (CBZ), Valproic acid (VPA), Felbamate, Phenytoin
- Few other drugs also reported to cause hepatotoxicity are Glucocorticoids, Antibiotics (Amoxicillin, Ciprofloxacin, Erythromycin), Oral contraceptives and antifungals (Fluconazole, itraconazole).

Limiting the unfavorable gastrointestinal impacts of medications

To mitigate adverse effects from drug therapy, ensure tablets and capsules are ingested with sufficient fluids to prevent esophageal obstruction. Avoid using modified-release preparations. NSAID toxicity can vary based on drug selection and dosage. When feasible, reduce dosage, administer a PPI, or consider a COX-2 inhibitor. Exercise caution when prescribing PPIs (and H2-receptor antagonists), as gastrointestinal infections should be ruled out if diarrhea occurs. Instruct patients to take medications with meals or snacks to alleviate gastric irritation. Promote adequate hydration to prevent constipation, a common side effect of many drugs. Consider co-prescribing probiotics with antibiotics to maintain gut microbiota balance and lower the risk of Clostridium difficile infection. Implementing these strategies can help healthcare providers mitigate gastrointestinal adverse effects from medications, thereby enhancing patient outcomes and quality of life.

Conclusion

Drug-induced gastrointestinal disorders (DIGIDs) encompass a range of adverse conditions caused by medication usage. DIGIDs

may involve effects on intestinal microbiota such as the gram-negative bacteria that may lead to the release of toxic bacterial lipopolysaccharides (LPS) that may cause irritable bowel syndrome and various other organ diseases. The use of various medications may need to be assessed to prevent the release of LPS into the gastrointestinal system that may lead to various organ diseases. Plasma LPS levels may need to be monitored with relevance to DIGIDs. Tailoring treatment to the individual's needs, closely monitoring for complications, and considering alternative therapies are crucial steps in optimizing outcomes for those affected by DIGIDs. With proper medical care and support, individuals can mitigate symptoms and improve their overall quality of life despite these challenges.

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