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Towards better models and mechanistic biomarkers for drug-induced gastrointestinal injury

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ABSTRACT

Adverse drug reactions affecting the gastrointestinal (GI) tract are a serious burden on patients, healthcare providers and the pharmaceutical industry. GI toxicity encompasses a range of pathologies in different parts of the GI tract. However, to date no specific mechanistic diagnostic/prognostic biomarkers or translatable pre-clinical models of GI toxicity exist. This review will cover the current knowledge of GI ADRs, existing biomarkers and models with potential application for toxicity screening/monitoring. We focus on the current gaps in our knowledge, the potential opportunities and recommend that a systematic approach is needed to identify mechanism-based GI biomarkers with potential for clinical translation.

Contents

Abbreviations: ADR, adverse drug reaction; COX, cyclooxygenase; DILI, drug-induced liver injury; DMTA, design-make-test-analyse; GI, gastrointestinal; iPSC, induced pluripotent stem cell; NSAID, non-steroidal anti-inflammatory drug; VOC, volatile organic compound.

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1. Introduction

Adverse drug reactions (ADRs) involving the gastrointestinal (GI) tract are a significant and frequent problem, creating a major burden to patients, as well as healthcare providers and the pharmaceutical industry (Pusztaszeri, Genta, & Cryer, 2007; Redfern et al., 2010). Drug toxicity to the GI tract covers a multitude of pathologies which reflects the complex physiological, histological and microbiome heterogeneity within this system. Upper gastrointestinal injuries, such as acute gastric erosions, reactive gastritis and peptic ulceration, caused by nonsteroidal anti-inflammatory drugs account for the commonest cause of ADRs in the UK with ~12,000 hospital admissions and 2000 deaths *per annum* (Blower et al., 1997). Lower GI toxicity (often manifested by clinical symptoms such as diarrhea, constipation and abdominal cramps), is a major dose-limiting safety concern for several classes of compounds (Pusztaszeri et al., 2007) including cytotoxic chemotherapeutic agents, targeted cancer therapies such as kinase inhibitors and immune checkpoint inhibitors. The incidence of chemotherapy-induced diarrhea has been reported to be as high as 50–80% of treated patients (Benson et al., 2004) with rates of severe or life-threatening diarrhea up to 30% with some regimens (Stein, Voigt, & Jordan, 2010). A recently approved selective, oral phosphatidylinositol 3-kinase delta inhibitor (idelalisib), for the treatment of several types of leukaemia and lymphoma, is associated with severe GI toxicity [6] and contains a black box warning in the US prescribing information for fatal and/or serious and severe diarrhea or colitis. Furthermore, T cell activation with systemically-administered immune checkpoint inhibitors of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death-1 (PD-1), for use in melanoma and other solid tumours, has been shown to result in GI adverse events including diarrhea and colitis and in rare cases, bowel perforation(Villadolid & Amin, 2015). However, if identified early, the GI-related adverse events can be reversible, or clinically manageable.

Diarrhea is also common in patients receiving oral small molecule tyrosine kinase inhibitors, such as erlotinib, lapatinib and sorafenib with an occurrence of between 30–60% for all grades of diarrhea (Stein et al., 2010) and is dose-dependent, although it is unknown whether the effects are associated predominantly with luminal or systemic exposure.

Diarrhea is thus a major cause of treatment discontinuation and decreased drug efficacy and is likely to affect the pharmacokinetics of oral dosage regimens. Despite the importance of drug-induced GI toxicity, there are substantial gaps in our knowledge of the mechanisms and pathogenesis. Given the novelty of targets which are being pursued particularly in cancer, we need to be cognisant of the possibility of novel mechanisms as has recently been shown for dasatinib, where decreasing immune tolerance against intestinal microflora (Eskazan, Hatemi, Ongoren Aydin, Ar, & Soysal, 2014) or an autoimmune etiology (Villadolid & Amin, 2015) has been implicated.

Pre-clinical safety assessment of new medicines does provide some degree of prediction of human toxicities, albeit that this varies with site of toxicity (*e.g.* prediction of liver and skin toxicity is worse than that for haematological, cardiovascular and GI toxicity) and the class of compounds being evaluated. Furthermore, a combination of rodent and non-rodent models (usually dog and non-human primate) is better than rodent models only (Olson et al., 2000). The availability of robust mechanism-based biomarkers and better pre-clinical (*in vitro* and *in vivo*) models would certainly help in translation to clinical applications. Mechanistic biomarkers are markers embedded in the pathogenesis of the toxicity and can therefore be considered more informative and more accurately reflect the underlying pathology. By contrast, monitorable biomarkers are usually by-products and often surrogate markers of the pathophysiological process. Mechanistic biomarkers, however, are considered more challenging to develop into validated clinically utilisable tools for safety monitoring.

This review discusses approaches to developing better *in vitro* models and mechanistic biomarkers for gastrointestinal injury and seeks to identify areas where collaborative efforts should be focused from the perspective of all stakeholders (pharmaceutical and biotechnology companies, contract research organizations, regulatory agencies and academia). Principally, the following specific points and themes are addressed:

- What pathologies come under the banner of GI toxicities and what do we understand about mechanisms in different parts of the GI tract and determinants of severity?
- What areas of GI toxicity (upper/middle/lower GI tract) are particular problems in drug development for the industry?
- What lessons can be learned from industry case-studies and existing paradigms of GI toxicity to inform ongoing research and development?
- Do we have validated *in vitro*/*in vivo* models to identify mechanisms based on pathologies?
- What *in vitro*/*in vivo* tools need to be developed for further understanding of mechanisms and translation?
- How does the pharmaceutical industry foresee using these tools for decision making?

2. Clinical problem and disease burden

The term "gastrointestinal toxicity" can be considered to encompass a great many pathologies affecting a number of different tissues and organs which constitute the GI tract. GI toxicity can manifest in a number of ways including: nausea/vomiting, intestinal inflammation, ulceration/perforation, altered fecal output and abdominal discomfort/pain. These symptoms do not necessarily imply toxicity involving a specific organ/region of the GI tract and are non-specific, arising as a result of a number of other non-drug-related conditions. The route of administration can have a bearing on the risk profile of drugs associated with GI toxicity and indeed many pathologies can be directly attributable to oral administration (*e.g.* aspirin) and consequent direct GI exposure. However, it should be pointed out that there are a plethora of examples of i.v. administered drugs that cause GI toxicity though systemic exposure (*e.g.* chemotherapeutics such as 5-fluorouracil (Lee, Ryan, & Doherty, 2014)).

2.1. Upper gastrointestinal tract

Given its function to rapidly transit ingested substance into the stomach, exposure of the esophagus to drugs is often only momentary. Thus, toxicity to the esophagus only occurs when the passage of drugs is interrupted and a toxic substance is left in contact with the mucosa long enough to induce damage. This is often referred to as "pill oesophagitis" and can sometimes also result in ulcer formation. Predisposing factors include impaired swallowing, insufficient water when taking tablets or a patient lying down after taking their medication. Symptoms include heartburn, chest pain, dysphagia and odynophagia. There are a significant number of drugs which are known to cause this localized topical toxicity (Petersen & Jaspersen, 2003) (summarized in Table 1). It is thought that oesophageal injury arises from caustic coatings, direct medication injury and poor oesophageal clearance of pills leading to acute inflammation. Further damage occurs when the toxic contents of a drug pill/capsule remain in the esophagus long enough to produce mucosal lesions (Jaspersen, 2000).

Due to the slower transit of food and drugs through the stomach, ingested compounds can remain *in situ* for several hours and this theoretically makes the stomach particularly vulnerable to drug toxicity. However, the highly efficient mucosal protective mechanism of the stomach means that most potential toxins are able to pass safely through without issue.