Metformin and digestive disorders

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Abstract

Digestive disorders (diarrhoea, vomiting) represent the most common metformin side-effects (around 30%) with this first-line drug treatment for type 2 diabetes. In healthy individuals, metformin affects glucose, vitamin B12 and the digestive uptake of bile salts. In the colon, it acts locally by modifying glucose cell metabolism. Different pathophysiological hypotheses have been proposed to explain the metformin-induced diarrhoea and vomiting, which can sometimes cause the patient to stop an effective treatment. These theories include stimulation of intestinal secretion of serotonin, changes in incretin and glucose metabolism, and bile-salt malabsorption. However, none of these hypotheses can be considered an adequate pathophysiological explanation of metformin digestive side-effects. In addition, there is a lack of experimental data to explain these highly patient-dependent adverse effects.
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1. Introduction

Metformin (1,1-dimethylbiguanide hydrochloride) belongs to the biguanide class of drugs that are guanidine derivatives. The active ingredient, extracted from the French lilac plant (\textit{Galega officinalis}), was used in Medieval Europe for treating diabetes. It is the only biguanide derivative on the market, and is also the first-line oral antidiabetic drug for the treatment of type 2 dia-

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betes not controlled by adequate diet, especially in overweight subjects [1]. Metformin has been used in Europe and Canada for more than 50 years (since 1957), although the US Food and Drug Administration (FDA) only approved it in December 1994. Its mechanism of action is poorly understood. In the presence of insulin, it promotes glucose uptake by tissues (\textit{via} glucose transporters) – especially those of skeletal muscles – and inhibits hepatic gluconeogenesis [2]. Activation of AMPK (AMP-activated protein kinase) appears to be the main mechanism of its antihyperglycaemic action, but metformin also acts on small-intestine glucose metabolism. Although its most serious and sometimes fatal side-effect is lactic acidosis, the more
commonly observed side-effects are gastrointestinal – including nausea, vomiting and diarrhea. These side-effects are observed in approximately 30% of patients, and have led to treatment discontinuation in 5% of patients [3–5].

The pathophysiology of the gastrointestinal disorders seen with metformin remains poorly understood. Also, in diabetes, the search for a common aetiology for the motor and secretory changes of the gastrointestinal tract is difficult, as the disease itself can cause digestive complications and comorbidities comparable to those induced by biguanides. These complications include autonomic dysfunction, infections and chronic pancreatitis [6]. The present study is a review of several reports on this topic to clarify the frequency of gastrointestinal complications, determine their potential mechanisms and describe the management of diabetic patients in clinical practice.

2. Metformin pharmacokinetics

Metformin has antihyperglycaemic effects by reducing basal and postprandial blood glucose. It does not stimulate insulin secretion and, therefore, does not cause hypoglycaemia.

2.1. Absorption

After oral administration of metformin hydrochloride, T\text{max} is reached in 2 h 30 min. Its bioavailability is approximately 50–60% without binding to proteins, and there is a large volume of distribution and maximum accumulation in the small intestine [7]. A large fraction is found in stools. No metabolite has been identified in humans, and metformin hydrochloride is excreted unchanged in urine.

After oral administration, the uptake of metformin hydrochloride is saturable and incomplete. With regular doses, however, steady-state plasma concentrations are achieved within 24–48 h (plasma half-life: 2.7–4 h) [8]. These concentrations at equilibrium are 1–2 μg/mL and, in general, tend to remain less than 1 μg/mL. In controlled clinical trials, the maximum plasma concentrations of metformin hydrochloride (C\text{max}) did not exceed 4 μg/mL, even with maximum doses.

Food intake decreases and slightly delays the absorption of metformin. After an oral dose of 850 mg, food intake causes a 40% decrease in the plasma peak, a 25% decrease in the area under the curve (AUC) and a 35-min time lag before it reaches maximum plasma concentration [9]. However, the clinical significance of these parameters remains unknown.

2.2. Distribution

Binding to plasma proteins is insignificant. Metformin hydrochloride diffuses into erythrocytes, but the blood peak is lower than the plasma peak, which occurs at approximately the same time. Red blood cells most likely represent a secondary compartment of distribution. The volume of distribution ranges from 63 to 276 L.

2.3. Elimination

Renal clearance of metformin hydrochloride is > 400 mL/min, indicating its elimination via glomerular filtration and tubular secretion. In patients with impaired renal function, renal clearance is decreased in parallel with the decrease in creatinine clearance. This leads to a longer elimination half-life and increased plasma concentrations.

3. Frequency and characterization of digestive disorders

Metformin gastrointestinal symptoms (nausea, vomiting, diarrhea, bloating, abdominal pain) are common (affecting up to 30% of patients in some studies), and gastrointestinal intolerance at rates of 5–10% absolutely prohibited metformin in early treatment studies, and were consistent with statements in the FDA registration dossier [10]. However, these disturbances are similar to the functional gastrointestinal disorders described in the Rome criteria [11], and are seen in patients with diabetes [12–17] regardless of metformin administration. In 5% of cases, these disorders led to treatment discontinuation.

In 1983, a questionnaire-based study found that 6% of patients treated with insulin or sulphonylureas, or diet alone, had diarrhoea. In contrast, 20% of patients receiving metformin with or without sulphonylureas had accelerated transit times [4]. Other effects, such as the metallic taste in the mouth, are rarer [4]. In that study, side-effects were not dose-dependent. Transit acceleration may be responsible for anal incontinence of varying degrees (with a possible total loss of control of the anal sphincter in extreme cases). This side-effect is reversible on stopping metformin administration.

In everyday medical practice, it is accepted that too-rapid escalation of therapy using ever-higher doses increases the frequency of side-effects [18]. However, there is no clinical study to support this assertion and, thus, it remains open to question [15].

In the absence of diabetes, metformin has been used in patients with polycystic ovary syndrome (PCOS). In these patients, metformin can result in nausea and vomiting (odds ratio [OR]: 3.91, range: 0.98–15.64), and other digestive disorders (OR: 4.62, range: 1.71–12.51) [19]. Another study revealed that digestive disorders were the main cause of treatment discontinuation in PCOS patients [20].

4. Changes of intestinal glucose metabolism by metformin

Experimentally, after an oral glucose load, metformin in the gut lumen of rats had minimal impact on blood glucose levels in portal blood, whereas lactate increased [21]. Lactate is mainly produced by the intestine and used by the liver as a substrate for gluconeogenesis. More recent studies have shown that metformin delays the intestinal absorption of glucose, which occurs more distally, and stimulates utilization of intestinal glucose, particularly anaerobic metabolism, which contributes to a reduction of glucose uptake in both animals and humans [22].
Fig. 1. After oral ingestion, intestinal absorption of metformin is incomplete (only 70% of ingested dose). It is rapidly distributed by diffusion and accumulates in the digestive tract. The drug has many sites of activity, including the stomach (suspected modification of ghrelin and acid secretion), duodenum (decrease in vasoactive intestinal peptide [VIP] secretion and increase in serotonin release) and ileum (inhibition of GLP-1 degradation, inhibition of vitamin B12 uptake and malabsorption of bile salts).

At concentrations higher than those obtained in clinical practice, metformin has no significant effect on intestinal absorption of glucose, whereas circulating metformin stimulates glucose utilization in the gut and increases lactate release [23,24].

In humans, injection of fluorine-18-fluorodeoxyglucose (18-FDG) for positron emission tomography–computed tomography (PET–CT) clearly shows increased radioactivity in the colon and small intestine in diabetic patients treated with metformin [25], thus demonstrating glucose uptake in those tissues. Moreover, this uptake raises the risk of false-positive results with this test in type 2 diabetics. Despite the fact that the regulatory genes of gluconeogenesis are all expressed in the small intestine of rats and humans [26,27], the data to support the idea that glucose can be produced by the intestine are conflicting [28].

Although significant concentrations of metformin have been detected in intestinal biopsy samples, histological studies have shown that metformin does not penetrate into the enterocytes, but accumulates in the lymphatics (lacteal ducts) of the intestinal villi instead [29,30]. In addition, intra-arterial administration of metformin reduces the uptake of glucose by isolated perfused ileojejunum segments [31,32]. Thus, the presence of metformin in the vascular system stimulates the intestinal anaerobic metabolism of glucose.

Biochemical measurements taken from freshly isolated enterocytes show that, even at high concentrations, metformin interferes with neither cellular respiration nor Na+/K+-ATPase activity. Indeed, metformin has localized intestinal activity with no toxicity and no penetration into enterocytes. It also increases glucose uptake and local synthesis of lactate.

5. Digestive disorders in diabetics unrelated to metformin

Motility in the gastrointestinal tract involves three main factors: smooth muscle cells; interstitial Cajal cells (ICC); and the enteric nervous system [33]. In the gut wall, smooth muscle fibres are organized into two layers: an inner circular layer; and an outer longitudinal one. Contractile activity of the smooth muscle cells is initiated by the spontaneous activity of the ICC lying next to them. These cells regulate the onset of the potential oscillations of smooth muscle cell membranes known as “slow waves”, and mechanical activity takes place when action potentials are activated over these slow waves [34]. Neuroendocrine activity regulates muscle activity. Innervation of the gut involves intrinsic (in the gut wall) and extrinsic (sympathetic and parasympathetic) nervous systems. The enteric nervous system is the source of the peristalsis reflex, while the extrinsic nervous system modulates motor activity. In diabetes, ICC damage is involved in the genesis of digestive problems [34].
While the intestinal motility modifications of diabetes are well known from manometry [15,35] and scintigraphy [35–37] investigations, there have been few studies of metformin effects. Thus, the pathophysiology of gastrointestinal disorders has been imperfectly elucidated and is currently based solely on animal models.

6. Digestive disorders in diabetics taking metformin

Digestive side-effects with metformin are frequently seen (diarrhoea, nausea, flatulence, abdominal pain with cramps, abdominal swelling, dysgeusia, vomiting, constipation, dyspepsia). Nevertheless, few studies have analyzed the structural and/or functional changes seen in the gastrointestinal tract. Earlier studies of healthy individuals have shown that metformin does not alter gastric-emptying [38], but that it does increase gastric secretion and, paradoxically, vasoactive intestinal peptide (VIP) secretion as well [39]. Moreover, it can induce duodenogastric reflux [38] (Fig. 1).

Histological examination of the intestines of animals treated with metformin revealed no lesions of the intestinal mucosa [29,30], even though it has been suggested that the talc used in the metformin formulation could be a local irritant.

Several studies have focused on the interaction of metformin with various bowel effectors. Metformin appears to interact with serotoninergic balance and bile acids, modify the secretion of ghrelin after glucose loading [40] and stimulate the secretion of glucagon-like peptide-1 (GLP-1).

6.1. Action of metformin on ghrelin

Ghrelin is an orexigenic peptide, derived from the stomach, found in concentrations that vary in relation to food, obesity and diabetes control, thus suggesting its physiological role. Plasma ghrelin levels display a preprandial peak and postprandial suppression. However, there are conflicting reports as to how metformin treatment of type 2 diabetes affects ghrelin concentrations: it has been found an association with increased plasma ghrelin concentrations [41], with decreased plasma ghrelin levels after a glucose load [40] and with no significant changes [42].

6.2. Changes in serotonin metabolism

Among the numerous neurotransmitters involved in the process of digestive motility, serotonin and 5-hydroxytryptophan (5-HT) appear to play key roles. The release of serotonin by serotoninergic neurons leads to altered activity of target neurons.

Serotoninergic receptors are grouped into seven major families – 5-HT1 to 5-HT7 – some of which also have subtypes [43]. Two main types of receptors are involved in the serotoninergic system: the GPCR (receptor coupled to G proteins), which modulates cellular activity via the production of a second messenger; and a channel receptor (5-HT3) that rapidly depolarizes the cell with the passage of cations.

Metformin has a similar structure to known selective-receptor type-3 serotonin (5-HT3) agonists [44–46]. Experimentally, it has been shown that administration of these 5-HT3 agonists causes vomiting and diarrhoea in animal models [47–49]. Some of the side-effects of anticancer drugs, such as cisplatin and dacarbazine, are due to the release of serotonin from enterochromaffin cells. Ondansetron, a 5-HT3 antagonist, has shown efficacy in the treatment of these complications [49]. However, experimental studies have also found that metformin induces serotonin release, independent of the 5-HT3 receptor, by human duodenal mucosa through neural and non-neuronal mechanisms [50]. Moreover, in clinical studies, ondansetron showed no efficacy in the treatment of nausea induced by metformin [51].

If metformin is structurally similar to these receptors or ligands, there is, to our knowledge, no other report of any experimental work or clinical trials showing a possible blockade by specific serotonin antagonists. It is likely that the serotonin released by the intestinal mucosa under the action of metformin originates from enterochromaffin cells. The observation that tetrodotoxin reduced the 5-HT released by metformin by half [50] suggests that metformin, either directly or indirectly through a neurotransmitter, may perhaps stimulate the release of 5-HT by enterochromaffin cells. In the presence of tetrodotoxin, somatostatin inhibits the release of 5-HT induced by metformin. This suggests the presence of somatostatin receptors with inhibitory effects on the enterochromaffin cell surface [50].

6.3. Action via GLP-1

GLP-1 and glucose-dependent insulinotrophic peptide (GIP) are two incretins – peptide hormones produced by the gastrointestinal tract in response to food intake – that stimulate insulin secretion. GLP-1 is produced by L cells mostly located in the ileum and colon and, to a lesser extent, in the duodenum and jejunum; GIP is produced by K cells in the proximal gut, and stimulates insulin secretion and at supra-physiological doses inhibits acid production by the stomach [52].

GLP-1 has anorectic effects, and stimulates insulin while reducing glucagon secretion. It also inhibits gastric-acid production and gastric motility by acting on the hypothalamus. GLP-1 and GIP are inactivated within just a few minutes by dipeptidyl peptidase-4 (DPP-4). This mechanism justifies the use of exenatide and liraglutide (GLP-1 analogues resistant to the action of DPP-4), and gliptins (sitagliptin and vildagliptin, DPP-4 inhibitors) in the treatment of type 2 diabetes.

In non-diabetic obese subjects, metformin increases concentrations of GLP-1 after a glucose load without altering the basal rate [53]. This result is interpreted as inhibition of the degradation of GLP-1 by metformin [53] and may, in fact, reflect pleiotropic effects, as this enzyme can inhibit the degradation of over 20 peptides in the human body [54]. The effect was seen in obese diabetics after 4 weeks of metformin treatment [55]. Metformin inhibits DPP-4 activity in type 2 diabetic patients in the fasting state, but not when taken with a meal, which lowers metformin serum concentrations [56]. The postprandial increase of GLP-1 30–60 min after a meal [53] causes a delay in gastric-emptying, and may explain the nausea, and have a direct
effect on the colonic response to eating by decreasing transit time [57]. Improvement in such digestive side-effects over time with exenatide and metformin may be suggestive of a common pathophysiological mechanism.

6.4. Alteration of bile-acid metabolism

The action of biguanides on ileal absorption of vitamin B12 and bile salts has long been suspected [58]. However, evidence of the malabsorption of bile salts remains controversial [58,59]. A recent randomized study demonstrated that metformin was associated with a mean decrease in vitamin B12 concentrations of 19%, with a relative 5% decrease in vitamin B12 deficiency (<150 pmol/L) [60]. Recent studies have suggested a direct action on enterocytes, thereby reducing the active transfer of bile salts independent of Na+/K+-ATPase activity [61]. Such action would contribute to the cholesterol-lowering effect of metformin [62]. The malabsorption of bile salts may also be responsible for the metformin-induced diarrhoea.

6.5. Other metformin actions

There appears to be no data available on the possible action of metformin on gut microbiotic flora, a domain that is currently being extensively studied. This is because, in obesity and type 2 diabetes, low-grade inflammation and increased calorie extraction from the gut, mediated by intestinal bacteria, appear to play crucial roles. Nevertheless, only one study has indirectly demonstrated no effect of metformin on endotoxin plasma levels related to gut bacterial activity [63]. Evidence from a preliminary report shows that metformin suppresses colonic epithelial proliferation and rectal aberrant crypt foci formation in humans, suggesting a promising role for the drug in the chemoprevention of colorectal cancer [64].

7. Prospects in clinical practice

Digestive disorders are common and may cause one patient in 20 to discontinue metformin treatment. However, there are no experimental data to explain these patient-dependent side-effects, and there is no further treatment or single approach to improve tolerability. The following prescribing advice should be borne in mind: metformin treatment is preferably taken with meals; and dose titration should be slow, preferably using slow-release formulas. However, these tips are not based on solid evidence (no randomized studies), and the dose-related activity and digestive side-effects were not supported by the findings of Garber et al. [10]. In fact, the more recent studies have failed to explain the most common side-effects of this first-line drug treatment for type 2 diabetes.

8. Conclusion

As revealed by measurements carried out after injection of 18-FDG, metformin exerts, in healthy individuals, preferential activity in the ileum and colon. In the intestine, it acts on the absorption of glucose, vitamin B12 and bile salts. In the colon, it acts locally by modifying cell metabolism. In type 2 diabetics, metformin side-effects are reduced when the treatment is taken in increasing dosages and after a meal.

The present review has outlined the various published pathophysiological hypotheses put forward to explain diarrhoea and vomiting – namely, stimulation of intestinal secretion of serotonin, changes in incretin and glucose metabolism, and malabsorption of bile salts. However, none of these hypotheses can be considered a definitive pathophysiological explanation. Furthermore, so far, not enough randomized clinical and intestinal flora studies have been carried out to arrive at any definitive conclusions.

Conflict of interest statement

The authors have not declared any conflict of interest.

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