

# BMJ Open Severity of coeliac disease and clinical management study when using a non-metabolised medication: a phase I pharmacokinetic study

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## ABSTRACT

**Objective** The non-metabolised antihistamine fexofenadine has oral absorption resulting from transporter activity. Uptake by enterocyte organic anion transporting polypeptides and efflux by an ATP-binding cassette transporter (P-glycoprotein) are primary determinants. Coeliac disease-mediated lesions to the small intestinal mucosa may alter oral absorption of the drug probe, fexofenadine.

**Design** A phase I, open-label, single-dose, pharmacokinetic study

**Setting** London, Ontario, Canada

**Participants** Patients with coeliac disease (n=41) with positive serology and healthy individuals (n=48).

**Main outcome measures** Patients with coeliac disease—duodenal histology and oral fexofenadine pharmacokinetics within a 3-week period. Healthy individuals—oral fexofenadine pharmacokinetics with water and grapefruit juice.

**Results** Patients with coeliac disease were stratified by disease severity: Group A (n=15, normal), B+C (n=14, intraepithelial lymphocytosis with/without mild villous blunting) and D (n=12, moderate to severe villous blunting). Patients with coeliac disease in groups A, B+C and D and healthy individuals receiving water had similar fexofenadine AUC<sub>0-8</sub> (2038±304, 2259±367, 2128±410, 1954±138 ng.h/mL; p>0.05; mean±SEM) and C<sub>max</sub> (440±73, 513±96, 523±104, 453±32 ng/mL; p>0.05), respectively. These four groups all had higher fexofenadine AUC<sub>0-8</sub> (1063±59; p<0.01) and C<sub>max</sub> (253±18; p<0.05) compared with those for healthy individuals receiving grapefruit juice. Coeliac groups had a positive linear trend between disease severity and fexofenadine T<sub>max</sub> (2.0±0.3, 2.7±0.4, 3.1±0.5 hours; p<0.05).

**Conclusions** Coeliac disease severity based on duodenal histopathology did not affect oral fexofenadine bioavailability. Increased T<sub>max</sub> suggested absorption distal to the duodenum (jejunum + ileum), where histology seems more normal which may be the key determinant. Patients with coeliac disease may not require consideration for alternative clinical drug management for a number of non-metabolised and transport-mediated medications.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Only unequivocally diagnosed patients with coeliac disease who differed in severity of disease were included.
- ⇒ The maximum time interval of 3 weeks between gastrointestinal biopsy and pharmacokinetic drug testing provided an accurate measure of their relationship.
- ⇒ Fexofenadine is a safe representative for a class of orally administered hydrophilic drugs that require enteric transport for absorption.
- ⇒ Healthy controls (negative, positive) underwent comparable testing to patients with coeliac disease and were of sufficient number to define fexofenadine population pharmacokinetics well.
- ⇒ A limitation was the incorporation of healthy subjects from several of our previously published peer-reviewed studies as controls.

## INTRODUCTION

The incidence of coeliac disease, estimated at 1% worldwide, is increasing.<sup>1-3</sup> This autoimmune condition occurs in genetically susceptible individuals following ingestion of gluten-containing foods like wheat, rye or barley.

Information about drug interactions mediated by coeliac disease is limited.<sup>1-3</sup> A recent study assessed the oral pharmacokinetics of the antihypertensive drug, felodipine, which served as a representative for a range of drugs.<sup>4</sup> Following oral administration, felodipine undergoes enteric metabolism by the cytochrome P450 enzyme, CYP3A4, which inactivates about 50% of all drugs.<sup>5,6</sup> Increased severity of coeliac disease was associated with greater felodipine bioavailability.<sup>4</sup> This result was attributed to the decrease in intestinal CYP3A4 content with coeliac disease-induced injury to the duodenal mucosa.<sup>7</sup>

Grapefruit can also augment the oral bioavailability of felodipine and other drugs

through reduction of intestinal CYP3A4 expression by a mechanism involving irreversible (mechanism-based) enzyme inactivation.<sup>8</sup> More than 100 medications have now been shown or predicted to be affected.<sup>4</sup> The primary concern is unintentional grapefruit-mediated drug overdose which may require altered medication management, especially when drug toxicity could be serious or life threatening. Risks for patients consuming grapefruit may be similar to those for patients with coeliac disease.<sup>4</sup>

The current investigation is a follow-up study that extends this area of enquiry in coeliac disease by learning the oral pharmacokinetics of a non-metabolised, transport-dependent medication. The antihistamine, fexofenadine, is a safe representative for drugs having the similar physicochemical property of hydrophilicity and oral pharmacokinetics involving drug transporters.<sup>9</sup>

Two major categories of drug transporters exist.<sup>10</sup> Uptake carriers facilitate the translocation of drugs from the extracellular to the intracellular compartment. Organic anion transporting polypeptides (OATPs) constitute a subgroup of sodium-independent transport proteins. OATP1A2 was the first to be identified as a human carrier protein for fexofenadine.<sup>11</sup> OATP1B3 and OATP2B1 were recognised later but appear to have less activity for fexofenadine uptake.<sup>12 13</sup> Their locations on the luminal surfaces of enterocytes and hepatocytes enable fexofenadine uptake into the gut circulation and liver, respectively.

Efflux carriers constitute the second group.<sup>10</sup> The ATP-binding cassette family requires energy to drive substrates from the intracellular environment against a concentration gradient to the extracellular milieu. P-glycoprotein, also known as multidrug resistance protein 1, is also a transporter of fexofenadine.<sup>11</sup>

OATPs (1A2, 2B1) and P-glycoprotein located together on the luminal surface of enterocytes result in corresponding opposing vectors of uptake and efflux of fexofenadine in the gut.<sup>9</sup> OATPs (1B3, 2B1) at the sinusoidal and P-glycoprotein at the bile canalicular membranes enable the uptake and transfer of fexofenadine through hepatocytes for excretion into bile and faeces, a major route for elimination of this drug.<sup>9</sup>

Selective inhibition of OATPs in the intestine by the grapefruit flavonoid glycoside, naringin, decreased systemic fexofenadine availability.<sup>14</sup> Conversely, selective inhibition of P-glycoprotein in gut and/or liver by itraconazole, lopinavir, ritonavir and verapamil increased it while induction of activity by carbamazepine, rifampicin, St John's wort decreased systemic fexofenadine availability.<sup>9</sup> Thus, these transporters likely play important roles in the overall clinical disposition of fexofenadine.

Coeliac disease affects the small intestine, and since OATPs and P-glycoprotein are both expressed on enterocytes, villous blunting in the more severe forms of coeliac disease may be associated with decreased transporter expression in the duodenum and change oral fexofenadine absorption, as well as that for other drugs which are OATPs and/or P-glycoprotein substrates. This study

**Table 1** Demographic profile of patients with coeliac disease

	Group A	Group B+C	Group D
Males	3	2	3
Females	12	12	9
Age	52 (17–71)	59 (44–77)	50 (21–79)
tTG-IgA	1.8	6.2	38.2

Age (years) expressed as mean (range).  
tTG-IgA is serum tissue transglutaminase antibody concentration expressed as the arithmetic mean of the log analysed data.

may provide insight about the need for altered clinical drug management for other non-metabolised, transport-mediated medications.

## METHODS

### Patients with coeliac disease

#### Study population

Patients with confirmed or suspected coeliac disease referred by their family physician/specialist for investigation or management were invited to join this study by their attending gastroenterologist. Reasons for exclusion were significant illness within 2 weeks before either pharmacokinetic testing or endoscopy or a current history of drug or alcohol abuse. Patients provided written informed consent which had been previously approved by the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects. A total of 44 patients with coeliac disease expressed interest, met entry criteria and signed the consent form with 41 of them completing both the fexofenadine pharmacokinetics and biopsy aspects of this investigation (8 males, 33 females, age range: 17–79 years). The demographic profiles of patients with coeliac disease in Groups A, B+C and D are shown in [table 1](#).

#### Experimental protocol

Patients completed the fexofenadine pharmacokinetic study within 3 weeks of their endoscopy. They avoided consumption of any substance(s) which might have an impact on fexofenadine bioavailability, including grapefruit, orange and apple juices and fruits, tobacco, alcoholic drinks, medications (prescription and over-the-counter) and natural health products, for at least 48 hours before and during this study. All medications taken were documented before entry into the study. No patients were receiving a medication that was either an inhibitor or inducer of OATPs or P-glycoprotein. Testing was preceded by a 10-hour overnight fast. Fexofenadine 120 mg (Allegra, Hoechst Marion Roussel Inc, Laval, Quebec, Canada) was consumed with 300 mL water. Plasma samples were obtained at specified times (0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 hours) relative to dosing for quantitation of fexofenadine concentrations.

A gluten-free standardised lunch was provided 4 hours after drug dosing (noon).

## Healthy subjects

### Study population

Subjects were from four of our previous peer-reviewed fexofenadine—grapefruit juice interaction study publications.<sup>14–16</sup> They had a history free of any underlying medical condition and normal findings on physical examination and routine laboratory testing that included haematologic and serum chemistry studies. They were not tested for tTG-IgA antibodies or total serum IgA. They provided written informed consent for the original investigation that had been previously approved by the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects. The study population consisted of 48 individuals (26 males, 22 females, age range: 19–52 years).

### Experimental protocol

Subjects avoided ingestion of the same substances outlined above for patients with coeliac disease for at least 48 hours before and during study days. They had a 10-hour overnight fast before testing. All studies had a randomised crossover design with fexofenadine 120 mg (Allegra, Hoechst Marion Roussel Inc, Laval, Quebec, Canada) consumed with 300 mL water or grapefruit juice. Plasma samples were obtained at the same specified times as those for the coeliac study. A standardised lunch was provided 4 hours after drug dosing (noon) that consisted of a sandwich, ginger ale and ice cream sandwich. The interval between study days was 1 week.

### Assay of plasma fexofenadine concentration

Analysis was determined according to a previously reported method.<sup>14</sup> A 100-mg C18 preparatory solid phase extraction column (Sep-Pak Vac cartridge; Waters Corp, Mississauga, Ontario, Canada) was washed with 1 mL volumes of isopropyl alcohol, methanol and water. A 500  $\mu$ L aliquot of aqueous 1% phosphoric acid was added, followed by a 500  $\mu$ L aliquot of the plasma sample for analysis. The column was washed once with a 1 mL volume of aqueous 1% phosphoric acid in water, 3 times with a 1 mL volume of water/methanol/glacial acetic acid (88:10:2 (vol/vol)), and three times with a 1 mL volume of water/methanol/concentrated ammonium hydroxide (88:10:2 (vol/vol)). The sample was eluted with 1 mL of methanol/triethylamine (99.8:0.2 (vol/vol)), and the effluent was evaporated to dryness at 40°C under a gentle stream of nitrogen. The residue was dissolved in a 100  $\mu$ L aliquot of high-pressure liquid chromatography mobile phase that consisted of acetonitrile/water/triethylamine (33:67:1 (vol/vol) at pH 3.0) with 1% phosphoric acid. Recovery of fexofenadine from the solid-phase extraction column was complete. The solution was filtered (0.45  $\mu$ m), and a sample (40  $\mu$ L) was injected onto a Prodigy 5  $\mu$ m octadecylsilane (2) column (150 mm  $\times$  3.2 mm; Phenomenex, Torrance, California, USA) with a mobile flow rate of 0.4 mL/min. Fluorescence detection (excitation

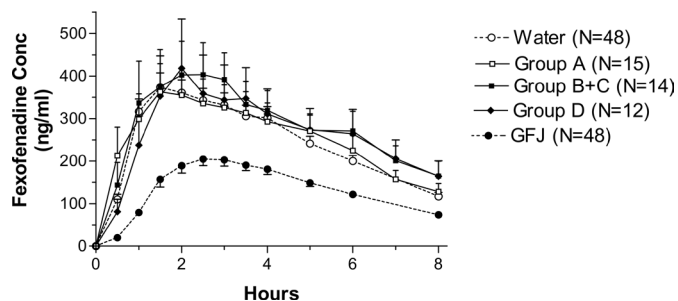
wavelength, 223 nm; emission wavelength, 290 nm) was used to monitor the effluent. The retention time of fexofenadine was 10.9 min. The standard curve of fexofenadine was linear over the range of concentrations measured in the plasma samples from the study (0–1000 ng/mL). The coefficient of variation was 4.8% at 25 ng/mL (n=5), and the limit of detection was 5 ng/mL.

### Pathological analysis

This was conducted as reported previously.<sup>14</sup> All patients had at least one biopsy sample from each of the gastric antrum, the second part of the duodenum ipsilateral to the ampulla of Vater and contralateral to the ampulla of Vater. Where endoscopic abnormalities were visible, additional biopsies were taken. Formalin-fixed, paraffin-embedded tissue was used to prepare haematoxylin and eosin-stained slides using standard techniques. Biopsies were reviewed histologically by two gastrointestinal pathologists (JP, DD) according to a previously reported modified method.<sup>17</sup> Briefly, samples were scored independently while blinded to clinical and pharmacokinetic data. Findings were then reviewed for any discrepancy between the pathologists in order to reach consensus. A modified Marsh-Oberhuber (M-O) classification: 0=normal; 1=increased intraepithelial lymphocytes (IELs) only; 2=increased IELs with crypt hyperplasia; and 3a–c=increased IELs with mild (3a), marked (3b) or complete (3c) villous atrophy was referenced. Two groups were combined since separating crypt hyperplasia from villous blunting was problematic as they could not be reliably distinguished from each other. The end result was Group A=normal (M-O score 0); Group B=increased IELs only (M-O score 1); Group C=increased IELs + mild architectural abnormality (M-O scores 2 and 3a); Group D=increased IELs + moderate to severe architectural abnormality (M-O scores 3b and 3c). Furthermore, Groups B and C were combined because of small sample size in the latter (Group C, n=5). The demographic data are shown in [table 1](#). A positive serum tTG-IgA along with the accompanying pathology results confirmed the diagnosis of coeliac disease in all tested individuals.<sup>1–3</sup>

### Pharmacokinetic analyses

Plasma fexofenadine concentrations were extrapolated using Microsoft Excel 2016 and analysed by the non-compartmental method. The author (DGB) who calculated the pharmacokinetic results was blinded to the histological reports. The terminal elimination rate constant ( $k_e$ ) was determined by log-linear regression (correlation coefficient of  $r > 0.95$  for the last three drug concentrations). The apparent elimination half-life ( $t_{1/2}$ ) was calculated as  $0.693/k_e$ . Area under plasma drug concentration–time profile from 0 to 8 hours ( $AUC_{0-8}$ ) used the linear trapezoidal method. The AUC from 0 to infinity ( $AUC_{0-\infty}$ ) was  $AUC_{0-8}$  plus  $AUC_{8-\infty}$  with the later calculated by dividing the final plasma drug concentration by  $k_e$ . Peak plasma drug concentration ( $C_{max}$ ) and the time to reach  $C_{max}$  ( $t_{max}$ ) were obtained directly from the experimental data.



**Figure 1** Plasma concentration–time profiles for fexofenadine for patients with coeliac disease in groups A, B+C and D and healthy controls with water or grapefruit juice. The number of subjects in each group is indicated in parentheses. Data are reported as mean±SEM.

### Statistical analyses

The initial comparisons of fexofenadine data were among the five treatment groups by means of a one-way analysis of variance. For those analyses with  $p < 0.05$ , post-test for linear trend (Groups A, B+C, D) and Bonferroni test for multiple comparisons between selected pairs of treatments (healthy subjects with water vs grapefruit juice, healthy subjects with grapefruit juice vs Groups A, B+C, D) were conducted using the statistical package in Prism V.3.00. Results are presented as the mean±SEM

### Patient and public involvement statement

Patients were initially invited by their gastroenterologist during a routine clinical appointment to participate in this research study. Those expressing interest received a copy of the approved human ethics letter of information

which noted that their decision would not affect their subsequent healthcare or patient–physician relationship. They were asked to attend a regularly scheduled meeting of the Celiac Society of London, Ontario. The principal investigator (George K Dresser MD PhD) and research coordinator (Linda Asher RN) introduced the project to those about to have an endoscopy as part of their standard of care. These patient advisers discussed aspects of the drug pharmacokinetics research testing including the inconvenience, benefits and risks. This group meeting format enabled open discussion among the patients and was likely a significant aspect determining their participation. Importantly, it provided a process for them to make a well-informed decision. Once published in a peer-reviewed medical journal, all participants will be invited to a follow-up meeting of the Celiac Society of London to thank them again for their important contribution and to disseminate how the findings of this study might improve drug therapy for them and others with this condition.

### RESULTS

Plasma concentration–time profiles for fexofenadine are shown in [figure 1](#). Patients with coeliac disease in Groups A, B+C, D and healthy subjects with water were not different ([table 2](#)). Fexofenadine AUCs and  $C_{max}$  for these groups were all higher than those for healthy subjects with grapefruit juice.

Fexofenadine  $T_{max}$  had a positive linear trend among Groups A, B+C and D.

**Table 2** Fexofenadine pharmacokinetics

	Patients with coeliac disease Group A (15)	Patients with coeliac disease Group B+C (14)	Patients with coeliac disease Group D (12)	Healthy controls Water (48)	Healthy controls Grapefruit (48)
Fexofenadine					
AUC <sub>0–8</sub> (ng.h/mL)	2038±304**	2259±367***	2128±410**	1954±138***	1063±59
AUC <sub>0–∞</sub> (ng.h/mL)	2558±354†	3256±684***	2997±596**	2508±190***	1413±82
$C_{max}$ (ng/mL)	440±73†	513±96**	523±104**	453±32***	253±18
$t_{max}$ (hour)	2.0±0.3†	2.7±0.4†	3.2±0.5†	2.1±0.2	2.7±0.2
$t_{1/2}$ (hour)	3.1±0.3	4.0±0.6	4.4±0.8	3.0±0.2	3.1±0.2

AUC<sub>0–8</sub>: area under concentration time curve between 0 and 8 hours.

AUC<sub>0–∞</sub>: area under concentration time curve between 0 and infinity.

$C_{max}$ : peak drug concentration.

$t_{max}$ : time to peak drug concentration.

$t_{1/2}$ : apparent elimination half-life.

Data are presented as mean±SEM.

The number of individuals in each group is indicated in parentheses.

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  vs healthy controls grapefruit.

† $p < 0.05$  Groups A, B+C, D for linear trend.

## DISCUSSION

This clinical investigation demonstrated that the area under plasma drug concentration–time profile (AUC) of fexofenadine, which reflects the relative amount orally absorbed into the systemic circulation, was unaffected by severity of coeliac disease. It also did not differ from that seen in healthy individuals given fexofenadine with water.

These findings contrasted with those previously reported for the antihypertensive medication, felodipine, which had higher oral systemic availability with greater extent of duodenal mucosal injury.<sup>4</sup> Felodipine is a lipophilic drug that is normally fully absorbed from the gastrointestinal tract likely by passive diffusion. However, it has limited absolute oral bioavailability averaging only 16% due to extensive oxidative metabolism by the CYP3A4 enzyme during first-pass through the small intestine and liver.<sup>18</sup> When coeliac disease is severe enough to cause loss of duodenal villi (Group D), there was an accompanying elimination of mucosal CYP3A4 content that we previously attributed as the basis for this interaction.<sup>4</sup>

Unlike felodipine, fexofenadine is a zwitterion and thus possesses pronounced polarity over a wide pH range.<sup>9</sup> This physicochemical property would support negligible passive diffusion through healthy intestinal mucosa. What is more, fexofenadine undergoes nominal drug metabolism. Thus, intestinal CYP3A4 would not be expected to be a factor affecting its bioavailability. Instead, several drug transporters appear to be responsible for fexofenadine having an estimated absolute oral bioavailability of 33%.<sup>9</sup>

The positive correlation between the time to peak plasma drug concentration (t<sub>max</sub>) of fexofenadine and severity of coeliac disease supported a longer time to reach the small intestinal site(s) of transporter-mediated drug absorption. The differences in t<sub>max</sub> among patients with coeliac disease (table 2) was not readily apparent in the plasma fexofenadine concentration–time profile (figure 1). However, it should be noted that these are two different types of datasets. They are routinely reported in analyses of all oral pharmacokinetic studies and focus on unique aspects. Modest t<sub>max</sub> differences among the Groups of patients with coeliac disease observed in this study (range: 2.0–3.1 hours) were not likely to be readily apparent in the plasma fexofenadine concentration–time profiles.

Two possibilities might be considered initially. First, this may be due to delayed gastric emptying. We recognise that dissolution of fexofenadine in gastric fluids from the regular release tablet, which we tested in this study, would be expected to be rapid. Given the first time that fexofenadine was measured in blood or plasma (lag time) was 30 min or less, this confirmed quick gastric emptying in coeliac Groups A, B+C, D and control group given water. In light of this, a graded delay in gastric emptying time is unlikely to explain the trend of longer fexofenadine T<sub>max</sub> with increasing coeliac disease severity.

Second, it is possible that fexofenadine absorption occurred more distally in the small intestine of patients

with more severe manifestations of the disease. Studies in patients with coeliac disease examining the distribution of mucosal injury show that intestinal injury is more severe proximally (duodenum), and dissipates distally (jejunum, ileum).<sup>19,20</sup> Consequently, the delayed T<sub>max</sub> in more severe disease may be explained on the basis that fexofenadine must be passed on to the longer segment of small bowel of the jejunum prior to transporter-dependent absorption.

The ileal mucosa was largely unaffected in coeliac disease.<sup>21–23</sup> Accordingly, felodipine enteric metabolism might occur primarily in the duodenum, whereas fexofenadine uptake may happen more distally in the jejunum as well as the ileum. However, future research is needed to validate these possibilities.

Inflammation in the small intestine might also disrupt the tight junctions around enterocytes and thereby allow for paracellular absorption of polar drugs like fexofenadine into the gut circulation.<sup>1–3</sup> Consequently, greater inflammation might be expected to cause higher fexofenadine paracellular absorption. The plasma concentrations of fexofenadine would then reflect both paracellular and transcellular absorption. Our results indicated that total absorption among the three coeliac groups was not altered. Moreover, fexofenadine absorption was not different from that seen with the control group, which has normal mucosa, given this drug with water. Although drug leakage from small intestine into the gut circulation may occur, this appears to be a minor component affecting oral absorption of this hydrophilic drug in coeliac disease.

Hepatocytes express fexofenadine transporters.<sup>10</sup> These include OATP2B1-mediated uptake from hepatic sinusoid and P-glycoprotein-enabled biliary secretion which together act sequentially to provide an important route for the elimination of fexofenadine from the circulation. Decreased expression of one or both of these transporters in coeliac disease might be expected to increase systemic fexofenadine availability. The converse is also true. However, the oral bioavailability of this drug was not different from that seen with the healthy aqueous control group. Hence, the activities of hepatic transporters for fexofenadine appear to be altered inconsequentially in coeliac disease.

Are other hydrophilic drugs, with similar disposition to fexofenadine, also unaffected by coeliac disease? Of note, grapefruit or orange juice inhibited OATP1A2 activity and diminished their oral drug bioavailability.<sup>9</sup> The beta-blockers atenolol, celiprolol and talinolol, the antibiotic ciprofloxacin, the thyroid hormone, L-thyroxine and the chemotherapeutic agent etoposide met these two criteria.<sup>9</sup> Methotrexate and sotalol are substrates for OATP1A2 although their interaction with grapefruit or orange juice has not been reported to our knowledge. Thus, an adjustment in the clinical management of the above may be of a lesser concern in coeliac disease. However, this does not exclude the need for careful monitoring, particularly when the medication is needed for treatment of a serious medical condition.

One criticism of this investigation may be the inclusion of previously tested healthy subjects as controls for the patients with coeliac disease. To explain the validity of this approach, we highlight that the experimental protocol and study testing environment of healthy subjects and patients with coeliac disease were essentially identical. This would simplify the design and reduce the effort in conducting the study by not needing a third testing arm of grapefruit juice administration to patients with coeliac disease. This in turn would likely provide greater compliance and higher numbers of patients with coeliac disease completing this investigation. Moreover, the inclusion of a high number of individuals of healthy volunteers as positive and negative controls might define descriptive and comparative statistics better than would have been otherwise possible. Another criticism may be the sex distribution (males/females) between patients with coeliac disease (8/33) and healthy subjects (26/22).

## CONCLUSION

This study suggests that patients with coeliac disease, regardless of the severity of their disease, may not experience a relevant change in oral pharmacokinetics and clinical effect with fexofenadine and other similarly disposed medications. This may be due to compensated OATP1A2-mediated drug uptake transport distal to the duodenum, for instance in the jejunum and ileum.

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**Contributors** MLC: drafting and critical revision of the manuscript and statistical analysis. DGB: guarantor, study concept and design, analysis and interpretation of data, drafting and critical revision of the manuscript, statistical analysis and obtained funding. LA: acquisition and finalising data, administrative and study supervision. JP: analysis and interpretation of data and critical revision of the manuscript. DD: analysis and interpretation of data and critical revision of the manuscript. JG: critical revision of the manuscript, administrative. GKD: guarantor, study concept and design, acquisition of data, drafting and critical revision of the manuscript, obtained funding and study supervision.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (10722). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available.

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