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Review

Loperamide and P-glycoprotein inhibition: assessment of the clinical relevance

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Abstract

Objectives Loperamide is a peripherally acting μ opioid receptor agonist and an avid substrate for P-glycoprotein. This may give rise to drug–drug interactions and increased risk for central adverse effects. The objective of this study was to re-evaluate the predictability of non-clinical data using loperamide as a probe P-glycoprotein substrate. We searched the literature for papers containing data on drug–drug interactions of loperamide-containing products in humans. We also reviewed the internal worldwide safety database of Johnson & Johnson for spontaneous case reports suggestive of a central opioid effect after coadministration of loperamide with a P-glycoprotein inhibitor or substrate.

Key findings Only one of the ten studies in our review supported the finding that inhibition of P-glycoprotein is associated with clinically relevant signs or symptoms of central nervous system (CNS) depression/opioid toxicity of loperamide. None of the 25 spontaneous case reports of interest were suggestive of signs or symptoms of CNS depression/opioid toxicity due to coadministration of loperamide and a P-glycoprotein inhibitor or substrate.

Summary Based on a review of the literature and a cumulative review of the spontaneous case reports, there is insufficient evidence that an interaction between loperamide and a P-glycoprotein inhibitor or substrate is associated with clinical symptoms of CNS depression/opioid toxicity when loperamide is taken at the recommended dose.

Keywords CNS depression; inhibition; loperamide; opioid toxicity; P-glycoprotein

Introduction

The role of transporter proteins in the disposition of drugs is increasingly recognised. These transporters are expressed at the apical and basal side of polarised cells in various tissues. Drugs can be substrates, inhibitors or inducers of these transporters. This can result in unwanted interactions, but can also be a potential target for drug development to modify drug disposition in certain organs or tissues.[1]

P-glycoprotein

P-glycoprotein, the product of the multidrug resistance (*MDR1* or *ABCB1*) gene, has been the most intensely studied transporter protein to date. P-glycoprotein is a transmembrane, adenosine triphosphate (ATP)-driven efflux pump expressed in transporting epithelia of a variety of human tissues, including the intestine, liver, kidney and blood–brain barrier, where it actively transports compounds out of the cell.[2,3] With an unusually broad substrate specificity and at least two non-identical binding sites,[4,5] P-glycoprotein has a key role in the absorption and disposition of many drugs in clinical use today and in preventing toxins (exogenous or endogenous) from entering cells.[3,6] Notably, many of the drugs that interact with P-glycoprotein, as a substrate, inhibitor or inducer, also interact with the cytochrome P450 (CYP)3A iso-enzyme.[7] Together with the observed overlapping tissue distribution of P-glycoprotein and CYP3A, this suggests that P-glycoprotein and CYP3A have complementary roles in drug disposition.[8]

Loperamide

Loperamide is a peripherally acting μ opioid receptor agonist indicated for the treatment of diarrhoea.[9,10] The recommended oral dose is 2 mg per day, up to a maximum of 16 mg

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per day, based on the frequency and amount of diarrhoeal stool and the overall course of the illness.[11,12] Loperamide oxide is an inactive prodrug of loperamide. Loperamide is gradually formed along the gastrointestinal tract by reduction of the prodrug and slowly absorbed into the systemic circulation.[13] The recommended maximum oral dose of loperamide oxide is 8 mg per day. Loperamide/simethicone is a combination product with simethicone acting as an inert surface-active agent that relieves symptoms associated with diarrhoea, in particular flatulence, abdominal discomfort, bloating and cramping. Simethicone is not absorbed.[14] The maximum administered dose of loperamide in the combination loperamide/simethicone is 8 mg per day.

Loperamide has a wide safety margin, which is probably due to its poor oral bioavailability, a result of considerable first-pass metabolism.[15,16] In-vitro data indicate that loperamide is metabolised primarily by CYP3A4 and CYP2C8.[17] The principal in-vivo metabolites are *N*-desmethylloperamide and *N*-hydroxymethyl-mono-desmethylloperamide, with a potency that is two to three times less than that of loperamide.[17,18]

Animal studies have shown that loperamide is also an avid substrate for P-glycoprotein-mediated efflux.[19,20] This suggests that intestinal P-glycoprotein further contributes to the low oral bioavailability, while P-glycoprotein at the level of the blood–brain barrier prevents entry into the brain. Indeed, even at high clinical doses, oral administration of loperamide is generally devoid of central opiate effects,[21] although rare reports exist on central nervous system (CNS) effects after loperamide intake in children under 3 years of age.[22–24] When administered to P-glycoprotein 'knock-out' mice, which do not express P-glycoprotein, loperamide levels in the brain increase significantly and central opiate effects become evident while plasma levels of loperamide increase to a much lesser extent.[19]

Authorities propose loperamide as a model substrate for the in-vitro evaluation of P-glycoprotein substrates and inhibitors in drug–drug interaction studies. As such, loperamide has been proposed as a positive control to ensure that cell systems have functional P-glycoprotein expression when used for transport experiments.[25]

Based on the observations of loperamide in P-glycoprotein knock-out mice, it can be postulated that, in humans, concurrent administration of loperamide with drugs that inhibit P-glycoprotein function may give rise to drug–drug interactions and increased risk of CNS side effects. However, to our knowledge, only one clinical study to date has shown that coadministration of loperamide with a drug with P-glycoprotein-inhibiting potential results in clinically relevant CNS effects not seen with loperamide alone.[26] In healthy volunteers, clinically relevant CNS effects of opiates, such as respiratory depression, sedation, analgesia or electroencephalographic (EEG) changes, occur at concentrations that are considerably higher than the concentrations that can induce miosis.[27,28] Also, when concomitantly administered with a potent, selective P-glycoprotein inhibitor such as tariquidar, loperamide did not appear to induce central opiate effects in humans.[29]

The purpose of this review is to summarise currently available results from human drug–drug interaction studies on loperamide, in order to re-evaluate the predictability of non-clinical data using loperamide as a probe P-glycoprotein substrate. Additionally, spontaneous case reports in the Johnson & Johnson internal worldwide safety database were reviewed to find data that would support the theory that the combination of loperamide and a P-glycoprotein inhibitor would result in CNS depression or opioid toxicity. We aimed at identifying results for all single-ingredient formulations of loperamide (i.e. loperamide hydrochloride, loperamide oxide and the loperamide/simethicone combination product) and their respective dosage forms.

Data sources

Literature

On 8 September 2008 we searched the internal literature management system of Johnson & Johnson, manufacturer of Imodium (loperamide hydrochloride), for papers containing data on drug–drug interactions of loperamide, loperamide oxide and loperamide/simethicone in humans. The Johnson & Johnson literature system includes publications that are systematically retrieved from MEDLINE, EMBASE, Cited Ref Sci, Derwent Drug File, SciSearch and Biosis Previews, as well as unpublished internal company reports (e.g. clinical study reports and health-authority submissions). The search terms were 'loperamide', 'loperamide oxide', 'loperamide simethicone', 'interaction', 'human', 'pharmacokinetics', 'absorption', 'distribution', 'metabolism', 'excretion' and 'blood–brain barrier'. All resulting publications were reviewed for an impact on any relevant pharmacokinetic parameter. Simultaneously, the publications were reviewed for pharmacodynamic interactions, with a focus on interactions suggestive of a CNS effect and a potential role for P-glycoprotein.

Post-marketing safety review

We also searched the internal worldwide safety database of Johnson & Johnson for spontaneous case reports suggestive of central opiate effects after administration of any loperamide-containing formulation in combination with drug(s) denoted as P-glycoprotein inhibitors or substrates by the US Food and Drug Administration[25] or in the medical literature[30] (see Table 1). All spontaneous reports received cumulatively as of 16 June 2008 by the company's worldwide safety database were retrieved and were reviewed if a case reported a drug–drug interaction, 'loperamide toxicity' (*excluding* overdose) or was suggestive of CNS depression or opioid toxicity.

Results

Literature

A total of 10 papers fulfilling our criteria were obtained from the literature. This included two papers that were published after the search of 8 September 2008, but that were identified during the writing of this article. The majority of these papers focused on interactions between loperamide and drugs with a known impact on P-glycoprotein and/or CYP3A function, including quinidine (four papers), 'azole' antifungals (two

Table 1 Drugs denoted as P-glycoprotein inhibitor or substrate by the US Food and Drug Administration or in the medical literature

Actinomycin-D	Fentanyl	Protriptylene
Aldosterone	Fexofenadine	Quercetin
Amiodarone	Fluorouracil	Quinidine
Amitriptyline	Fosamprenavir	Ranitidine
Amprenavir	Grepafloxacin	Reserpine
Astemizole	Hydrocortisone	Rifampin
Atazanavir	Hypericin	Risperidone
Atorvastatin	Indinavir	Ritonavir
Celiprolol	Itraconazole	Saquinavir
Chlorpromazine	Kaempferol	Silibinin
Cimetidine	Ketoconazole	Sirolimus
Cisplatin	Levomeprazine	Sparfloxacin
Clarithromycin	Lidocaine	St John's wort
Clotrimazole	Lopinavir	Tacrolimus
Colchicine	Lovastatin	Talinolol
Cortisol	LY335979	Tamoxifen
Ciclosporin A	Methadone	Terfenadine
Cytarabine	Methotrexate	Testosterone
Daunorubicin	Methylprednisolone	Tetracycline
Dexamethasone	Midazolam	Teniposide
Digoxin	Mitomycin	Tipranavir
Diltiazem	Morphine	Topotecan
Docetaxel	Nefazodone	Verapamil
Domperidone	Nelfinavir	Vinblastine
Doxorubicin	Nicardipine	Vincristine
Elacridar	Nitrendipine	Vindesine
Erythromycin	Ondansetron	Valspodar
Estradiol	Paclitaxel	
Etoposide	Prednisolone	
Felodipine	Progesterone	

Sources: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). *Draft Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*. September 2006 [online]. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf. Pal D, Mitra AK. CYP3A4 and MDR Mediated Interactions in Drug Therapy. *Clin Res Reg Aff* 2006; 23: 125–163.

papers), HIV protease inhibitors (three papers), ciclosporin (one paper), and selective P-glycoprotein inhibitors (two papers). A summary of the study designs, including details on the study population, study dose and, if applicable, CNS endpoints, is presented in Table 2. A summary of changes in relevant pharmacokinetic parameters in these studies is provided in Table 3.

Interaction studies with quinidine, ciclosporin and ketoconazole

Four clinical studies investigating drug–drug interactions between loperamide and quinidine, a potent inhibitor of P-glycoprotein,[25,30] were identified in the literature. Quinidine also exerts CYP3A4-inhibiting potential but to a lesser extent than the 'azole' antifungals itraconazole and ketoconazole or the antiretroviral ritonavir.[31]

In one interaction study with loperamide and quinidine, eight healthy male subjects received a single dose of 16 mg of loperamide 1 h after administration of 600 mg quinidine or placebo.[26] Each subject was studied on two separate days and received quinidine or placebo in a random, double-blind fashion. Plasma concentrations of loperamide and *N*-desmethylloperamide were measured before drug administration and hourly for 6 h thereafter; results were reported for the first 4 h only. Opiate-induced respiratory depression was evaluated every 30 min by the respiratory response to CO_2 for 4 h after loperamide administration. The 4-h cut-off was chosen because all subjects had returned to baseline respiratory function after this time point.

After coadministration of loperamide and quinidine, marked increases were seen in the highest plasma concentration observed for loperamide (from ~2.7 to ~6.5 ng/ml; values were not reported but are estimated from published figures). The area under the plasma concentration–time curve ($AUC_{0–4}$) for loperamide increased 2.5-fold (Table 3). The respiratory response to CO_2 was significantly impaired for more than 2 h when loperamide and quinidine were coadministered ($P < 0.001$). The impairment was observed within 30 min of loperamide intake. For at least 60 min, when the loperamide plasma concentrations after administration of quinidine and placebo were similar, there was a reduction in respiratory response in the quinidine-treated group, independent of the loperamide plasma concentration.

To date, this has been the only clinical study to suggest that inhibition of P-glycoprotein at the level of the blood–brain barrier increases the risk of clinically relevant CNS effects (i.e. respiratory depression) of loperamide. A replication of the above experiment with a higher dose of quinidine and a combined P-glycoprotein and CYP3A4 inhibitor could not confirm the pharmacodynamic interaction between loperamide and quinidine. In that two-part, placebo-controlled, randomised, double-blind crossover study, eight and ten healthy male subjects were studied to evaluate the ability of ketoconazole and quinidine, respectively, to inhibit P-glycoprotein function at the blood–brain barrier as assessed by pupillometry as a surrogate measure of the CNS effects of loperamide.[32] In the first part of the study, increasing single doses of quinidine (100, 400 or 800 mg) were added to a single 16-mg dose of loperamide. In the second part of the study, loperamide doses of up to 16 mg were administered after reaching steady-state with ketoconazole (400 mg). Each subject also received morphine (30 mg) as a positive control.

Both the peak plasma concentration (C_{max}) and $AUC_{0–24}$ of loperamide increased in a dose-dependent manner. The increase was about 5-fold after coadministration of the 16-mg dose with ketoconazole. The effect of 800 mg quinidine on loperamide pharmacokinetics was less pronounced (see Table 3). The effect of quinidine on pupil diameter was not dose-dependent. In addition, the maximum effect (E_{max}) on pupil diameter after administration of loperamide alone was comparable to that after coadministration with ketoconazole or 800 mg quinidine. The area under the effect–time curve (AUEC) of loperamide after coadministration with ketoconazole increased from 6.7 to 10.6 mm.h ($P < 0.05$), but changed minimally after coadministration with quinidine (from 6.7 to 7.31 mm.h). In contrast, the effect with the positive control, morphine, showed a 3-fold increase in E_{max} (from 0.81 to 2.49 mm, $P < 0.05$) and a 4-fold increase in AUEC (from 6.7 to 25.2 mm.h, $P < 0.05$). These results indicate that the pharmacokinetic interactions observed in this study had minimal central pharmacodynamic

Table 2 Drug–drug interaction studies with loperamide

No. of subjects	Age (years), mean ± SD and/or range	Weight (kg), mean ± SD and/or range	Height (cm), mean ± SD and/or range	Study dose[a]	CNS endpoint
Sadeque *et al.*[26]					
8 men	25–44	91 ± 11	Not available	LOP: 16 mg QIN: 600 mg	Respiratory response to CO_2
Fullerton *et al.*[32]					
18	Not available	Not available	Not available	LOP: up to 16 mg KET: 400 mg QIN: up to 800 mg	Pupil diameter
Passchier *et al.*[33]					
6	Not available	Not available	Not available	[^{11}C]LOP: 8.4 nmol (i.v.) QIN: 600 mg CYC: 10 mg/kg (i.v.)	None
Skarke *et al.*[34]					
8 women 13 men	27.8 ± 3.5	68.8 ± 12.3	176 ± 8	LOP: 24 mg QIN: 800 mg	Pupil diameter Serious side effects
Niemi *et al.*[37]					
6 women 6 men	21 ± 2 (19–25)	70 ± 14 (48–95)	176 ± 8 (158–184)	LOP: 4 mg GEM: 600 mg b.i.d. ITR: 100 mg b.i.d. GEM plus ITR: 100/600 mg b.i.d.	DSST Subjective drowsiness (by VAS)
Tayrouz *et al.*[46]					
6 women 6 men	21–45	19.9–27.5 kg/m^2 (BMI)	Not available	LOP: 16 mg RTV: 600 mg	Pupil diameter Cold pressor test Transcutaneous P_{CO_2}, P_{O_2}
Mukwaya *et al.*[47]					
10 women 14 men	33.5 ± 9.3 (21–52)	76.5 ± 12.8 (51–107)	170.3 ± 7.5 (152–180)	LOP: 16 mg RTV: 200 mg b.i.d. TPV: 750 mg b.i.d. RTV plus TPV: 200/750 mg b.i.d.	Pupillary response Respiratory response to CO_2
Mikus *et al.*[48]					
6 women 6 men	24–46	20.6–26.6 kg/m^2 (BMI)	Not available	LOP: 16 mg SAQ: 600 mg	None
Kurnik *et al.*[29]					
1 woman 8 men	24.1 ± 4.4	25.0 ± 4.1 kg/m^2 (BMI)	Not available	LOP: 32 mg TAR: 150 mg (i.v.)	Pupil diameter DSST Subjective drowsiness (by VAS)
Kim *et al.*[50]					
18 men	Not available	Not available	Not available	LOP: 16 mg HM: up to 180 mg QIN: 600 mg	Pupil diameter

[a]All study medication was administered orally, unless indicated otherwise. b.i.d., twice daily; BMI, body mass index; CNS, central nervous system; CYC, ciclosporin; DSST, digit symbol substitution test; GEM, gemfibrozil; HM, HM30181A; ITR, itraconazole; i.v., intravenous; KET, ketoconazole; LOP, loperamide; QIN, quinidine; RTV, ritonavir; SAQ, saquinavir; SD, standard deviation; TAR, tariquidar; TPV, tipranavir; VAS, visual analogue scale.

consequences and suggest that the clinical relevance of the interaction between loperamide and quinidine, and loperamide and ketoconazole at the level of the blood–brain barrier is limited.

A third study, investigating the blood–brain barrier permeability of [^{11}C]loperamide, also did not show clinically relevant signs of increased brain uptake of [^{11}C]loperamide after coadministration with quinidine.[33] In this study, estimates of brain uptake (K_1) were obtained after intravenous administration of [^{11}C]loperamide in combination with a single oral dose of quinidine (600 mg, three subjects) or a high, single intravenous dose of another P-glycoprotein inhibitor, ciclosporin (10 mg/kg, three subjects). At baseline, all subjects showed very little brain uptake of [^{11}C]loperamide (K_1: 0.0021 ml/min.cm^3). Coadministration of quinidine did not cause a significant increase in brain uptake (K_1: 0.0028 ml/min.cm^3),

Table 3 Pharmacokinetic parameters of loperamide and *N*-desmethylloperamide in clinical drug–drug interaction studies

Dose		C_{max} (ng/ml)		t_{max} (h)		$t_{1/2}$ (h)		$AUC_{0-\infty}$ (ng.h/ml)		CL_{oral} (l/h)		CL_{renal} (l/h)		Ae (μg)	
		LOP	DML	LOP	DML	LOP	DML	LOP	DML	LOP	DML	LOP	DML	LOP	DML
Sadeque *et al.*[26]															
LOP 16 mg	PLC	~2.7[a]	~3.8[a]					99.55[b]	149.15[b]						
	QIN 600 mg	~6.5[a]	~10.0[a]					247.0[b]	289.55[b]						
Fullerton *et al.*[32]															
LOP 16 mg	PLC	3.10						40.8[c]							
	KET 400 mg	16.0						208[c]							
	QIN 800 mg	7.78						88.1[c]							
Skarke *et al.*[34]															
LOP 24 mg	PLC	8.9[d]						33.6[d,e]							
	QIN 800 mg	16.7[d]						57.6[d,e]							
Niemi *et al.*[37]															
LOP 4 mg	PLC	0.62	13.3[f]	5	10.5	11.9		11.3	510[g]			4.72		45.0	659[h]
	GEM 600 mg b.i.d.	0.97	13.7[f]	5	12	16.7		24.5	588[g]			3.40		61.8	660[h]
	ITR 100 mg b.i.d.	1.78	14.7[f]	5	12	18.7		42.9	717[g]			4.10		135	750[h]
	GEM plus ITR	2.62	10.6[f]	7	48	36.9		142	616[g]			3.14		238	517[h]
Tayrouz *et al.*[46]															
LOP 16 mg	PLC	4.1	4.1	4.5	6.0	16.9	35.7	40.7	154.8[i]	343.2		1.8	4.1	94.9	613
	RTV 600 mg	4.8	2.8	7.0	24.0	17.5	48.9	131.4	143.9[i]	104.5		2.0	4.8	266.7	788
Mukwaya *et al.*[47]															
LOP 16 mg	PLC	3.2	5.5					58.3	227.4	275					
	RTV 200 mg b.i.d.	5.5	5.3					121.1	309.8	132					
	TPV 750 mg b.i.d.	1.4	1.9					22.0	64.4	728					
	RTV plus TPV	1.2	1.1					28.8	51.9	556					
Mikus *et al.*[48]															
LOP 16 mg	PLC	3.2	4.4	3.5	7.0	14.8	29.7	55.3	188.9	270		2.7		127.4	
	SAQ 600 mg	3.9	3.8	3.5	5.0	15.7	32.5	78.2	191.2	192		2.8		192.7	
Kurnik *et al.*[29]															
LOP 32 mg	PLC	5.7						87.8[j]							
	TAR 150 mg	8.5						126.5[j]							
Kim *et al.*[50]															
LOP 16 mg	HM 15 mg							1.46[k]							
	HM 60 mg							1.63[k]							
	HM 180 mg							1.35[k]							
	QIN 600 mg							2.2[k]							

Pharmacokinetic parameters are presented as (geometric) mean or median. Empty cell = data not reported. The study by Passchier *et al.*[33] is not included in this table, as the study did not investigate the pharmacokinetic parameters displayed in the table. [a]Values are estimated from published figures; [b]AUC_{0-4}; [c]Time interval not indicated; [d]Maximum value among the 21 study subjects – this maximum value was observed in six subjects with genotype GT2677/TT3435; [e]AUC_{0-last}; [f]Measured in U/ml; [g]AUC_{0-72}, measured in U.h/ml; [h]Measured in 10^3 U; [i]AUC_{0-72}; [j]AUC_{0-48}; [k]Geometric mean ratios of $AUC_{0\text{-}last}$ for combination versus loperamide alone. Pharmacokinetic parameters: Ae, amount excreted in urine; $AUC_{0-\infty}$, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-x}, area under the plasma concentration–time curve from the time of dosing up to x hours after dosing; AUC_{0-last}, area under the plasma concentration–time curve from the time of dosing up to the last time point with a measurable concentration after dosing; C_{max}, maximum plasma concentration; CL_{oral}, oral clearance; CL_{renal}, renal clearance; $t_{1/2}$, elimination half-life; t_{max}, time to reach maximum plasma concentration. Other abbreviations: b.i.d., twice daily; DML, *N*-desmethylloperamide; GEM, gemfibrozil; HM, HM30181A; ITR, itraconazole; KET, ketoconazole; LOP, loperamide; PLC, placebo; QIN, quinidine; RTV, ritonavir; SAQ, saquinavir; TAR, tariquidar; TPV, tipranavir.

while coadministration of high-dose ciclosporin caused a modest change in brain uptake (K_1: 0.0044 ml/min.cm^3) ($P = 0.047$). Pharmacodynamic measures were not performed.

The fourth interaction study with loperamide and quinidine evaluated the modulation of CNS effects of loperamide resulting from mutations in the *ABCB1* gene in a randomised, placebo-controlled, two-way crossover design with open-label loperamide and double-blind quinidine.[34] Quinidine was employed as a positive control to reveal P-glycoprotein function-related changes in the CNS effects of loperamide. Healthy subjects received quinidine 800 mg or placebo 1 h before the administration of a single supra-therapeutic dose of 24 mg loperamide suspension. Loperamide and quinidine plasma concentrations were measured for 6 h. CNS effects were measured for 6 h after loperamide intake by assessment of pupil diameter. The focus in this study was on *ABCB1* mutations at positions 2677 and 3435, which are common genetic polymorphisms of the *ABCB1* gene. The 3435TT genotype has previously been associated with a 40% lower duodenal expression of P-glycoprotein in

individuals homozygous for this polymorphism compared with individuals homozygous for the 3435CC genotype.[35] Individuals with the G2677AT variant have been suggested to have less placental P-glycoprotein.[36]

Of the 26 subjects recruited for this study, three subjects receiving quinidine and two subjects receiving placebo discontinued prematurely for reasons not attributable to opioid effects. In the remaining 21 subjects, coadministration of loperamide and quinidine led to almost a doubling in loperamide C_{max} and $AUC_{0\text{-last}}$ among all *ABCB1* genotypes tested (Table 3). In the overall study population, pupil diameter decreased less with loperamide alone than with coadministration of quinidine (AUEC: –18.5%.h vs –33.2%.h, $P = 0.002$). *ABCB1* genotype had no relevant influence on the miotic effects of loperamide. In a post-hoc analysis involving all 21 subjects, the presence of the single nucleotide polymorphism 3435TT was associated with an increase in AUEC ($P = 0.009$), but not in E_{max}, when loperamide was coadministered with quinidine. No significant change in AUEC was observed with loperamide alone. Serious adverse events requiring medical intervention were not reported.

Interaction study with gemfibrozil and itraconazole

One randomised crossover study investigated the effects of the probe inhibitors itraconazole, gemfibrozil and their combination on the pharmacokinetics of loperamide.[37] Itraconazole is a known potent inhibitor of the CYP3A isoenzyme family and, based on in-vivo data, has been suggested to be a P-glycoprotein inhibitor as well.[38] *In vitro*, gemfibrozil inhibits CYP2C9 and, to a lesser extent, CYP2C8, while *in vivo*, the glucuronide metabolite of gemfibrozil potently inhibits CYP2C8.[39] In-vitro data further indicate that gemfibrozil is neither a substrate for nor an inhibitor of P-glycoprotein.[40,41]

This four-phase interaction study included 12 healthy subjects who received 100 mg itraconazole, 600 mg gemfibrozil, both itraconazole and gemfibrozil, or placebo twice daily for 5 days. On day 3 of each phase subjects also received a single, low 4 mg dose of loperamide. Loperamide and its metabolite *N*-desmethylloperamide were measured in plasma for up to 72 h and in urine for up to 48 h. Potential CNS effects of loperamide were assessed by subjective drowsiness, by means of a 100-mm long horizontal visual analogue scale (VAS), and by the digit symbol substitution test (DSST).

Itraconazole, gemfibrozil and their combination increased exposure to loperamide, as illustrated by marked increases in both C_{max} and $AUC_{0-\infty}$ (Table 3). Coadministration of loperamide with the combination itraconazole–gemfibrozil resulted in a synergistic 4.2-fold (range: 1.5- to 8.7-fold) increase in loperamide C_{max} and a synergistic 12.6-fold (range: 4.3- to 21.8-fold) increase in loperamide $AUC_{0-\infty}$. The amount of loperamide excreted in urine (Ae) within 48 h of drug intake increased 3.0-fold, 1.4-fold and 5.3-fold after coadministration with itraconazole, gemfibrozil and their combination, respectively. Although previous clinical data have suggested that itraconazole can decrease renal clearance of digoxin through inhibition of P-glycoprotein-mediated tubular secretion,[38] the renal clearance (CL_{renal}) of loperamide did not change after coadministration with itraconazole (Table 3). Coadministration of loperamide and gemfibrozil alone or in combination with itraconazole resulted in a 28–34% decrease in loperamide CL_{renal} despite the fact that gemfibrozil is not a P-glycoprotein substrate or inhibitor.[40,41]

Despite the marked pharmacokinetic interaction between loperamide and itraconazole–gemfibrozil, none of the maximum response, the $AUEC_{0-12}$ for the DSST or the VAS for subjective drowsiness showed a relevant effect on psychomotor function for itraconazole, gemfibrozil or their combination compared with placebo.

Interaction studies with protease inhibitors

Loperamide is commonly used for the treatment of diarrhoea in individuals with HIV infection. All available HIV protease inhibitors are substrates of CYP3A4, while some are also known as inducers or inhibitors of P-glycoprotein.[42]

We identified three studies that investigated drug–drug interactions between loperamide and protease inhibitors in humans, including one study with ritonavir (an inhibitor of both CYP3A and P-glycoprotein[43]), one study with ritonavir with or without coadministration of tipranavir (a substrate, an inducer and an inhibitor of CYP3A and a potent inducer of P-glycoprotein[42,44]), and one study with saquinavir (a substrate for CYP3A and a substrate and inhibitor (in-vitro) of P-glycoprotein[45]). None of these studies confirmed a clinically relevant pharmacodynamic interaction with loperamide.

In the first interaction study, a single 16 mg dose of loperamide was given to 12 healthy subjects in combination with either 600 mg ritonavir or placebo in a randomised, double-blind, two-way crossover design.[46] The pharmacokinetics of loperamide and its metabolite *N*-desmethylloperamide were determined over 72 h. Potential CNS effects of loperamide were measured for 6 h after dosing through evaluation of pupil diameter, the cold pressor test for pain and transcutaneous partial pressure analysis of carbon dioxide (P_{CO_2}) and oxygen (P_{O_2}) as a measure of respiratory depression.

After coadministration of loperamide and ritonavir, loperamide C_{max} increased from 4.1 to 4.8 ng/ml and loperamide $AUC_{0-\infty}$ from 40.7 to 131.4 ng.h/ml. Loperamide CL_{renal} minimally changed after coadministration of ritonavir (Table 3). None of the pharmacodynamic measures showed a relevant change during coadministration of loperamide with ritonavir. In addition, the combination of loperamide and ritonavir was safe and well tolerated; if present, adverse events were mild and transient, and no serious adverse events occurred.

The pharmacokinetics, CNS effects and safety of loperamide alone and in combination with ritonavir, with or without tipranavir, were evaluated in a randomised, open-label, parallel-group study in 24 healthy subjects.[47] Loperamide was administered as a single dose of 16 mg on day 1. On days 4–9, subjects took ritonavir 200 mg twice daily or tipranavir 750 mg twice daily, with a single dose of 16 mg of loperamide being added on day 9. On days 12–22, the combination of tipranavir and ritonavir was administered, with a single dose of 16 mg of loperamide being added on

day 22. Respiratory response and pupillary response to loperamide were assessed as surrogate markers for potential CNS effects.

Marked increases in loperamide C_{max} and $AUC_{0-\infty}$ were observed after concurrent intake with ritonavir (Table 3). The tipranavir-containing regimens caused a decrease in the C_{max} and $AUC_{0-\infty}$ of loperamide (Table 3). The respiratory response after coadministration of ritonavir and loperamide was similar to that with loperamide alone. In addition, the mean pupillary response, measured as the mean pupil-to-iris diameter ratio, did not show relevant differences between loperamide alone, loperamide plus ritonavir or the baseline prior to drug administration. If reported, adverse events were not considered serious or severe, and none of the subjects withdrew from the study due to adverse events.

The third interaction study with loperamide and a protease inhibitor tested the potential for interaction between loperamide and saquinavir in 12 healthy subjects who received a single dose of 600 mg saquinavir, a single dose of 16 mg loperamide or their combination in a randomised, double-blind, double-dummy, three-way crossover design.[48] This study did not include evaluation of pharmacodynamic parameters.

Coadministration of saquinavir and loperamide led to a 1.4-fold increase in loperamide $AUC_{0-\infty}$ and a 1.2-fold increase in loperamide C_{max} (Table 3). Renal clearance of loperamide remained unchanged. Simultaneously, loperamide reduced saquinavir $AUC_{0-\infty}$ and C_{max} approximately 1.5-fold. As the pharmacokinetic interaction was observed after single-dose administration, it was assumed that loperamide impacted the absorption of saquinavir from the gastrointestinal tract as no change was observed in saquinavir half-life and saquinavir lag time after loperamide administration.

Interaction study with selective P-glycoprotein inhibitors

Even when coadministered with a selective P-glycoprotein inhibitor (tariquidar (XR-9576) and HM30181A), loperamide has not been demonstrated to induce clinically relevant central opiate effects in humans.

Tariquidar is a potent, selective, third-generation inhibitor of P-glycoprotein and does not inhibit CYP3A4. It is under development for the treatment of multidrug-resistant tumours. After intravenous administration of 2.0 mg/kg in healthy subjects it completely inhibited P-glycoprotein-mediated substrate efflux from lymphocytes for 24 h.[49]

An open-label dose-finding study in 15 healthy volunteers was performed to determine the dose of loperamide that could be safely coadministered in a subsequent double-blind study with the maximum single dose of tariquidar approved for human studies (150 mg, intravenous).[29] All subjects were pre-treated with 150 mg tariquidar (intravenous). Thereafter, an oral loperamide dose of 0.5, 1, 2, 4, 6, 8, 12, 14, 16, 32 or 48 mg was serially given on separate days to one subject. At the highest dose of 48 mg a clinically relevant central activity (decreased systolic blood pressure, sedation) was observed. In two additional subjects treated with the 32 mg dose no adverse effects were observed. Hence, an oral dose of 32 mg was chosen for the subsequent double-blind study.

In the double-blind, randomised, two-way crossover study, nine healthy subjects received high-dose loperamide (32 mg) together with intravenous tariquidar (150 mg) or placebo.[29] Pupil diameter and alertness (short-term memory recall by DSST and subjective drowsiness by VAS) were assessed before loperamide intake and every 30 min thereafter for 12 h as a surrogate measure for central opiate activity. The pharmacokinetics of loperamide were assessed up to 48 h after intake. The functional activity of P-glycoprotein in lymphocytes from each individual subject was determined by a dye efflux method.

Tariquidar did not significantly impact the pharmacokinetics of loperamide. The median AUC_{0-48} and C_{max} were about 1.5-fold higher with tariquidar than with placebo ($P = 0.12$ and $P = 0.52$, respectively) (Table 3). In addition, there was no significant effect on pupil size when loperamide was coadministered with tariquidar (median $AUEC_{0-12}$: 49.4 mm.h vs 65.8 mm.h with placebo, $P = 0.11$; median per cent decline: 6.9%). No changes in alertness were seen between tariquidar and placebo administration. Ex-vivo lymphocyte P-glycoprotein activity was almost completely blocked (93.7%). One of the nine subjects in the study showed marked pupil constriction after tariquidar intake, resulting in a decline in pupil size AUEC of 36.5%; this was accompanied by a marked 1.33-fold increase in loperamide AUC_{0-48} and a doubling of the C_{max} (from 3.7 to 8.9 ng/ml). In all, the results of this study suggest that tariquidar had a negligible effect on the blood–brain barrier and the brain disposition of loperamide.

HM30181A is a novel P-glycoprotein inhibitor under development for the enhancement of the oral bioavailability of drugs that are affected by P-glycoprotein. A four-period, single-sequence crossover study was conducted in 18 healthy subjects who were allocated in a 1:1:1 fashion to 15, 60 or 180 mg HM30181A.[50] In the first period, loperamide 16 mg was administered alone. In the second and third periods, loperamide 16 mg was given with quinidine 600 mg and HM30181A, respectively. In the fourth period, loperamide 16 mg was administered alone. Pupil diameter was serially measured.

Although the extent of inhibition of P-glycoprotein was not as large as with quinidine, HM30181A increased loperamide bioavailability (see Table 3), and this was mainly through inhibition of intestinal P-glycoprotein. The inhibitory effect of HM30181A lasted for 3 days. During coadministration of loperamide and quinidine, pupil size decreased significantly compared with loperamide alone. During the other treatment periods, no significant change in pupil diameter was observed.

Post-marketing safety review

A total of 8848 spontaneous cases reported for loperamide (all formulations) have been collected in the internal Johnson & Johnson worldwide safety database over a period of 37 years since the first approval. In the database, there were 595 cases that described the coadministration of loperamide and a P-glycoprotein substrate or inhibitor. Of these 595 cases, five cases reported a drug–drug interaction, eight cases reported 'loperamide toxicity' and 20 cases reported signs and symptoms suggestive of CNS depression or opioid toxicity.

The eight cases reporting 'loperamide toxicity' were all found to be associated with loperamide overdose, which precluded further assessment. Three of the five cases reporting a drug–drug interaction did not report any signs or symptoms suggestive of CNS depression or opioid toxicity. The other two cases of drug–drug interaction are summarised in Table 4. Neither of these two cases described a typical clinical course of opioid toxicity or symptoms of CNS depression, or reported plasma levels for loperamide. In one of the two cases, a toxicology screen was positive for opioids and the patient responded to treatment with naltrexone. This case described a woman who experienced delirium after recent ingestion of loperamide. An alternative explanation may exist in a potential interaction between St John's wort and valerian root. Extract of St John's wort has been shown to have a potent affinity for the adenosine, serotonin, dopamine, opioid, benzodiazepine and gamma-aminobutyric acid (GABA) receptors and to weakly inhibit monoamine oxidase (MAO).[51]

In the other case, an elderly patient presented with CNS symptoms (miosis, altered state of consciousness, somnolence and confusional state) in the context of underlying acute renal failure and anaemia, which represent an alternative aetiology for the CNS symptoms. This patient was also on a multiple-drug regimen, including ciclosporin (a P-glycoprotein inhibitor[25,30]), fluconazole (a CYP3A4 inhibitor[25,30]) and several other drugs. The reporter of this case attributed the events to accumulation of loperamide due to the acute renal failure and/or an interaction between loperamide and fluconazole.

Of the 20 cases reporting signs or symptoms suggestive of CNS depression or opioid toxicity, four cases provided insufficient information, one case reported an implausible temporal relationship and eight cases reported a co-medication or underlying disease which offered an alternative aetiology for the events. The remaining seven cases that are suggestive of CNS depression or opioid toxicity are summarised in Table 4. None of these seven cases described a typical clinical course of opioid toxicity or symptoms of CNS depression, reported a drug–drug interaction or provided plasma levels for loperamide. Six of the seven cases involved elderly patients (≥70 years of age) and one case involved an infant. All elderly patients were taking multiple co-medications, including three patients who were on cholesterol-lowering therapy with atorvastatin. Atorvastatin has been proposed *in vivo* as a weak inhibitor of P-glycoprotein. Clinical studies of identical design previously concluded that coadministration of 10 mg atorvastatin did not alter digoxin pharmacokinetics, while coadministration of 80 mg atorvastatin resulted into a 20% increase in steady-state digoxin concentrations, apparently due to an increase in the extent of digoxin absorption. These observations were supported by findings in the Caco-2 cell model system.[52] Data from in-vitro studies further suggest that atorvastatin may inhibit the activity of CYP2C8 and CYP3A4,[53,54] both of which have been suggested to be primarily responsible for the biotransformation of loperamide.[17] The case describing an 18-month-old infant reported miosis accompanied by cyanosis, dyspnoea, abdominal distension, flatulence, hypertonia and hypotonia, which occurred 1 day after treatment with domperidone and loperamide was initiated for gastroenteritis. There were no additional symptoms indicating CNS depression. Laboratory tests revealed severe anaemia and salmonellosis intestinal infection.

Discussion

Both human and animal studies have shown that P-glycoprotein is involved in regulating the absorption, distribution and elimination of many drugs and their metabolites, including prevention of their accumulation in the brain. Inhibition of the P-glycoprotein transport system could therefore potentially increase the extent of drug absorption, reduce elimination and increase penetration across the blood–brain barrier.

One drug interaction study out of a total of 10 papers has suggested that inhibition of P-glycoprotein-mediated efflux at the level of the blood–brain barrier could play a role in the observed decrease in ventilatory response when loperamide is coadministered with quinidine. No other endpoints to assess CNS depression were measured in this study and the results may have been confounded by the CNS effects of quinidine itself.[55] All other published studies that were part of our review did not support the theory that inhibition of P-glycoprotein-mediated efflux is associated with signs or symptoms of CNS depression or opioid toxicity – even when supra-therapeutic doses of loperamide are used or in combination with selective metabolic inhibitors.

Loperamide is a widely used drug that is available as a prescription medication and, in some countries, over the counter. The first approval of a loperamide-containing formulation was in April 1973. Currently, loperamide and loperamide oxide are licensed worldwide in 137 and 15 countries, respectively. For the period between January 1988 and June 2008, the worldwide post-marketing exposure to loperamide and loperamide/simethicone (2 mg strength) was approximately 13 billion units and to loperamide oxide 390 million units (1 mg).[56]

Based on the cumulative review of 595 post-marketing cases that described the coadministration of loperamide and a P-glycoprotein substrate or inhibitor, there is insufficient evidence to conclude that an interaction between loperamide and a P-glycoprotein inhibitor or substrate is associated with clinical symptoms of CNS depression or opioid toxicity when loperamide is administered at recommended doses. Those cases that did present potential symptoms of CNS depression/opioid toxicity were confounded by underlying disease or coadministration of other drugs with CNS effects, lacked pharmacokinetic evidence and/or did not describe a typical course of CNS depression/opioid toxicity.

In all, our findings from the literature and from review of the Johnson & Johnson internal worldwide safety database provide no evidence that selective inhibition of P-glycoprotein in humans during coadministration of loperamide will result in clinically relevant CNS depression or opioid toxicity. The observations *in vitro* or in animals could be explained by (1) different sensitivity of P-glycoprotein inhibition in different tissues (which can be overcome with higher doses of the P-glycoprotein inhibitor), (2) involvement of other drug transporters in loperamide brain uptake or (3) differences in P-glycoprotein expression.

Table 4 Spontaneous reports: summary of loperamide cases suggestive of drug–drug interaction or of CNS depression or opioid toxicity

Case	Source	Sex/age	Loperamide formulation, dose	P-glycoprotein drug (inhibitor/substrate, dose)	Other concomitant medication	Adverse events of interest
Cases reporting a drug–drug interaction and symptoms or signs that are suggestive of CNS depression or opioid toxicity						
1	Literature[64]	Female/39 years	Loperamide HCl, dose not reported	St John's wort (P-gp substrate and inhibitor, dose not reported)	Valerian root	Delirium, drug interaction
2	Health authority	Male/72 years	Loperamide oxide, dose not reported	Ciclosporine (P-gp substrate and inhibitor, dose not reported)	Irbesartan, amlodipine besilate, metoclopramide, allopurinol, ofloxacin, omeprazole, urapidil, atenolol	Altered state of consciousness; confusional state; somnolence; miosis; drug interaction
Cases not reporting a drug–drug interaction, but reporting symptoms or signs that are suggestive of CNS depression or opioid toxicity						
3	Health authority	Male/85 years	Loperamide HCl, dose not reported	Risperidone (P-gp substrate, dose not reported)	Donepezil, lisinopril, fenofibrate, Berodual (ipratropium and fenoterol)	Confusional state; somnolence
4	Spontaneous, medically confirmed	Female/70 years	Loperamide HCl, 2 mg, 3 times a day	Nicardipine (P-gp inhibitor, dose not reported)	Metoclopramide, alfa-calcidol, folic acid, pyridoxine	Somnolence
5	Spontaneous, patient-reported	Female/76 years	Loperamide HCl, 2 mg, single dose	Digoxin (P-gp substrate, dose not reported)	Unspecified anti-neoplastic therapy	Somnolence
6	Spontaneous, patient-reported	Female/81 years	Loperamide/ simethicone, 2 caplets	Atorvastatin (P-gp inhibitor, dose not reported)	Hydrochlorothiazide, acetylsalicylic acid, lisinopril	Somnolence
7	Spontaneous, patient-reported	Female/73 years	Loperamide HCl, single dose	Atorvastatin (P-gp inhibitor, 20 mg/day)	Lisinopril, hydrochlorothiazide, aspirin, glucosamine, chondroitin, multivitamin	Loss of consciousness
8	Spontaneous, patient-reported	Female/80 years	Loperamide HCl, 2 mg, single dose	Atorvastatin (P-gp inhibitor, dose not reported)	Unspecified vitamins	Lethargy
9	Spontaneous, medically confirmed	Unknown/18 months	Loperamide HCl, 1 mg, 3 times a day	Domperidone (P-gp substrate, 5 mg 3 times a day)	None	Miosis

CNS, central nervous system; HCl, hydrochloride; P-gp, P-glycoprotein. Source: Johnson & Johnson internal worldwide safety database; cut-off date: 16 June 2008.

Different sensitivity of P-glycoprotein inhibition in different tissues

In patients suffering from metastatic cancer, intravenous administration of 150 mg of the potent and selective P-glycoprotein inhibitor tariquidar resulted in increases of 36–263% of the tumour/heart ^{99m}Tc-sestamibi AUC_{0-3} in 8 out of 13 patients.[57] When high-dose loperamide was administered to healthy volunteers together with tariquidar, no increase in CNS depression or opioid toxicity suggestive of inhibition of P-glycoprotein at the blood–brain barrier was observed.[29] This different sensitivity of inhibition of P-glycoprotein in different tissues was also demonstrated in animals. After intravenous administration of tariquidar and radiolabelled loperamide, and in the absence of changes in loperamide plasma levels, the loperamide dose–response curves for testes/plasma and brain/plasma concentrations were shifted 6- and 25-fold to the right, respectively, compared with the rhodamine efflux curve from lymphocytes.[58]

Involvement of other drug transporters in loperamide brain uptake

A more recent explanation for the findings in humans is offered by observations from in-vitro experiments suggesting the involvement of transporters other than P-glycoprotein in the cellular efflux of loperamide. Following a detailed kinetic analysis of P-glycoprotein-mediated transport in MDCKII-cells stably transduced with *ABCB1*, Acharya *et al*.[59] found that a basolateral uptake transporter is involved in loperamide transport in this cell line. However, the effects of this unidentified transporter were negligible at concentrations exceeding 3 μM and at time points shorter than 3 h. The authors postulated that loperamide transport is not uniquely mediated by P-glycoprotein. To further understand the possible contribution of multiple transporters in the transport of loperamide, we evaluated loperamide transport in three well-established models: human P-glycoprotein (*ABCB1*), murine breast cancer resistance protein 1 (Bcrp1/Abcg2) and human multidrug resistance protein 2 (MRP2/ABCC2, canalicular multispecific organic anion transporter [cMOAT]).[60] The clinical relevance of the first two ABC-transporters is clearly established, whereas the in-vivo pharmacokinetic function of MRP2 is limited.[61] The results from our experiments confirmed the existence of P-glycoprotein-mediated loperamide transport, but did not provide any evidence that Abcg2 or ABCC2 is involved in loperamide transport (data not shown).[60]

Differences in P-glycoprotein expression

A decrease in P-glycoprotein expression may also be involved in changes in loperamide disposition, although results are not consistent. Skarke *et al*.[34] reported a significant increase in miosis after a high dose of loperamide and quinidine in a group of *ABCB1*–3435TT carriers. This single nucleotide polymorphism has been reported to be associated with lower intestinal P-glycoprotein expression in Caucasians.[35] When digoxin as a probe substrate for P-glycoprotein was administered as a single oral dose to healthy volunteers, a significantly higher AUC_{0-4} and AUC_{0-24} for digoxin was observed in 3435TT carriers compared with 3435CC and 3435CT carriers. There was no significant difference for t_{max}.[62] The data by Skarke *et al*.[34] were from a selected population with 11 out of 21 subjects being carriers of the single nucleotide polymorphism 3435TT compared with 24% in a larger population.[35] The effect of a lower intestinal expression of P-glycoprotein that would result in increased loperamide plasma concentrations was not confirmed, as no statistical differences in AUC or C_{max} between carriers and non-carriers existed before and after administration of quinidine. Pauli-Magnus *et al*.[63] also found no effect of *ABCB1* genetic polymorphisms on loperamide disposition and CNS effects. When a group of healthy subjects homozygous for the 3435TT allele was compared with a control group there was no difference in pharmacokinetics between carriers of the 3435TT allele and carriers of the reference sequence 3435CC. The same was true for ventilatory response, which was used as a marker of increased brain entry of loperamide.

Conclusions

Based on a review of the published literature relevant to loperamide drug interactions and a cumulative review of 595 spontaneous case reports, data do not support that an interaction between loperamide and a P-glycoprotein inhibitor or substrate is associated with clinical symptoms of CNS depression or opioid toxicity when loperamide is taken at the recommended dose. Miotic effects have been observed during concomitant administration of loperamide and a P-glycoprotein inhibitor at supra-therapeutic doses, although not in a dose-dependent manner. A more limited sensitivity for P-glycoprotein inhibition in humans at the level of the blood–brain barrier may be involved. Mechanisms other than P-glycoprotein-mediated efflux may also be involved in brain disposition of loperamide, which would question its use as a robust P-glycoprotein substrate.

Declarations

Conflict of interest

All the authors are employees of Johnson & Johnson Pharmaceutical Research & Development or a division thereof. Otherwise they have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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