

Class: Prokinetic anti-emetic.

Indications: Nausea and vomiting, dysmotility dyspepsia, gastro-oesophageal reflux.

Pharmacology

Domperidone is a dopamine type 2-receptor antagonist. It is structurally related to the butyrophenones but does not normally cross the blood-brain barrier.¹ Domperidone has a dual anti-emetic effect. First, it acts on dopamine receptors in the chemoreceptor trigger zone (CTZ) in the area postrema. (Although situated on the surface of the brain stem, the CTZ is outside the physiological blood-brain barrier.) Second, it acts on D₂-receptors at the gastro-oesophageal and gastroduodenal junctions, and thereby counteracts the gastric 'dopamine brake' associated with nausea from any cause. Domperidone may also inhibit cholinesterase activity.² Because negligible amounts of domperidone penetrate the blood-brain barrier, there is negligible risk of extrapyramidal effects (mediated via the basal ganglia). Domperidone is the prokinetic and anti-emetic of choice in Parkinson's disease; it counteracts the emetic effect of **levodopa** and **bromocriptine** without adversely affecting the antiparkinsonian (dopaminergic) effect of these drugs.³

Although almost completely absorbed from the gastro-intestinal tract, bio-availability is relatively poor because of extensive gut-wall and hepatic first-pass metabolism. Bio-availability is increased by a third or more if taken *after* a meal. Maximal absorption requires an acid environment; H₂-receptor antagonists, proton pump inhibitors and antacids all reduce absorption, and bio-availability. Under standard conditions, absorption is linear up to 40mg single dose. Following absorption, domperidone is metabolised to inactive compounds via the hepatic CYP450 mixed oxidase system, principally CYP3A4 (see Cautions). The plasma half-life is increased by up to 50% in renal failure but the plasma concentrations do not increase (possibly because of an altered volume of distribution). Further, because renal clearance is a minor route of elimination, cumulation is not a concern.⁴ Although rectal bio-availability is almost the same as by mouth, the recommended rectal dose is three times the oral dose. This stems from pharmacodynamic studies, and possibly relates to slower absorption from the rectum.

The effect of domperidone on the lower oesophageal sphincter is equivocal.² Domperidone is as effective as **cisapride** in functional dyspepsia.⁵ Because domperidone, unlike **metoclopramide**, does not have any 5HT₄-receptor agonist action, it might be anticipated that domperidone would be less effective in treating gastroparesis. However, the results of a systematic review indicate otherwise (Table 4.13).⁶ Domperidone is also more effective than **cisapride** in children with diabetic gastropathy.⁷ Domperidone may be effective even when there is no response to **metoclopramide**.^{2,8}

Domperidone 20mg q.d.s. causes less frequent and less severe undesirable effects than **metoclopramide** 10mg q.d.s., e.g. less somnolence and loss of mental acuity.⁹ In diabetic patients, the prokinetic effect for solids attenuates after 1–2 months, although the effect on liquid emptying persists.^{10,11}

Table 4.13 Comparison of prokinetic drugs⁶

<i>Drug</i>	<i>Erythromycin</i>	<i>Domperidone</i>	<i>Metoclopramide</i>	<i>Cisapride</i>
Mechanisms of action				
Motilin agonist	+	-	-	-
D ₂ -receptor antagonist	-	+	+	-
5HT ₄ -receptor agonist	-	-	+	+
Response to treatment^a				
Gastric emptying (mean % acceleration)	45	30	20	30
Symptom relief (mean % improvement)	50	50	40	30

a. all percentages rounded to nearest 5%

The usefulness of domperidone is limited by the absence of a parenteral formulation. It was withdrawn in the early 1980s, after several patients died from ventricular arrhythmias when given IV domperidone.¹² Domperidone does not significantly alter the pharmacokinetics or pharmacodynamics of other drugs. Because the prokinetic effect of domperidone is mediated through a cholinergic final common pathway, its prokinetic effect will be impaired by concurrently administered antimuscarinic drugs.¹³

Bio-availability 12–18% PO (fasting), 24% PO (after food); 12% PR.²

Onset of action 30min.

Time to peak plasma concentration 0.5–2h PO; 1h PR.

Plasma half-life 7–16h; increasing up to 21h in severe renal impairment.²

Duration of action 12–24h (estimate based on half-life).

Cautions

Renal and hepatic impairment. The concurrent use of an antimuscarinic drug is likely to reduce the prokinetic effect of domperidone (but will not affect its central anti-emetic effect).

The main metabolic pathway of domperidone is CYP3A4 mediated. The concurrent use of drugs which significantly inhibit this enzyme may result in increased plasma levels of domperidone. The AUC and the peak plasma concentration of domperidone is *trebled* when oral **ketoconazole** is administered concurrently. The QT interval is slightly prolonged (<10msec) by this combination, greater than with **ketoconazole** alone. QT prolongation is *not* seen when domperidone is given alone, even at doses of 160mg/day (Unpublished data on file). Other strong CYP3A4 inhibitors include **erythromycin** and **ritonavir**.

Undesirable effects

For full list, see manufacturer's SPC.

Very common (>10%): gynaecomastia, galactorrhoea, amenorrhoea (secondary to increased prolactin secretion), reduced libido, transient colic.²

Common (<10%, >1%): pruritus, rash, cramp, headache.²

Very rare (<0.01%): extrapyramidal effects (acute dystonias), which resolve rapidly and completely once domperidone is stopped.¹⁴ In two women with polycystic ovaries, hyperoestrogenism may have been a predisposing factor.²

Dose and use

Although the SPC recommends administration t.d.s.-q.d.s., b.d. administration may well be satisfactory:

- starting dose 20mg PO b.d.
- increase if necessary to 40mg PO b.d. *or* 20mg PO q.d.s.

In patients with diabetic gastropathy, up to 120mg/day has been used for many years.²

Note: 30mg PR is approximately equivalent to 10mg PO.

Supply

Domperidone (non-proprietary)

Tablets 10mg, 28 days @ 20mg b.d. = £9.37.

Motilium® (Sanofi-Synthelabo 01483 505515)

Tablets 10mg, 28 days @ 20mg b.d. = £8.77.

Oral suspension 5mg/5ml, 28 days @ 20mg b.d. = £10.08.

Suppositories 30mg, 28 days @ 60mg b.d. = £29.68.

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