Subject: Galactagogues
Genre: Facts Sheet
Source: Janssen-Cilag
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Preface:

This facts sheet was published in New Zealand by the original manufacturer of Domperidone in the year 2000; however, it is similar to fact sheets published in other countries for the same medication. Because of the date of this publication, if you are considering using this medication for any purpose, you should look for more recent information published by the current manufacturer.

MOTILIUM®

Domperidone

Presentation:

MOTILIUM 10 mg tablets are white, circular, film-coated, biconvex tablets with m/10 imprinted on one side and JANSSEN on the other.

Uses:

Actions:

Domperidone is a dopamine antagonist with antiemetic properties similar to those of metoclopramide and certain neuroleptic medicines. Unlike these medicines; however, domperidone does not readily cross the blood-brain barrier. It seldom causes extrapyramidal side effects, but does cause a rise in prolactin levels. Its antiemetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of central dopamine receptors in the chemoreceptor trigger zone which lies in the area postrema and is regarded as being outside the blood-brain barrier. Animal studies have shown that domperidone has no effect on plasma concentrations of homovanillic, a metabolite of dopamine.

It also antagonises the behavioural effects of dopamine much more effectively when administered intracerebrally than when given systemically. These findings, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in humans have shown intravenous and oral domperidone to increase the duration of antral and duodenal contractions, to increase the gastric emptying of

liquids and semi,solids in healthy subjects and in patients in whom it was delayed, and to increase lower oesophageal sphincter pressure in healthy subjects. Domperidone has no effect on gastric secretion. Intravenous domperidone 10, 20 and 40 mg had no effect on cardiac output, cardiac electric conduction, heart rate or blood pressure in healthy volunteers up to one hour after administration.

Pharmacokinetics:

Absorption:

Domperidone is rapidly absorbed following intramuscular and oral administration with peak plasma concentrations occurring at approximately 10 and 30 minutes, respectively. Systemic bioavailability of intramuscular domperidone is about 83% whereas that of oral domperidone is 13% to 17%.

The low oral bioavailability is probably due to first pass metabolism in the liver and gut wall. Oral bioavailability is decreased by prior administration of cimetidine or sodium bicarbonate (see Interactions). The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral medicine is taken after a meal.

Metabolism:

Oral domperidone does not appear to accumulate or induce its own metabolism: a peak plasma level after 90 minutes of 21 ng/mL after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/mL after the first dose.

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Distribution:

Domperidone is 91% to 93% bound to plasma proteins. Distribution studies with radio-labeled medicine in animals have shown wide tissue distribution with low brain concentration. Small amounts of medicine cross the placenta in rats and the medicine is excreted in the breast milk of this species.

Elimination:

Urinary and faecal excretion amounts to 31% and 66%, respectively, of the oral dose. The proportion of the medicine excreted unchanged is small (10% of faecal

excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

Indications:

- Symptomatic treatment of the dyspeptic symptom complex which is often associated with delayed gastric emptying or gastro-oesophageal reflux and oesophagitis: epigastric sense of fullness, feeling of abdominal distension, upper abdominal pain, eructation, flatulence, heartburn.
- Treatment of nausea and vomiting of various origins including functional, organic, infectious, dietetic, radiotherapy, medicine therapy.
- As a diagnostic agent administered in radiology before a barium meal to increase the rate of passage of barium through the gastrointestinal tract.

Dosage and Administration:

General:

MOTILIUM should be taken 15-30 minutes before meals and, if necessary, before retiring.

Adults:

1, 10 mg, three to four times daily. If necessary this dose may be doubled after two weeks if an adequate therapeutic response is not attained.

For acute and subacute conditions (e.g. nausea and vomiting) 20 mg three to four times daily.

Children aged 2 and above:

0.2-0.4 mg/kg by mouth at 4-8 hourly intervals.

Use in Renal Impairment:

It is unlikely that the dose needs to be adjusted for single administration in patients with renal insufficiency. However, on repeated administration the dosing frequency will need to be reduced to once or twice daily depending on the severity of the impairment (see Warnings and Precautions). The dose may also need to be reduced. Generally, patients on prolonged therapy should be reviewed regularly.

Contraindications:

MOTILIUM should not be used whenever stimulation of gastrointestinal motility might be dangerous such as in the presence of gastrointestinal haemorrhage,

mechanical obstruction, or perforation.

MOTILIUM is also contraindicated in patients with known intolerance to domperidone, and in patients with prolactinoma (a prolactin releasing pituitary tumour).

Warnings and Precautions:

Warnings:

MOTILIUM produces an increase in plasma prolactin. The raised level persists with chronic administration but falls to normal on discontinuing the medicine. During chronic oral administration of 30 mg daily for two weeks the plasma prolactin level measured 90 minutes after medicine intake remained fairly constant at 25 ng/mL in males (normal value was 5 ng/mL) whilst in females the level of 117 ng/mL after the first dose decreased to 56 ng/mL after 14 doses (pretreatment normal value was 9 ng/mL).

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the administration of domperidone is contemplated in a patient with a past history of breast cancer. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with other prolactin-elevating medicines, the clinical significance of elevated serum prolactin levels is unknown. An increase in mammary neoplasms has been found in rodents after chronic administration of domperidone and other prolactin-stimulating medicines.

Neither clinical studies nor epidemiological studies conducted to date have shown an association between chronic administration of these medicines and mammary tumorigenesis. Domperidone does not affect plasma growth hormone or aldosterone levels.

Precautions:

Carcinogenicity, Mutagenicity, Teratogenicity: MOTILIUM was administered to mice for 18 months and rats for 24 months in carcinogenicity studies. No dose-related effects were observed except for an increased incidence of malignant mammary tumours at 25 times the maximum human dose in female mice and rats and an increased incidence of pituitary tumours at 25 times the human dose in male rats.

No evidence for mutagenic potential was seen in dominant lethal studies in male and female mice, micronucleus tests in female mice and female rats, a study of chromosomal aberrations in human lymphocytes, a sex-linked recessive lethal test

on Drosophila melanogaster, and in the Ames metabolic activation test with Salmonella typhimurium. Minor teratogenic effects were seen in one study where MOTILIUM was administered to rats orally at approximately 125 times the maximum human dose level. These findings were not confirmed by another study where the medicine was administered orally to rats at dosage levels as high as 400 times than that given to man.

Embryotoxicity without maternal toxicity was encountered when MOTILIUM was administered intravenously to rats (> 6 times the maximum human dose level) and orally to mice (44 times the maximum human dose level). Concurrent embryotoxicity and maternal toxicity were inconsistently found at oral dose levels approximately 6 times the maximum human level in rabbits and in rats and approximately 24 times the maximum human dose level.

Use in Hepatic Impairment:

Since domperidone is highly metabolised in the liver, MOTILIUM should be used with caution in patients with hepatic impairment.

Use in Renal Impairment:

In patients with severe renal insufficiency (creatinine serum levels > 6 mg/100mL, i.e. > 0.6 mmol/L) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours but plasma drug levels were lower than in healthy volunteers. Since very little unchanged medicine is excreted via the kidneys, it is unlikely that the dose needs to be adjusted for single administration in patients with renal insufficiency. However, on repeated administration the dosing frequency will need to be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced. Generally, patients on prolonged therapy should be reviewed regularly.

Use in Pregnancy:

There are no adequate and well-controlled studies of MOTILIUM in pregnant women. Domperidone given to animals at doses up to 160 mg/kg/day did not produce teratogenic effects. However, as with most medicines, MOTILIUM should only be used during the first trimester of pregnancy if this is justified by the anticipated therapeutic benefit. Up to now, there has been no evidence of any increased risk of malformations in humans.

Use in Lactation:

MOTILIUM was present in the milk of breast feeding mothers at approximately one-fourth mean plasma levels (2.6 ng/ml) 1.75-3 hours following a 10 mg oral dose. It

is not known whether this is harmful to the newborn. Accordingly, caution should be exercised when MOTILIUM is administered to a breastfeeding mother.

Paediatric Use:

In treating nausea and vomiting, thorough investigations of the possible causes of these symptoms should be performed. Since the metabolic and blood-brain barrier functions are not fully developed during the first months of life, any medicine in young infants should only be given very cautiously and under close medical supervision. Since the typical absence of neurological side effects with domperidone is mainly due to its poor penetration through the blood-brain barrier, the possible occurrence of such effects cannot be totally excluded in babies under one year of age.

Adverse Effects:

The most frequent reactions to MOTILIUM are those related to elevated prolactin levels including breast tenderness, galactorrhoea, gynaecomastia and amenorrhoea. These effects are dose-related and gradually resolve after lowering the dose or discontinuing treatment.

Other rarely reported adverse reactions include headache, diarrhoea, dizziness, mild and transient abdominal cramps, dry mouth and drowsiness. Rare allergic reactions, such as rash and urticaria, have also been reported.

Extrapyramidal reactions occur rarely in young children, very rarely in adults and usually resolve completely and spontaneously after cessation of treatment.

Interactions:

Concomitant administration of anticholinergic medicines may antagonise the antidyspeptic effect of MOTILIUM. If administered prior to atropine, domperidone reduces the relaxant effect of atropine upon the lower oesophageal sphincter, but has no reversing effect if atropine is administered first. Since MOTILIUM has gastro-kinetic effects it could influence the absorption of concomitantly orally administered medicines, particularly those of sustained release or enteric-coated formulations.

However, in patients already stabilised on digoxin, paracetamol or haloperidol, concomitant administration of domperidone did not influence the blood levels of these medicines.

Antacids and antisecretory agents should not be given simultaneously with

MOTILIUM because they lower its bioavailability.

The main metabolic pathway of domperidone is through the cytochrome P450 isoenzyme CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Examples of CYP3A4 inhibitors include; azole antifungals, macrolide antibiotics, HIV protease inhibitors and nefazodone.

Domperidone has been used with:

- neuroleptics, without potentiation of their activity.
- dopaminergic agonists (bromocriptine, L-dopa) for suppression of unwanted peripheral effects such as digestive disorders, nausea and vomiting, without affecting their central activity.

Overdosage:

Symptoms:

Symptoms of overdosage may include drowsiness, disorientation and extrapyramidal reactions, especially in children.

Treatment:

Anticholinergics, anti-parkinsonian agents or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. In the event of accidental overdosage supportive measures including gastric lavage with sodium bicarbonate, should be employed. There is no specific antidote. Close observation and supportive therapy are recommended. Symptoms are self-limiting and usually disappear within 24 hours.

Pharmaceutical Precautions:

Shelf Life:

4 years when stored at or below 30°C

Special Precautions for Storage:

Protect from light. Store at room temperature.

Medicine Classification:

Prescription Medicine.

Package Quantities:

Bottles of 100 tablets.

Further Information:

MOTILIUM 10 mg tablets also contain lactose, maize starch, microcrystalline cellulose, pregelatinized potato starch, polyvidone, magnesium stearate, hydrogenated vegetable oil, sodium lauryl sulfate and hypromellose.

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