METHYLSULFONYLMETHANE (MSM)

Pharmacy Compounding Advisory Committee
October 27-28, 2015

A.J. Day, PharmD, RPh
Director of Pharmacy Consulting
PCCA

FDA briefing information

- Stability: As it is stable under these extreme conditions, it is likely to be very stable in all dosage forms
- Purity: The presence of these and other impurities would result in a lower melting point, and the presence of either liquid starting material would result in a non-crystalline semi-sold.
- Polymorphs: There appear to be no polymorphs, with only one crystalline form reported (FDA Response Letter, 2008). It is also reported to have an aqueous solubility of 150 mg/mL (Remizov et al., 1980). Consequently physicochemical characteristics are not expected to influence its performance when administered as a powder or solid oral dosage form.
- **Conclusion**: From the viewpoint of characterization and physicochemical properties, MSM is suitable for use in compounding.

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- Pharmacology: MSM is an organic sulfur-containing compound that is an oxidized metabolite of DMSO. MSM is found in a number of foods including milk, grains, meat, eggs, fish and vegetables (Richmond, 1986). The mechanism(s) of action of MSM have not been fully characterized. However, MSM has been reported to possess anti-oxidant, anti-apoptotic, and anti-inflammatory properties (Karabay et al., 2014; Ahn et al., 2015; Amirshahrokhi et al., 2013). MSM has also been shown to exert beneficial effects in rodent models of osteoarthritis due to its sulfur concentration, which contributes to cysteine, a 4 sulfur-containing amino acid required for the production of keratin (Ezaki et al., 2013).

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- Acute toxicity – GRAS, Center for Food Safety and Applied Nutrition (CFSAN): In a response letter to the GRAS notice dated February 18, 2008, CFSAN replied that they had no questions regarding the submitter's conclusion that MSM is GRAS for use in foods under the conditions of use stated in the notice (for use as an ingredient in meal supplement and meal replacement foods, fruit smoothie-type drinks, and fruit-flavored thirst quencher-type beverages at levels up to 4,000 mg/kg and in food bars such as granola bars and energy-type bars at levels up to 30,000 mg/kg).

FDA briefing information

- Repeat dose rat toxicity: One report of a repeat-dose toxicology study of MSM is available in the published literature (Hovarth et al., 2002).
- A no observed adverse effect level (NOAEL) of >1.5 g/kg was identified by the authors (this corresponds to a human equivalent dose (HED) of 14.5 g/60 kg person/day based on a body surface area comparison). No other repeat-dose toxicology studies were found in the published literature.
  - Specifically, we have not been able to find any topical, intravenous, or ophthalmic toxicology data.

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Toxicokinetics: Magnusun (2007)

- 500 mg/kg of [35S]MSM (identical to MSM, except for the addition of a sulphur-35 radiolabel tag) was administered to 8 male Sprague-Dawley rats.
- Significant levels of MSM were detected in brain (similar to those found in liver, indicating that MSM readily crosses the blood brain barrier).
  - **N = 8 (tests only done on 6** – 3 rats from blood group & 3 from urine/feces group**)**
  - The dose represented 3 times the maximum reported dose in humans of 182 mg/kg (*14*) and approximately 5 times the dose of 6000 mg/day used in adults in a recent clinical study (*2*).

FDA briefing information

- Magnusun (2007)

Experimental Design. Each rat received a single oral (gavage) dose of [^{35}S]MSM formulation at 5 mL/kg to deliver approximately 500 mg/kg MSM and 50 μCi/rat. The dose represented 3 times the maximum reported dose in humans of 182 mg/kg (*14*) and approximately 5 times the dose of 6000 mg/day used in adults in a recent clinical study (*2*). Five rats were designated group 1 (blood group), and three rats were designated group 2 (urine and feces group). Samples of blood were

Magnusun (2007)

Table 3. Tissue Concentrations of Radioactivity and Tissue/Blood Ratios following [^{35}S]MSM Administration to Rats

		concentration[a] (μg equiv/g)		tissue/blood ratio	
tissue	*N*	48 h	120 h	48 h	120 h
blood[b]	3	63.7 ± 12.3	N/A	N/A	N/A
liver	3	54.7 ± 11.4	BLQ	0.856	N/A
heart	3	59.4 ± 11.7	BLQ	0.932	N/A
kidney	3	71.1 ± 15.7	BLQ	1.11	N/A
spleen	3	58.2 ± 14.4	BLQ	0.909	N/A
testes	3	69.4 ± 16.2	BLQ	1.08	N/A
brain	3	58.7 ± 11.8	BLQ	0.921	N/A
eye	3	66.7 ± 12.9	BLQ	1.05	N/A
skin	3	51.8 ± 13.7	BLQ	0.807	N/A
bone	3	35.2 ± 0.9	BLQ	0.563	N/A

[a] Values are expressed as means ± SD. BLQ, below the limit of quantification; *N*, number; N/A, not applicable. [b] This mean blood concentration uses only the same three animals utilized for tissue analysis.

- It should be noted that in the present study, elimination of total $_{35}$S was measured and not the elimination of MSM. The $_{35}$S half-life in blood of approximately 12 h from MSM indicates that approximately 75% of the radioactivity from MSM is cleared in 24 h, and almost complete elimination of radiolabel is expected by 60 h (5 half-lives). The results of the present study indicate that no radioactivity was detected in tissues at 120 h and support the rapid elimination kinetics of MSM. **The fact that the administered radioactivity may remain in the animal body for longer periods does not mean it is present as MSM**. There are many opportunities for sulfur to incorporate into biological molecules, especially when the animal feed has low sulfur content. **Studies have demonstrated that sulfur from MSM can be incorporated into tissue proteins (*9*, *17*).**

Magnusun (2007); Richmond (1986) – Radiolabeling

Richmond (*9*) also reported that administration of [^{35}S]MSM to guinea pigs resulted in incorporation of radiolabel into serum proteins, particularly in the amino acids methionine and cysteine. These observations also indicate that the partial elimination of radiolabel (~59%) by 24 h in the present study may be partly because of the incorporation of ^{35}S from MSM into proteins that may have a half-life of > 1 day. For example, proteins with

FDA briefing information

- Conclusions: Pharmacology studies have shown that significant levels of MSM are present in the brain following oral administration in **humans and rats**. The clinical significance of MSM crossing the blood brain barrier is uncertain as there are limited toxicology data in the published literature and very little detail regarding the histopathological evaluations of brain tissue.
  - Humans: Lin (2001) – 4 patients
    - (3 of whom were only examined once)
    - Retrospective review of charts, perform MRS
    - "No adverse clinical or neurochemical effects were observed."
  - Rats: Magnusun (2007) discussed previously

2. Patients/methods

The study population was drawn from subjects referred by their physician to the clinical MRS Unit of Huntington Medical Research Institutes between January 1991 and March 2001, for diagnosis of common neurological disorders including mild cognitive impairment, Alzheimer's Disease, stroke, brain tumor, Parkinson's Disease, infection, CFS, hepatic and toxic encephalopathies.

FDA briefing information

- From the nonclinical perspective, there do not appear to be any data suggesting adverse effects; however, the data for oral toxicity is limited, and there are no data for the other routes of administration.

FDA briefing information

d. The availability of alternative approved therapies that may be as safe or safer

- Approved therapies for osteoarthritis and joint pain include the following drugs and drug classes: **acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), duloxetine, opioids and opioid combination products**. **All of these therapies carry risks (GI, cardiovascular, renal, and hepatic toxicities, abuse and addiction), especially with longterm administration.** The safety profile of MSM reported in the literature is poorly characterized and includes minor symptoms, but more notably, both the literature and the FAERS search ***suggest that there may be an interaction with warfarin and risk for bleeding***, even with relatively short-term exposure, as well as a risk for hypertension (literature only). This is important because the treatment of osteoarthritis can be chronic and there are no safety data to indicate whether risk increases over time. The lack of long-term safety data for MSM makes it difficult to reliably compare the safety of MSM relative to approved therapies.

FDA proposed criteria to evaluate the nominated substances

- (1) The physical and chemical characterization of the substance;
- (2) Any safety issues raised by the use of the substance in compounded drug products;
- (3) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature; and
- (4) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists.

- No single one of these criteria is dispositive. Rather, the agency is considering each criterion in the context of the others and balancing them, on a substance-by-substance basis, in deciding whether a particular substance is appropriate for inclusion on the list.

Safety concerns

- FDA bibliography includes publications from 35 years ago

The Office of Surveillance and Epidemiology conducted a search of the FDA Adverse Events Reporting System (FAERS) database for reports of adverse events for MSM through March 19, 2015. Sixteen unique adverse event reports were identified, nine of which were serious. The most commonly reported events were fatigue, nausea, cough, drug ineffective, drug interaction, dyspnea, hematoma, headache, increased international normalized ratio (INR), product quality issue, and somnolence.

Level 3 (Moderate) (3 results)

Drug to Drug Interactions

Anticoagulants and **Nonsteroidal antiinflammatory drugs**

Anticoagulants cause additive effects that may result in increased risk of bleeding with Nonsteroidal antiinflammatory drugs.

An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.

Anticoagulants and **Duloxetine**

Anticoagulants have an additive effect with Duloxetine.

Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication in patients receiving anticoagulants. Elevations in prothrombin time, activated partial thromboplastin and INR values have been reported post-marketing when venlafaxine was added to established warfarin therapy. The causality and mechanism of this potential interaction have not been established. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with an anticoagulant medication and to promptly report any bleeding events to the practitioner.

Duloxetine and **Nonsteroidal antiinflammatory drugs**

Duloxetine has an additive effect with Nonsteroidal antiinflammatory drugs.

Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving NSAIDs. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with medications which impair platelet function and to promptly report any bleeding events to the practitioner.

Level 4 (Minor) (1 result)

Drug to Drug Interactions

Acetaminophen and **Warfarin Sodium**

Acetaminophen increases effect of Warfarin Sodium.

Although acetaminophen is routinely considered safer than aspirin and agent of choice when a mild analgesic/antipyretic is necessary for a patient receiving therapy with warfarin, acetaminophen has also been shown to augment the hypoprothrombinemic response to warfarin. Concomitant acetaminophen ingestion may result in increases in the INR in a dose-related fashion. Clinical bleeding has been reported. Single doses or short (i.e., several days) courses of treatment with acetaminophen are probably safe in most patients taking warfarin. Clinicians should be alert for an increased INR if acetaminophen is administered in large daily doses for longer than 10 to 14 days.

Centers for Disease Control and Prevention – 2015 September

Draft Recommendation 1

- Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks.

NSAIDs in OA

Hauser RA. The Acceleration of Articular Cartilage Degeneration in Osteoarthritis by Nonsteroidal Anti-inflammatory Drugs. J Prolotherapy. 2010 Feb(2),1:305-22

- “In OA, there is a disruption of the homeostatic state and the catabolic processes of chondrocytes. It is clear from the scientific literature that NSAIDs from *in vitro* and *in vivo* studies in both animals and humans have a significantly negative effect on cartilage matrix which causes an acceleration of the deterioration of articular cartilage in osteoarthritic joints. The preponderance of evidence shows that NSAIDs have no beneficial effect on articular cartilage in OA and accelerate the very disease for which they are most often used and prescribed. Some of the effects of NSAIDs on the articular cartilage in OA include inhibition of chondrocyte proliferation, synthesis of cellular matrix components, glycosaminoglycan synthesis, collagen synthesis and proteoglycan synthesis. The net effect of all or some of the above is an acceleration of articular cartilage breakdown.”

NSAIDs, Acetaminophen, and ESRD

Perneger et al. Risk of Kidney Failure Associated with the Use of Acetaminophen, Aspirin, and Nonsteroidal Antiinflammatory Drugs. New Eng J Med. 25(331):1675-9. 1994

- Results
  - 716 patients, 361 control subjects
  - Approximately 8-10% of the overall incidence of ESRD was attributable to acetaminophen use
  - Heavy users of acetaminophen (>365 pills per year) had an increased risk of ESRD
  - A cumulative dose of 5000 or more pills containing NSAIDs was also associated with an increased odds of ESRD (OR 8.8), but the use of aspirin was not.

FDA briefing information - Conclusions

- Usha et. al. (Usha et al., 2004) found that patients with knee OA treated with 500 mg MSM three times daily for 12 weeks showed a 33% pain reduction on the visual analogue scale (VAS). Kim et. al. (Kim et al., 2006) found that knee OA patients treated with MSM 3 g twice daily for 12 weeks showed a 25% reduction in WOMAC pain score. Debbi et. al., (Debbi et al., 2011) in a study of patients with knee OA dosed with MSM 1.125 grams three times daily vs. placebo for 12 weeks showed a mean pain decrease of 21% on the WOMAC that did not reach statistical significance and a decrease of 5.5% of the VAS pain scale that was statistically significant. There were trends in all studies in favor of MSM in physical function.
- Based on the minimal evidence of efficacy, **the possibility of a potentially serious interaction with anticoagulants and risk of bleeding**, **and the availability of approved alternatives**, MSM should not be included on the list of bulk drug substances that can be used to compound drug products in accordance with section 503A of the FD&C Act.

MSM in Compounding

- MSM is not intended to be monotherapy for the long-term management of OA. It is adjunctive, and screening patients for drug-drug and drug-nutrient interactions is the standard of care.
  - The ability to appropriately screen patients is enhanced when a valid prescription is presented and filled
- Typical combination therapies include: glucosamine, chondroitin, NSAID

MSM (Methylsulfonylmethane)

View 1624 Products Containing: MSM (Methylsulfonylmethane)

View 12 USP-Verified Products Containing: MSM (Methylsulfonylmethane)

View 393 Canadian Licensed Products Containing: MSM (Methylsulfonylmethane)

Scientific Name

Methylsulfonylmethane; Dimethylsulfone.

Most popular

Schiff Glucosamine Plus MSM, 1500 mg, Coated Tablets - 150 count

$10.79 from 50+ stores Also available nearby

★★★★½ 72 product reviews #1 in Vitamins & Supplements › MSM

Schiff · Glucosamine · MSM · Pill

This formula combines Glucosamine and Chondroitin Sulfate with **MSM** (Methylsulfonylmethane). **MSM** is a naturally occurring organic sulfur source ...

Schiff Move Free Advanced plus MSM, Tablets, 1500 mg - 120 count

$17.87 from 50+ stores Also available nearby

★★★★½ 81 product reviews #2 in Vitamins & Supplements › MSM

Schiff · Bone & Joint Health · MSM · Pill

Schiff move free advanced tablets help maintain your joint health. These dietary supplementary tablets have a dual bioflavonoid antioxidant system ...

Schiff Move Free, Advanced Plus MSM & Vitamin D3, Triple Strength,...

$17.99 from 50+ stores Also available nearby

★★★★½ 18 product reviews #3 in Vitamins & Supplements › MSM

Schiff · Bone & Joint Health · Vitamin D · MSM · Pill

Move Free Advanced Plus **MSM** Vitamin D has the Advantage of 4 (Glucosamine, Chondroitin, Uniflex, and Joint Fluid), plus we add **MSM** and Vitamin D ...

Hyaluronic Acid with MSM 120 vcaps

$18.63 from 25+ stores

★★★★½ 24 product reviews #4 in Vitamins & Supplements › MSM

NOW · Bone & Joint Health · MSM · Capsule

Hyaluronic Acid with **MSM** 120 vcaps Joint Support With **MSM** Important Joint Lubricant Hyaluronic Acid is a compound present in every tissue of the ...

Other size options: 60 Vcaps ($11)

MSM – USP monographs

- Methylsulfonylmethane USP
  - USP 38

- Methylsulfonylmethane Tablets USP
  - USP 38

THANK YOU

Questions?

DEOXY-D-GLUCOSE

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FDA briefing information

Cancer Analysis – Rat Data

- Cardiac and/or respiratory changes seen with:
  - IV doses of 250, 500, 1000, 2000 mg/kg in mice
    - Time-dependent decrease in MAP only (no other parameters changed)
  - PO doses of 500, 1000, 2000 mg/kg
    - Decreased respiratory frequency
- Ockuly (2012): However, IP doses up to 1000 mg/kg/day x 14 days had no apparent detrimental neurological effects
- Minor (2010): Reduced median survival & max lifespan
  - PO 0.4% diet (0.2 g/kg)
  - *However, 0.04% group showed no observable cardiomyopathic changes by histopathology*

FDA briefing information

Cancer Analysis – Human Data

- Singh (2005): PO 200, 250, 300 mg/kg
  - 300 mg/kg led to hypoglycemia, no other serious adverse effects noted
- Dwarakanath (2009): IV 50-200 mg/kg
  - For clinical efficacy as monotherapy, high doses & long duration of therapy are required. This leads to unacceptable toxicity.
- Raez (2012): pharmacokinetics are linear with dose and did not lead to accumulation.

FDA briefing information

Cancer Analysis

- “2-Deoxy-D-glucose is a physicochemically well-characterized substance of small molecular weight.”
- “Use of 2-deoxy-D-glucose for the treatment of cancer, based on two trials, appears to be beyond the reach of tolerable dosing in both intravenous and oral dosing regimens. Lower doses are being explored in combination treatments with chemotherapy and radiotherapy, with toxicity profiles that appear manageable.”
  - “2-Deoxy-D-glucose exhibited a synergistic anticancer effect when combined with other therapeutic agents or radiotherapy (Zhang D et al., 2014).”

DDG – Cancer Analysis

- Xi (2014): Based on our current understanding as explained above, 2-DG as monotherapy is expected to be efficacious only in select tumor types that are sensitive to this agent in normoxic conditions. Thus, retrospectively, lack of efficacy in earlier studies is not surprising and therefore clinical use of 2-DG was more recently revisited.

FDA briefing information

HSV Analysis

- While there are some *in vitro* data suggesting 2-deoxy-D-glucose could have antiviral activity, the overall data do not demonstrate antiviral activity of 2-deoxy-D-glucose in the treatment of experimental cutaneous or genital infections due to HSV in animal models. Direct antiviral activity has not been conclusively demonstrated due to methodologic flaws with the studies such as lack of evaluation for cytotoxicity.

Blough 1979

- Throughout therapy all patients were interviewed subjectively twice weekly , and evaluated objectively twice weekly
- **Evidence for cytotoxic effect was evaluated in all patients by routine pap smears**. Hypersensitivity, if encountered, was confirmed by physical exam and rectified by a change of the vehicle
- Mixed infections were found: 2 with T vaginalis; 2 with C albicans; 1 with HSV and trichomonas and monilial infections

0.19% DDG	Placebo
Pain & Dysuria relief	Pain & Dysuria relief
12-72 hrs	192-240 hrs (8-10 days)

FDA-suggested alternatives to DDG

Oral HSV

- Penciclovir cream 1%
- Acyclovir cream 5%
- Famcyclovir, 1500 mg single oral dose
- Valacyclovir, 2g twice daily for one day
- Acyclovir/hydrocortisone cream
- Acyclovir buccal tablets, single dose
- Docosanol cream 10%

Genital HSV

- Acyclovir ointment
- Acyclovir oral formulations
- Famciclovir oral formulations
- Valacyclovir oral formulations

Docosanol

- Docosanol is not directly virucidal. It appears to interfere with one or more of the common pathways for viral entry into the target cell and subsequent migration to the cell nucleus.

Source: *Clinical Pharmacology* Database, Elsevier Gold Standard, Copyright 2015

Acyclovir & Valacyclovir

- Mechanism Of Action (valacyclovir is rapidly converted to acyclovir):
  - selectively binds the thymidine kinase (TK) enzyme to inhibit viral DNA synthesis. The viral TK enzyme converts acyclovir into acyclovir monophosphate (a nucleotide analogue), which is further converted into acyclovir diphosphate and then acyclovir triphosphate.
    - Acyclovir triphosphate competitively inhibits and inactivates viral DNA polymerase.
    - It is also incorporated into and terminates the viral DNA chain.
  - Acyclovir is effective only against actively replicating viruses; therefore, **it does not eliminate the latent herpes virus genome**.
  - **Viral resistance** can result from qualitative and quantitative changes in the viral TK enzyme and/or viral DNA polymerase. HSV isolates with reduced acyclovir susceptibility have been recovered from immunocompromised patients, **and immunocompetent patients with genital herpes**. Viral resistance should be considered in patients who show poor clinical response during therapy. Repeated systemic treatment may lead to the development of viral resistance in immunosuppressed patients

Source: *Clinical Pharmacology* Database, Elsevier Gold Standard, Copyright 2015

Penciclovir & Famciclovir

- Penciclovir is the active antiviral compound produced by biotransformation of famciclovir.
- Resistance of HSV and VZV to penciclovir can result from mutations in the viral TK and DNA polymerase genes. Mutations in the viral TK may lead to the **complete loss of viral TK activity**, reduced levels of TK activity, or alterations in the ability of viral TK to phosphorylate thymidine. **The most common type of resistance is the loss of viral TK activity (TK negative isolates).**

Source: *Clinical Pharmacology* Database, Elsevier Gold Standard, Copyright 2015

DDG Antiviral Mechanism

- “The multiplication of a number of enveloped RNA and DNA viruses is inhibited by 2-deoxy-D-glucose through an effect on the incorporation of sugars into viral glycoproteins (Kilbourne, 1959; Kaluza et al, 1972, 1973; Gandhi et al, 1972; Scholtissek, 1975; Courtney et al, 1973; Stohrer and Hunter, 1979).”
- “The compound exhibits antiviral activity against those enveloped viruses that require intact glycoproteins for viral assembly or for some critical replicative function.”

Spivack et al. A study on the Antiviral Mechanism of Action of 2-Deoxy-D-Glucose: Normally Glycosylated Proteins Are Not Strictly Required For Herpes Simplex Virus Attachment But Increase Viral Penetration and Infectivity. Virology. 1982 July;123:123-38.

DDG Antiviral Mechanism – Spivack 1982

uncoating. The results presented in this paper demonstrate that virus produced in medium containing 2dGlc was capable of attaching to Vero cells almost as well as control virus, even though there was greater than a 10-fold difference in infectivity. The slight decrease in attachment was not sufficient to completely explain the reduced infectivity of this virus. The rate of ad-

In conclusion, a major contributing factor to why virus grown in the presence of 2dGlc lacks infectivity appears to be the result of a defect in penetration. These viruses can attach to host cells almost as well as control virus, so that the decrease in attachment makes a slight contribution to the antiviral action of 2dGlc. The DNAs isolated from these viruses are equally infective. Thus, all the steps subsequent to the completion of uncoating of the virus grown in 2dGlc seem unaffected. The inhibition of penetration can be partially overcome by stimulating the fusion of the viral envelope with the plasma membrane of the cell. However, the results obtained can not rule out the possibility of an effect of 2dGlc on the uncoating of progeny virus.

DDG in Compounding

- 0.19 – 2% in topical applications to herpetic & shingles lesions on skin
  - Only use higher concentrations in non-penetrating delivery vehicles
- 0.1-0.25% for mouth rinses

- Combined with acyclovir 2-5%
  - Optimize delivery vehicle

- Assuming patient uses 10ml of 0.25% (2.5mg/ml) oral rinse, they are exposed to 25mg DDG
  - Lowest human PO dose published was 200 mg/kg, producing hypoglycemia

DDG in Compounding

- DDG is soluble in water
- When using a vehicle that forms a barrier on the skin such as lanolin or petrolatum, the active ingredient will not penetrate the virus within the dermis
- Hydroalcoholic gels may not be ideal for non-lipophilic molecules
  - Minimal disruption of the lipid bilayer via alcohol, which is volatile so will leave the surface rapidly
- Choosing appropriate vehicle
  - Oil-in-water emulsion containing penetration enhancers
  - PLO, Lipoderm®

THANK YOU

Questions?

DOMPERIDONE

Pharmacy Compounding Advisory Committee
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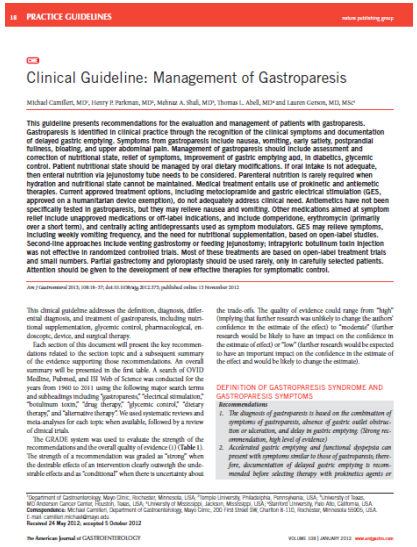
Background

- Domperidone:
  - A peripherally acting dopamine2-receptor antagonist, usually prescribed for gastroparesis
    - Inhibits the inhibitory effects of dopamine on the upper GI system
    - Differs from cisapride, which increased postganglionic acetylcholine in the enteric nervous system
    - Also inhibits dopamine in CTZ
  - Does not readily cross the BBB like metoclopramide
    - Reduced incidence of extrapyramidal side effects with domperidone.

Background (cont.)

- Domperidone is commercially available in 112 countries around the world
  - Mostly under the trade name: Motilium (Janssen)
  - Many other commercial names
  - Marketed worldwide since 1978
    - Oral tablet, Oral suspension and Suppository
    - 37 years of history – well known API

The American College of Gastroenterology



PRACTICE GUIDELINES

Clinical Guideline: Management of Gastroparesis

Michael Camilleri, MD[1], Henry P. Parkman, MD[2], Mahmud A. Shafi, MD[3], Thomas L. Abell, MD[4] and Lauren Gerson, MD, MSc[5]

This guideline presents recommendations for the evaluation and management of patients with gastroparesis. Gastroparesis is identified in clinical practice through the recognition of the clinical symptoms and documentation of delayed gastric emptying. Symptoms from gastroparesis include nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain. Management of gastroparesis should include assessment and correction of nutritional state, relief of symptoms, improvement of gastric emptying and, in diabetics, glycemic control. Patient nutritional state should be managed by oral dietary modifications. If oral intake is not adequate, then enteral nutrition via jejunostomy tube needs to be considered. Parenteral nutrition is rarely required when hydration and nutritional state cannot be maintained. Medical treatment entails use of prokinetic and antiemetic therapies. Current approved treatment options, including metoclopramide and gastric electrical stimulation (GES, approved on a humanitarian device exemption), do not adequately address clinical need. Antiemetics have not been specifically tested in gastroparesis, but they may relieve nausea and vomiting. Other medications aimed at symptom relief include unapproved medications or off-label indications, and include domperidone, erythromycin (primarily over a short term), and centrally acting antidepressants used as symptom modulators. GES may relieve symptoms, including weekly vomiting frequency, and the need for nutritional supplementation, based on open-label studies. Second-line approaches include venting gastrostomy or feeding jejunostomy; intrapyloric botulinum toxin injection was not effective in randomized controlled trials. Most of these treatments are based on open-label treatment trials and small numbers. Partial gastrectomy and pyloroplasty should be used rarely, only in carefully selected patients. Attention should be given to the development of new effective therapies for symptomatic control.

Am J Gastroenterol 2013; 108:18–37; doi:10.1038/ajg.2012.373; published online 13 November 2012

This clinical guideline addresses the definition, diagnosis, differential diagnosis, and treatment of gastroparesis, including nutritional supplementation, glycemic control, pharmacological, endoscopic, device, and surgical therapy.

Each section of this document will present the key recommendations related to the section topic and a subsequent summary of the evidence supporting those recommendations. An overall summary will be presented in the first table. A search of OVID Medline, Pubmed, and ISI Web of Science was conducted for the years from 1960 to 2011 using the following major search terms and subheadings including "gastroparesis," "electrical stimulation," "botulinum toxin," "drug therapy," "glycemic control," "dietary therapy," and "alternative therapy". We used systematic reviews and meta-analyses for each topic when available, followed by a review of clinical trials.

The GRADE system was used to evaluate the strength of the recommendations and the overall quality of evidence (1) (Table 1). The strength of a recommendation was graded as "strong" when the desirable effects of an intervention clearly outweigh the undesirable effects and as "conditional" when there is uncertainty about the trade-offs. The quality of evidence could range from "high" (implying that further research was unlikely to change the authors' confidence in the estimate of the effect) to "moderate" (further research would be likely to have an impact on the confidence in the estimate of effect) or "low" (further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate).

DEFINITION OF GASTROPARESIS SYNDROME AND GASTROPARESIS SYMPTOMS

Recommendations:

1. *The diagnosis of gastroparesis is based on the combination of symptoms of gastroparesis, absence of gastric outlet obstruction or ulceration, and delay in gastric emptying. (Strong recommendation, high level of evidence)*
2. *Accelerated gastric emptying and functional dyspepsia can present with symptoms similar to those of gastroparesis; therefore, documentation of delayed gastric emptying is recommended before selecting therapy with prokinetics agents or*

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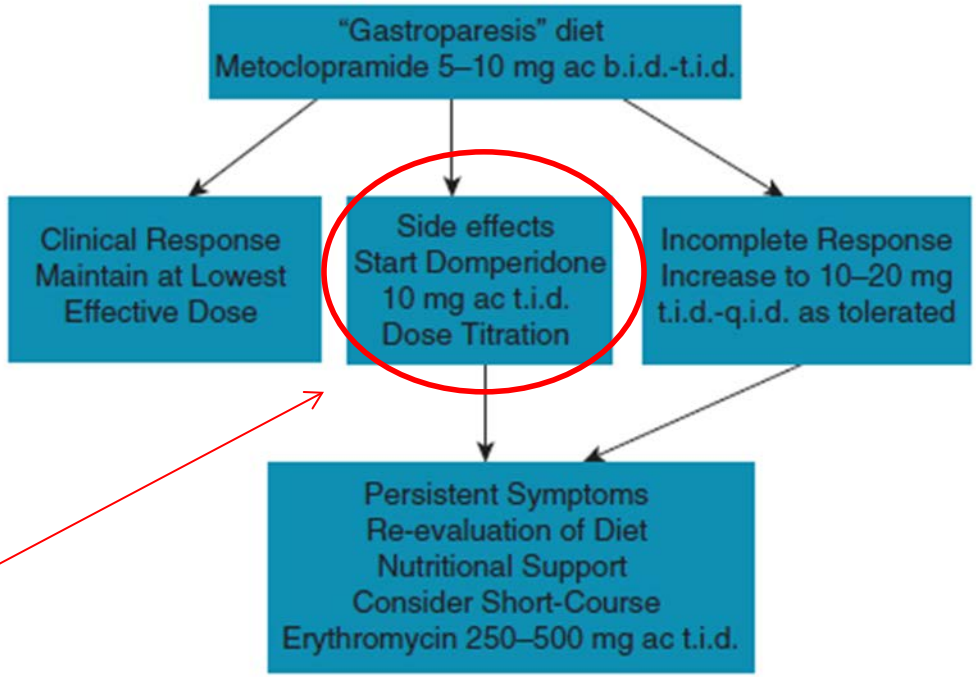


Figure 3. Algorithm for prokinetic therapy in gastroparesis.

Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013;108(1):18-37; quiz 38. doi:10.1038/ajg.2012.373.

Safety

- Non-Clinical Cardiac Studies
  - From FDA Briefing document:

Table 1. Effect of domperidone on cardiac parameters

Assay	Prep	Effective Dose	Ref / Yr
hERG	CHO cells	IC_{50} = 162 nM	Drolet et al., 2000
	HEK293	IC_{50} = 57 nM	Claassen et al., 2005
APD (repolarization)	Guinea pig heart	100 nM*	Drolet et al., 2000
	Guinea pig heart	100 nM*	Hreiche et al., 2009
	Rabbit heart	30 nM*	Hondegehm, 2011 and 2013
TRIaD	Rabbit heart	100 nM*	Hondegehm, 2011 and 2013

*Effect did not saturate at doses tested; no IC_{50} (drug concentration producing 50% current inhibition) was determined

Typical steady state free drug plasma concentrations are reported to be between 3nM and 19nM (Hondegehm, 2011 and 2013)…much higher concentrations used in these animal models.

Safety (cont.)

- Commentary in Sugiyama (Br J Pharmacol. 2008 Aug; 154(7): 1528–1537).
  - Discussion on “predictive” animal models - in this case, perfused rabbit models and isolated arterially perfused left ventricular wedge models

These *in vitro* models described above are devoid of the influence of metabolic, humoral and nervous systems, so direct extrapolation of the drug effects *in vitro* to those in patients is difficult even when the concentrations are similar between patient plasma and perfusion solution. Torsadogenic potential depends on interactions with metabolites, autonomic nervous system and pathophysiology of the heart, which can be explored only *in vivo* preparations. For this reason, *in vitro* preparations are used primarily for the determination of potential to produce TdP, whereas *in vivo* models are adopted to directly demonstrate the drug-induced TdP.

Ventricular Arrhythmia, and Sudden Cardiac Death

- This has been the most publicized concern
- Recent studies to look at
  - Epidemiologic studies
  - Case Control and Nested Case Control
- Europe and UK have revised guidelines of use as a result of these studies

Safety – In Perspective

Find By Multiple Criteria

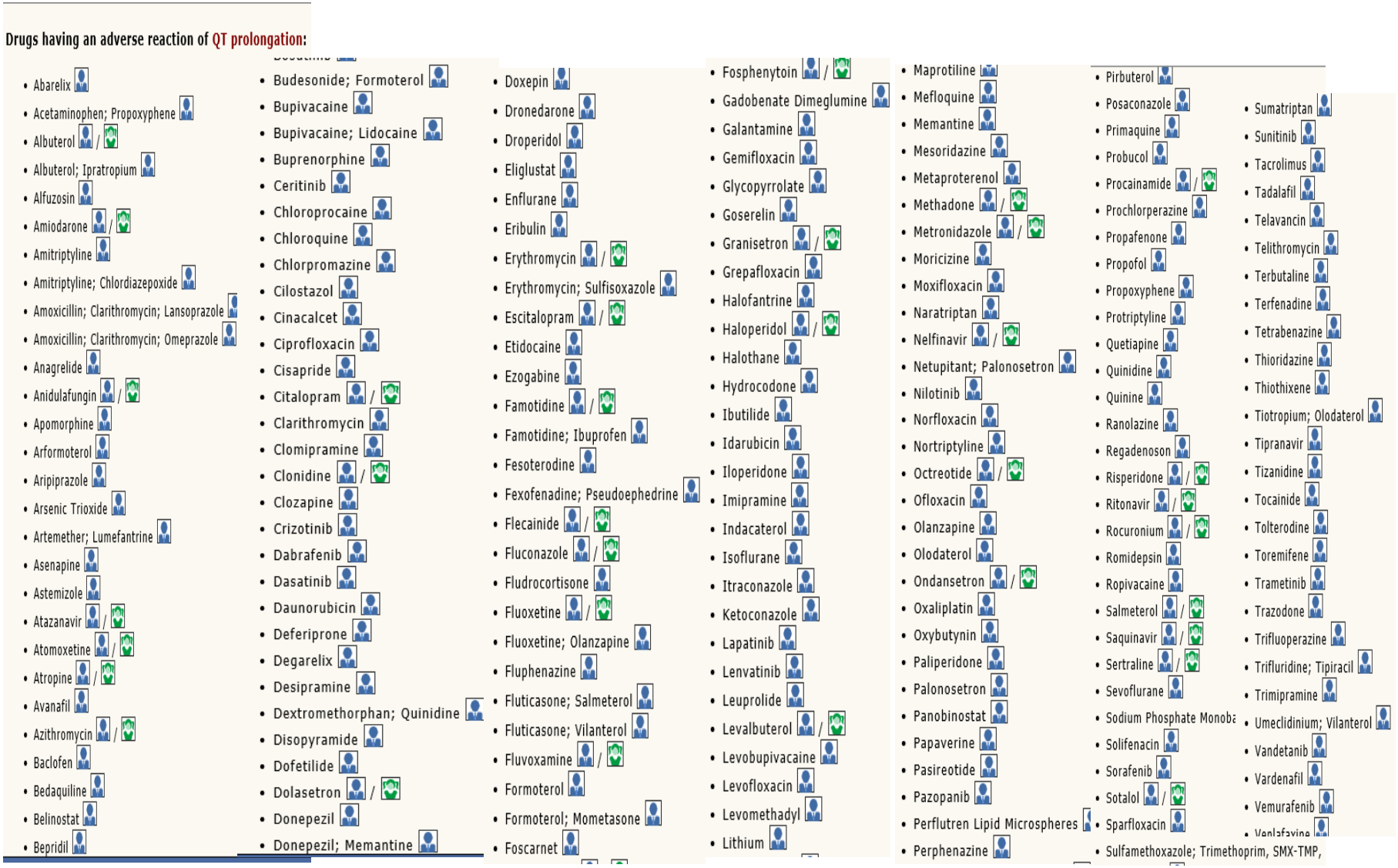
Drugs Satisfying the Following Criteria:

- **Causes an Adverse Reaction of: QT prolongation**
- **And Causes an Adverse Reaction of: torsade de pointes**

- Amiodarone /
- Amitriptyline
- Amitriptyline; Chlordiazepoxide
- Amoxicillin; Clarithromycin; Lansoprazole
- Amoxicillin; Clarithromycin; Omeprazole
- Anagrelide
- Apomorphine
- Aripiprazole
- Arsenic Trioxide
- Astemizole
- Azithromycin /
- Bepridil
- Bortezomib
- Ceritinib
- Chloroquine
- Chlorpromazine
- Ciprofloxacin
- Cisapride
- Citalopram /
- Clarithromycin
- Clozapine
- Deferiprone
- Disopyramide
- Dofetilide
- Dolasetron /
- Donepezil
- Donepezil; Memantine
- Doxepin
- Dronedarone
- Droperidol
- Escitalopram /
- Flecainide /
- Fluconazole /
- Fluoxetine /
- Fluphenazine
- Fluvoxamine /
- Gemifloxacin
- Grepafloxacin
- Halofantrine
- Haloperidol /
- Halothane
- Ibutilide
- Levofloxacin
- Levomethadyl
- Lomefloxacin
- Lopinavir; Ritonavir /
- Maprotiline
- Memantine
- Mesoridazine
- Methadone /
- Moricizine
- Moxifloxacin
- Nelfinavir /
- Norfloxacin
- Ofloxacin
- Ondansetron /
- Oxaliplatin
- Papaverine
- Pazopanib
- Perphenazine
- Perphenazine; Amitriptyline
- Pimozide
- Posaconazole
- Probucol
- Procainamide /
- Propafenone
- Quetiapine
- Quinidine
- Quinine
- Risperidone /
- Saquinavir /
- Sertraline /
- Sevoflurane
- Solifenacin
- Sotalol /
- Sparfloxacin
- Sulfamethoxazole; Trimethoprim, SMX-TMP, Cotrimoxazole
- Sunitinib
- Tacrolimus
- Telithromycin
- Terfenadine
- Thioridazine
- Thiothixene
- Trazodone
- Trifluoperazine
- Vandetanib
- Venlafaxine
- Voriconazole
- Ziprasidone

Source: Clinical Pharmacology

Safety – In Perspective



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REGULAR ARTICLE

Effects of domperidone on QTc interval in infants

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Keywords
Cardiac arrythmias, Drug reaction,
Gastro - oesophageal reflux disaese

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ABSTRACT

Aim: To prospectively evaluate the effects of oral domperidone on the QTc interval in infants.

Methods: Infants (0–1 year) with a diagnosis of gastro-oesophageal reflux (GOR) disease were included. A 12-lead electrocardiography (ECG) was performed in all infants at baseline and 1 h after the intake of domperidone after 7–14 days; the corrected QTc interval was calculated by one investigator (MV) according to Bazett's formula.

Results: Forty-five infants were enroled in this study. The mean gestational age was of 38.6 weeks (35.5–42.0), and the mean age at the start of domperidone was 75.3 days (19–218 days). No statistically significant difference in corrected QTc was observed between baseline and the second ECG (0.389 ± 0.02 vs. 0.397 ± 0.31; p 0.130)). A trend was observed regarding gender: Although there was no difference in QTc change in girls (p 0.622), there was a strong trend in boys (p 0.051). Two infants (both boys) had a clinically significant QTc prolongation (>460 msec) without symptoms. The Spearman correlation test showed no relation between the QTc change and age (r: –0.05822; p 0.7284). There was no relation between domperidone dosage and QTc change.

Conclusion: Overall, the group-analysis showed no statistical significant difference in QTc duration induced by domperidone. However, 2/45 (4.4%) infants had a prolonged QTc interval (>460 msec) induced by domperidone. As a consequence, QTc measurement should be recommended in routine in infants when domperidone is started.

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Effect of domperidone on the QTc interval in premature infants

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Objective: To evaluate the effect of domperidone use on corrected QT interval in premature infants.

Study Design: A prospective study of premature infants receiving domperidone was included in this study. A baseline electrocardiogram was obtained just before and 3, 7 and 14 days after initiation of domperidone. Corrected QT was considered prolonged if it exceeded the upper limit for age.

Result: A total of 40 premature infants were enrolled in this study. The mean birth weight of 1109 ± 332 g, mean gestational age of 28.8 ± 2.4 years and mean age at the onset of domperidone were 32.8 ± 2 days. No difference in corrected QT interval was observed between just before and 3, 7 and 14 days after the start of the treatment. Two infants had corrected QT interval prolongation without any clinical side effect that resolved spontaneously.

Conclusion: Our experience suggests that domperidone administered cautiously in modest doses does not result in arrhythmias or conduction defects in premature infants statistically. Additional data are needed to give optimal advice regarding the safety of domperidone treatment in premature infants.

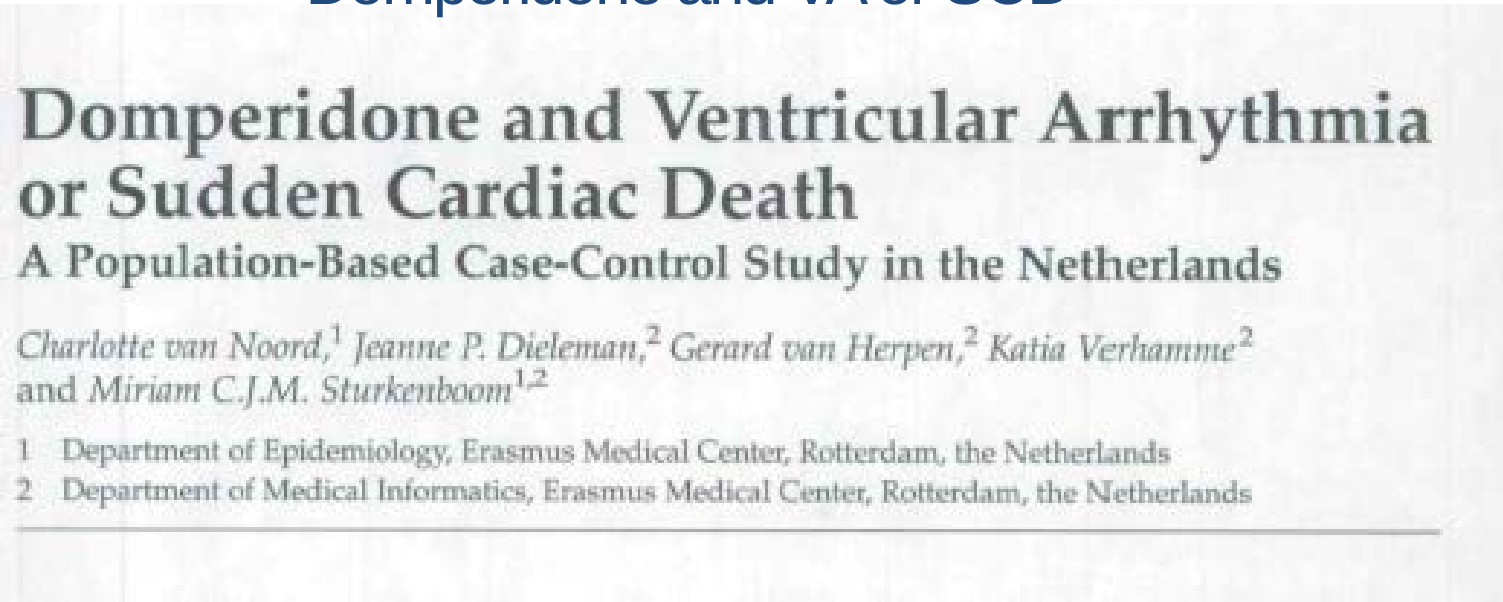
Journal of Perinatology (2010) **30**, 50–53; doi:10.1038/jp.2009.96; published online 23 July 2009

on the central nervous system, such as dystonic reactions, are rare.[1,2] On account of its apparent favorable safety profile, domperidone might seem to be safer as an alternative to cisapride and metoclopramide.

However, QT interval (QT) prolongation and life-threatening ventricular tachyarrhythmias have been reported with domperidone.[2–6] Domperidone possesses cardiac electrophysiological effects similar to those of cisapride and class III antiarrhythmic drugs. These effects are observed at clinically relevant concentrations of the drug. The experimental studies carried out by Drolet *et al.*[7] showed that domperidone can prolong cardiac repolarization in a reverse rate-dependent manner by blocking the cardiac potassium current (IKr: rapidly activating delayed rectifier K^+ current). Excessive IKr block may lead to triggered tachyarrhythmias and sudden death.[8] The study by Drolet *et al.*[7] provided a new explanation for QT prolongation and ventricular tachyarrhythmia during domperidone treatment. Domperidone should be one of the next compounds to add to the growing list of drugs associated with acquired long QT syndrome. Therefore, domperidone should not be considered a no-risk alternative to cisapride.

In the literature, no systematic study has been performed to evaluate the effect of d

Domperidone and VA or SCD



Domperidone and Ventricular Arrhythmia or Sudden Cardiac Death

A Population-Based Case-Control Study in the Netherlands

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van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Saf*. 2010;33(11):1003-14.

Highlights of van Noord Study

- 1366 patients in database identified with SCD or SVA.
  - 14114 controls
  - 95% had SCD (1304)
  - 5% had SVA (62)
- None of users of domperidone had SVA
- 92% of patients with SCD did not use domperidone
- 7% (94) of SCD pts were past users
- 0.8% (10) of SCD pts were current users
- Researchers determined no statistically significant risk with past users
- But increased risk with current users on more than 30mg
  - However n = Too small to make broad based conclusions

Results: sudden cardiac death

Table II. Risk of sudden cardiac death[a]

Use of domperidone	Cases	Controls	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Overall population	1 304	13 480			
Never use	1 200	12 781	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	94	671	*1.56 (1.23, 1.98)*	*1.36 (1.05, 1.75)*	1.28 (0.99, 1.65)
recent past (8 d–3 mo)	10	54	1.91 (0.95, 3.86)	1.56 (0.73, 3.33)	1.39 (0.65, 2.99)
moderate past (3–6 mo)	7	34	2.30 (0.98, 5.38)	2.24 (0.93, 5.41)	2.00 (0.83, 4.86)
distant past (6–12 mo)	13	83	1.59 (0.86, 2.96)	1.26 (0.67, 2.39)	1.03 (0.53, 2.00)
very distant past (>12 mo)	64	500	*1.46 (1.09, 1.94)*	1.29 (0.95, 1.75)	1.26 (0.93, 1.70)
Current use	10	28	*3.72 (1.72, 8.08)*	*2.44 (1.01, 5.89)*	1.99 (0.80, 4.96)
<30 mg	2	10	NA	NA	NA
30 mg	4	15	2.57 (0.79, 8.36)	1.41 (0.38, 5.32)	1.02 (0.23, 4.42)
>30 mg	4	3	*16.0 (3.49, 73.6)*	*11.2 (2.02, 62.45)*	*11.4 (1.99, 65.2)*

a Italicized text denotes statistically significant associations.

b OR matched for age, sex, practice and index date.

c Overall population: OR adjusted for heart failure, insurance type, CYP3A4 inhibitors, *hERG*-inhibiting drugs, laxatives, digoxin, diuretics, corticosteroids, β-adrenergic receptor agonists. Publicly insured: OR adjusted for heart failure, *hERG*-inhibiting drugs, laxatives, diuretics, corticosteroids and digoxin. Privately insured: OR adjusted for heart failure, diuretics, corticosteroids, β-adrenergic receptor agonists and digoxin. Not insured: OR adjusted for heart failure, diuretics, corticosteroids, CYP3A4 inhibitors, *hERG*-inhibiting drugs, digoxin and β-adrenergic receptor agonists.

d Additionally adjusted for general practitioner visits.

CYP = cytochrome P450; ***hERG*** = human ether-à-go-go-related gene; **NA** = not applicable (<3 cases); **OR** = odds ratio; **ref** = reference.

van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Saf*. 2010;33(11):1003-14.

Results: non-fatal ventricular arrythmia

Table III. Risk of sudden cardiac death and non-fatal ventricular arrhythmia[a]

Use of domperidone	Cases	Controls	OR (95% CI)[b]	OR (95% CI)[c]	OR (95% CI)[d]
Overall population	1 366	14 114			
Never use	1 258	13 384	1.0 (ref)	1.0 (ref)	1.0 (ref)
Past use	98	700	*1.57 (1.24, 1.99)*	*1.35 (1.05, 1.73)*	1.26 (0.98, 1.62)
Current use	10	30	*3.54 (1.64, 7.64)*	2.35 (0.99, 5.62)	1.92 (0.78, 4.73)
<30 mg	2	11	NA	NA	NA
30 mg	4	16	2.45 (0.76, 7.86)	1.36 (0.37, 5.04)	0.99 (0.23, 4.23)
>30 mg	4	3	*16.0 (3.48, 73.4)*	*11.2 (2.02, 62.3)*	*11.4 (1.99, 64.9)*

van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Saf*. 2010;33(11):1003-14..

Limitations of van Noord Study

- Significant differences in baseline characteristics
  - Limits external validity and ability to extrapolate to broader population
- Mean age: **72.5** years
- High frequency of cardiovascular co-morbidities at baseline
- Results cannot be extrapolated to all age groups and all users
  - Study participants were older at baseline (65 and older) with multiple cardiovascular associated co-morbidities.
- No associations can be made between domperidone use and the risk of non-fatal VA based on the results of this study.

van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. *Drug Saf*. 2010;33(11):1003-14.

Combined risk of SVA/SCD in cohort of users of domperidone

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2010; **19**: 881–888
Published online 22 July 2010 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2016

ORIGINAL REPORT

Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study

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Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2010;19(9):881-8.

Highlights of Johannes Study

- Evaluated combined risks of SVA and SCD in past and current users of domperidone
- Looked at current, past, and non-users who died had SVA or from combined SVA/SCD as a combined outcome.
  - Excluded: those with cancer, deaths of hospital in-patient, death from non-cardiac causes
- Confounding variables identified by the authors were adjusted for
- No significant increase in SVA/SCD in past users
- In Current users 10% (169) had SVA/SCD
- **No doses mentioned**

Numerous morbidities /medications that could influence

Table 1. Distribution of potential confounding variables and their individual relation to the combined outcome of SVA/SCD evaluated by conditional logistic regression

Variables	SVA/SCD cases $n = 1608$		Matched controls[a] $n = 6428$		Odds ratio (95%CI)[b]
	N	(%)	N	(%)	
Medical conditions[c]					
Cardiomyopathy	53	3.3	30	0.5	7.04 (4.50–11.02)
Heart failure	565	35.1	771	12.0	4.16 (3.64–4.76)
History of VT/VF	3	0.2	3	0.0	4.00 (0.81–19.82)
Valvular heart disease	98	6.1	135	2.1	3.03 (2.32–3.96)
Ischemic heart disease	601	37.4	1173	18.2	2.71 (2.40–3.06)
Liver failure	22	1.4	36	0.6	2.50 (1.46–4.28)
Other arrhythmias (not VT/VF) or conduction disorders	215	13.4	412	6.4	2.24 (1.88–2.66)
Pulmonary heart disease	39	2.4	77	1.2	2.05 (1.39–3.02)
Autonomic neuropathy	2	0.1	5	0.1	1.60 (0.31–8.25)
Cerebrovascular disease	134	8.3	384	6.0	1.44 (1.17–1.76)
Symptoms involving digestive system	81	5.0	242	3.8	1.36 (1.05–1.76)
Gastritis and duodenitis	166	10.3	527	8.2	1.29 (1.07–1.55)
Gastroesophageal reflux disease	27	1.7	88	1.4	1.24 (0.80–1.92)
Gastric or peptic ulcer	60	3.7	203	3.2	1.19 (0.89–1.59)
Hypercholesterolemia	200	12.4	801	12.5	1.00 (0.84–1.19)
Disorders of stomach/duodenum	67	4.2	270	4.2	0.99 (0.75–1.31)
Dyspepsia	9	0.6	39	0.6	0.92 (0.44–1.92)
Hypertension	410	25.5	1884	29.3	0.82 (0.72–0.93)
Medication use evaluated at index date *vs.* no exposure					
QT class 1 and/or 2 drugs					
Current exposure	357	22.2	682	10.6	2.61 (2.26–3.03)
Past exposure	302	18.8	1001	15.6	1.51 (1.30–1.75)
CYP3A4 inhibitors					
Current exposure	181	11.3	616	9.6	1.26 (1.06–1.51)
Past exposure	163	10.1	431	6.7	1.62 (1.34–1.97)
Medication use evaluated in the 365 days before the index date (any use *vs.* no use)					
Antiarrhythmic agents with action on repolarization time	58	3.6	81	1.3	2.98 (2.11–4.21)
Other cardiac medications	1089	67.7	3107	48.3	2.31 (2.05–2.60)
Antihypertensives	804	50.0	2219	34.5	2.01 (1.79–2.25)
Drugs that may cause arrhythmia or prolong the QT interval—class 3	648	40.3	1987	30.9	1.52 (1.35–1.70)
Gastrointestinal medications (other than domperidone or PPI)	663	41.2	2423	37.7	1.17 (1.04–1.31)
Antiarrhythmic agents without action on repolarization time	241	15.0	708	11.0	1.43 (1.22–1.68)
Health care utilization					
Number of hospitalization episodes *vs.* none					
1 or 2	639	39.7	2270	35.3	1.50 (1.33–1.70)
3 or more	297	18.5	605	9.4	2.68 (2.27–3.16)
Number of physician visits *vs.* 0–7 visits					
8 to 14	362	22.5	1999	31.1	1.12 (0.94–1.34)
15 to 22	386	24.0	1454	22.6	1.68 (1.41–2.00)
23 or more	603	37.5	1415	22.0	2.72 (2.30–3.21)

CI, confidence interval; PPI, proton pump inhibitors; VT, ventricular tachycardia; VF, ventricular fibrillation and/or flutter.
[a]Controls were matched to cases on date of case event, age at index date, sex, and diabetes status.
[b]Individual conditional logistic regression with SVA/SCD as the dependent variable, accounting for the matching variables.
[c]History of VT/VF was evaluated in the baseline period (365 days before cohort entry). All other medical conditions were evaluated in the 365 days before the index date. The reference category was the absence of the condition in this time period.

Results of Johannes Study

Table 2. Results of conditional logistic regression models, adjusted for matching variables and fully adjusted, evaluating the risk of SVA/SCD with domperidone exposure relative to no exposure to either study drug and relative to PPI exposure

	SVA/SCD cases $n = 1608$		Matched controls[a] $n = 6428$		Risk relative to no exposure to either study drug		Risk relative to current PPI exposure	
					Adjusted only for matching variables[b]	Fully adjusted[c]	Adjusted only for matching variables[b]	Fully adjusted[c]
	N	(%)	N	(%)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Current exposure to domperidone	169	10.5	481	7.5	1.67 (1.37–2.04)	1.59 (1.28–1.98)	1.09 (0.87–1.38)	1.44 (1.12–1.86)
Current exposure to both domperidone and PPI	37	2.3	86	1.3	2.09 (1.40–3.11)	1.39 (0.89–2.16)	1.37 (0.91–2.05)	1.25 (0.80–1.97)
Past exposure to domperidone	168	10.4	730	11.4	1.10 (0.90–1.33)	0.86 (0.69–1.06)	0.72 (0.57–0.90)	0.78 (0.61–1.00)
Current exposure to PPI	316	19.7	1002	15.6	1.53 (1.31–1.78)	1.11 (0.93–1.31)	Reference	Reference
Past exposure to PPI	178	11.1	631	9.8	1.36 (1.13–1.64)	1.05 (0.86–1.30)	0.89 (0.72–1.10)	0.95 (0.76–1.20)
No exposure to either study drug	740	46.0	3498	54.4	Reference	Reference	0.65 (0.56–0.76)	0.91 (0.76–1.07)

Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2010;19(9):881-8.

Results following adjustments

Table 3. Results of multivariable conditional logistic regression with case and control pairs stratified by diabetes, age, and sex

	Diabetes		Age		Sex	
	Yes	No	≤60 years	>60 years[a]	Male	Female
	$n = 1786$	$n = 6250$	$n = 534$	$n = 7502$	$n = 3782$	$n = 4254$
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Exposure categories compared with non-use of domperidone or PPI						
Current exposure to domperidone	1.27 (0.79–2.03)	1.69 (1.32–2.17)	1.10 (0.35–3.47)	1.64 (1.31–2.05)	2.23 (1.59–3.13)	1.25 (0.93–1.67)
Current exposure to both domperidone and PPI	1.36 (0.54–3.45)	1.33 (0.80–2.21)	0.0	1.57 (1.01–2.45)	1.22 (0.56–2.68)	1.52 (0.88–2.63)
Past exposure to domperidone	0.63 (0.39–1.03)	0.91 (0.71–1.16)	0.40 (0.15–1.12)	0.90 (0.72–1.13)	0.92 (0.66–1.27)	0.84 (0.63–1.12)
Current exposure to PPI	0.91 (0.64–1.30)	1.16 (0.95–1.42)	0.89 (0.38–2.08)	1.11 (0.93–1.33)	1.25 (0.97–1.62)	1.01 (0.80–1.28)
Past exposure to PPI	0.79 (0.51–1.23)	1.13 (0.89–1.43)	1.30 (0.55–3.07)	1.04 (0.84–1.29)	1.15 (0.86–1.54)	0.93 (0.69–1.27)

Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2010;19(9):881-8.

Limitations of Johannes Study

- Mean age: **79.4** years
- The use of SVA/SCD composite endpoint
- No doses mentioned
- Nested studies tend to decrease the power of the study, increasing chances of Type II errors.
- Wide range for 95% CI

Johannes CB, Varas-Lorenzo C, McQuay LJ, Midkiff KD, Fife D. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. *Pharmacoepidemiol Drug Saf*. 2010;19(9):881-8.

Alternatives to Domperidone

Gastroparesis and Nausea/Vomiting: There is one FDA- approved pharmacotherapy for gastroparesis, metoclopramide. Metoclopramide is a dopamine antagonist, and has an indication for "the relief of symptoms associated with acute and recurrent diabetic gastric stasis". As per guidelines, metoclopramide administered in a liquid formulation is the first line of prokinetic therapy (Camilleri et al., 2013). Metoclopramide has a boxed warning for tardive dyskinesia, a serious movement disorder that is often irreversible. Erythromycin is used off-label for gastroparesis. As per guidelines, both IV and oral

- Metoclopramide
  - EU Medicines Agency changes guidelines for use of metoclopramide
    - Safety concerns over side effects and concerns over efficacy for nausea & vomiting

Alternatives to Domperidone (Metoclopramide)

- EUMA Analysis confirmed well-known risks of neurological effects (EPS, tardive dyskinesia)
  - Risks increase with long-term treatment
- Analysis uncovered “very rare cases of serious effects on the heart or circulation”
- EUMA recommendations
  - Metoclopramide prescribed for short term use (up to 5 days)
  - Not to be used in children below 1 yr of age
    - Only used as 2nd-choice for children 1-18 yrs
  - Maximum recommended doses in adults and children should be restricted

Source: https://www.medicines.org.uk/media/3763/annex-1-summary-of-product-characteristics-commission-decision.pdf

2015-05-06_exportPDF.pdf

Health Canada Santé Canada

Canada Vigilance
Summary of Reported Adverse Reactions

Report Runtime:	2015-05-06 - 05:53:38 PM
Initial Received Date:	1965-01-01 to 2014-12-31
Latest Received Date:	N/A
Total Number of Reports:	133 Report(s)

Brand Name/Active Ingredient: domperidone
Search Date Criteria: 1965-01-01 to 2014-12-31
Reaction Term(s): All/Tous
Serious report?: Yes
Type of Report: All
Source of Report: All
Gender: All
Report Outcome: All
Age: All

Of the 133 serious events with Domperidone between 1985 & 2014 (4.6/yr):

- 1 was a death (0.75%)
- 12 were life threatening (9%)
  - Patients were on several medications that contribute to QTc issues
  - One patient had 29 concomitant medications and a pacemaker
- 11/12 patients were on at least 6 medications
  - 1/12 was only taking lorazepam and phenobarbital with their domperidone.

Search Results Summary

Search Criteria

Your search generated 122 adverse reaction reports based on the following search criteria:

- **Brand Name/Active Ingredient:** metoclopramide
- **Initial Received Date:** 1965-01-01 **to** 2014-12-31
- **Latest Received Date:**
- **Reaction Term(s):** All/Tous
- **Serious report?** Yes
- **Source of Report:** All
- **Gender:** All
- **Report Outcome:** All
- **Age:** All

Search Results

Help with Search Results Section

Export Results | Modify Search Criteria | New Search

Select hyperlinked column titles below to sort reports in ascending order according to a particular report element. For additional details on a particular report, select its Adverse Reaction Report (AER) Number. The contents of the Caveat and Privacy Statement should be considered when viewing the results below.

Displaying Reports 1 to 20 of 122

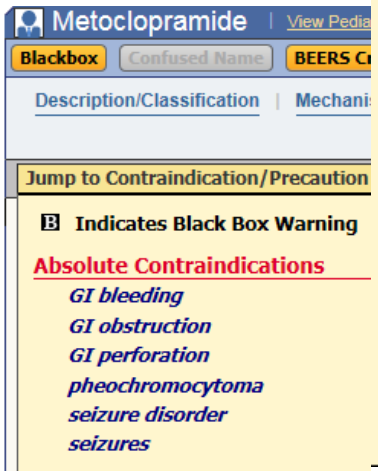
Of the 122 serious events with Metoclopramide between 1994 and 2014 (5.8/yr)

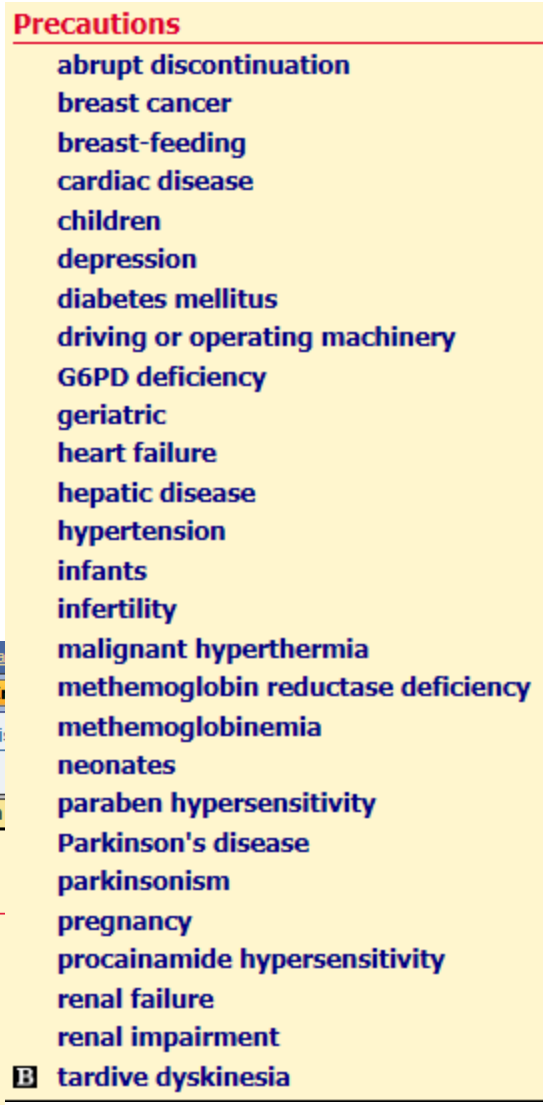
- 15 were deaths (12.3%)
- 7 were life threatening (5.7%)

Alternatives to Domperidone (Metoclopramide)

US FDA side effect profile

- agranulocytosis
- akathisia
- angioedema
- AV block
- bradycardia
- breast enlargement
- bronchospasm
- confusion
- depression
- diarrhea
- dizziness
- drowsiness
- dystonic reaction
- edema
- fatigue
- galactorrhea
- gynecomastia
- hallucinations
- headache
- heart failure
- hyperprolactinemia
- hypertension
- hypotension
- impotence (erectile dysfunction)
- infertility
- insomnia
- involuntary movements
- jaundice
- leukopenia
- menstrual irregularity
- nausea
- neuroleptic malignant syndrome
- neutropenia
- pseudoparkinsonism
- rash (unspecified)
- restlessness
- seizures
- supraventricular tachycardia (SVT)
- tardive dyskinesia
- trismus
- urinary incontinence
- urinary urgency
- urticaria
- withdrawal





Domperidone vs. Metoclopramide

FDA briefing information

A randomized active-controlled 4-week trial in 95 diabetic gastroparesis patients showed similar reduction in TSS from baseline after domperidone 20 mg PO QID (41%) (n=48) vs. metoclopramide 10 mg PO QID (39%) (n=47) (Patterson et al., 1999). TSS was the sum of investigator-assessed scores ranging from 0 to 3 for: nausea, vomiting, early satiety, and bloating/distension (Patterson et al., 1999). Although reductions appeared to be similar (they did not reach statistical significance), the trial was not designed as a non-inferiority (NI) trial (which specifically aims to demonstrate that a novel treatment is not clinically worse than an active treatment based on a specific NI margin). As noted for the previous trial, a key limitation of this trial is the investigator-assessment for the primary endpoint instead of PRO measures as currently recommended (FDA Draft Guidance, "Gastroparesis: Clinical Evaluation of Drugs for Treatment," 2015).

Domperidone Risk To Infants

British Journal of Obstetrics and Gynaecology
February 1985, Vol. 92, pp. 141–144

Domperidone: secretion in breast milk and effect on puerperal prolactin levels

G. J. HOFMEYR *Consultant and Lecturer, Johannesburg Hospital and University of Witwatersrand,* B. VAN IDDEKINGE *Senior Consultant and Senior Lecturer, Baragwanath Hospital and University of Witwatersrand* & J. A. BLOTT *Senior House Officer, Johannesburg Hospital, South Africa*

Summary. The possible effect on the infant of dopamine antagonists used to promote lactation is cause for concern. Domperidone (Motilium) may be safer than other drugs in this group as it does not cross the blood–brain barrier. The mean serum level of prolactin 2 h after treatment with 20 mg of domperidone in the puerperium was 255 ng/ml compared with 150 ng/ml after a placebo. The mean domperidone level in all breast milk samples during treatment with 10 mg, three times daily, was 2·6 ng/ml. This was significantly more than levels after a single 20 mg dose sampled at 2 h (0·24 ng/ml) and at 4 h (1·1 ng/ml), and considerably less than values available for metoclopramide and sulpiride, relative to the therapeutic dosage. The effectiveness of domperidone to augment lactation requires further study.

Domperidone Risk To Infants

- RCT, placebo-controlled
- Domperidone 20mg single dose
  - 0.24 ng/mL 2hrs post dose
  - 1.1 ng/mL 4hrs post dose

Results compared to other studies

- Metoclopramide 10mg single dose (Lewis 1980)
  - 125.7 ng/mL 2hrs post dose

- Domperidone 10mg Q8H
  - 2.6 ng/mL

Hofmeyr et al. Domperidone: Secretion in breast milk and effect on puerperal prolactin levels. Br J Obstet Gynaecol. 1985;92(2):141-4

Domperidone Risk to Infants

- Metoclopramide level in breast milk was 500x greater than domperidone
  - Metoclopramide crosses BBB more readily than domperidone, lipophilic

Table 1. Comparison of dopamine antagonist levels in breast milk

Treatment	Serum		Milk			
	Sampling (h)	Level (ng/ml)	Sampling (h)	Level (ng/ml)	Level per 10 mg of drug taken (ng/ml)	Milk: serum ratio
Domperidone 20 mg single dose	2	8·0	2	0·24[a]	0·12	0·03
			4	1·1[b]	0·6	—
Domperidone 10 mg 8-hourly (Hofmeyr & van Iddekinge 1983)	1·75–3·0	10·3	All samples	2·6[c]	2·6	0·25
Metoclopromide 10 mg single dose (Lewis *et al.* 1980)	2	68·5	2	125·7	125·7	1·8
Sulpiride 50 mg twice daily (Aono *et al.* 1979)	—	—	2	970·0	194·0	—

a *vs* b: $P<0·05$; b *vs* c: $P<0·05$; a *vs* c: $P=0·0001$.

Domperidone Risk To Infants

What about the Q8H dosing with higher levels found?

- 2.6 ng/mL = 6.1nM

- 13 – 17% oral bioavailability (package insert)
  - 0.442 ng/mL (1.037 nM) potential serum levels in infant

Table 1. Effect of domperidone on cardiac parameters

Assay	Prep	Effective Dose	Ref / Yr
hERG	CHO cells	IC_{50} = 162 nM	Drolet et al., 2000
	HEK293	IC_{50} = 57 nM	Claassen et al., 2005
APD (repolarization)	Guinea pig heart	100 nM*	Drolet et al., 2000
	Guinea pig heart	100 nM*	Hreiche et al., 2009
	Rabbit heart	30 nM*	Hondegehm, 2011 and 2013
TRIaD	Rabbit heart	100 nM*	Hondegehm, 2011 and 2013

*Effect did not saturate at doses tested; no IC_{50} (drug concentration producing 50% current inhibition) was determined

Domperidone Risk To Infants

FDA Briefing Information:

Other published clinical studies show that domperidone increases prolactin levels to 150%-600% of baseline, within 15-45 minutes, in nonpregnant and lactating women, and increases milk production by 1.5-2 times baseline in lactating women (Wan et al., 2008; Brouwers et al., 1980; Knoppert et al., 2013; Wagner et al., 2011; Camanni et al., 1980; Ingram et al., 2012). Doses in the studies were most commonly 30 mg orally daily, but

Compared to metoclopramide?

Domperidone has been shown to raise the serum prolactin level in non-lactating women from 8·1 to 110·9 ng/ml after one 20-mg dose while metoclopramide 20 mg raised the levels from 7·4 to 124·1 ng/ml (Brouwers *et al.* 1980).

Australian Government
Department of Health and Ageing

ATC	ITEM TYPE	CODE	FORM AND STRENGTH	2010 DDD	UNITS	SCRIPTS	COST($)
PROPULSIVES							
A03FA03	DOMPERIDONE						
	A	11309	Tablet 10mg 100	30.00	MG	15,488	–
	P	1347X	Tablet 10mg	30.00	MG	321,156	4,078,502

2011 statistics

A03FA03	DOMPERIDONE						
	A	11309	Tablet 10mg 100	30.00	MG	17,576	–
	P	1347X	Tablet 10mg	30.00	MG	348,065	4,423,328

Motilium package insert (AUS)

INDICATIONS

MOTILIUM is indicated for the short-term treatment in adults of:

- Symptoms associated with idiopathic or diabetic gastroparesis (once control of diabetes has been established by diet and/or insulin, an attempt should be made to discontinue MOTILIUM).

- Intractable nausea and vomiting from any cause.

CONTRAINDICATIONS

MOTILIUM is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma).
- Co-administration with potent CYP3A4 inhibitors, which **have been shown to cause QT interval prolongation* such as clarithromycin, **erythromycin, itraconazole, oral ketoconazole, posaconazole, ritonavir, saquinavir*, telithromycin, **telaprevir and voriconazole* (see **PRECAUTIONS** and **INTERACTIONS WITH OTHER MEDICINES**)
- Whenever stimulation of gastric motility might be dangerous, e.g. in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment (see **Pharmacokinetics**).
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure
- **Use with medicines that prolong the QT interval should be avoided.*

Motilium package insert (AUS)

Cardiac effects

MOTILIUM is associated with an increased risk of sudden cardiac death of approximately 4 per 1000 per years compared with no use of medication. This risk is increased in patients aged over 60 years or who have cardiac disease or diabetes. The risk is also increased with MOTILIUM doses >30 mg daily and when taken in combination with medicines that prolong the QT interval and medicines that inhibit CYP3A4. Long term use and use with medicines that prolong the QT interval and medicines that inhibit CYP3A4 should be avoided. The lowest dose needed to alleviate symptoms should be taken for the shortest period of time.

MOTILIUM should be used with caution in older patients or those with current or a history of cardiac disease.

Conclusions

- Domperidone is a widely utilized medication
- Vast global availability, 37 years of clinical use
  - 112 countries
- Experts in gastroenterology have determined a need for this medication
  - Has been compounded extensively
  - Fewer CNS side effects versus metoclopramide
  - Millions of doses prepared prior to Drug, Quality and Safety Act
- There are some safety concerns at higher doses, particularly with other medications affecting cardiac rhythm
  - Clinical studies have multiple methodology flaws
    - Conclusions cannot be extrapolated to larger patient population
  - However, body of evidence points to safety
    - No risk found in study on infants

THANK YOU

Questions?