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FEATURE ARTICLE

Domperidone Update

On June 7, 2004, citing safety concerns, the U.S. Food and Drug Administration (FDA) warned breastfeeding women not to use the drug domperidone (Motilium®). Warning letters were sent to pharmacies that compound products containing domperidone as well as firms that supply domperidone for use in compounding. Recipients were advised that further violations of the Federal Food, Drug, and Cosmetic Act could result in enforcement actions including seizure and injunction.

What is known about domperidone?

- Domperidone was developed by Janssen Pharmaceutica Products and first marketed in Belgium in 1978.
- Trade names include Motilium™, Cilroton™, Emiken™, Eucitro™, Gastrocure™, Gastronorm™, Nauzelin™, Peridys™, Praxis™, and Seronex™.
- Domperidone is used primarily to treat gastrointestinal conditions, specifically motility disorders including diabetic gastroparesis, dyspepsia, and reflux esophagitis. It is also used to prevent gastrointestinal symptoms secondary to the use of chemotherapeutic agents or dopamine agonists in Parkinson's Disease and to relieve nausea and vomiting in infants and children.

Caught In The Web

CDC Reports U.S. Breastfeeding Rates

Each year since 1994, the Centers for Disease Control Prevention (CDC) has conducted the National Immunization Survey (NIS). This nationwide survey provides estimates of immunization rates for U.S. children aged 19 to 35 months.

In 2001, the NIS piloted breastfeeding questions to approximately 13% of respondents. Since January 2003, these breastfeeding questions have been asked of all survey respondents to assess the population's breastfeeding practices. The 2003 survey results provide overall population estimates for the initiation, duration, and exclusivity of breastfeeding, as well as geographically-specific breastfeeding rates. Key findings of the 2003 NIS regarding breastfeeding practices include:

- In 14 states 75% of mothers initiate breastfeeding; in 6 states 50% of mothers breastfeed at least 6 months, and in 8 states 25% of mothers breastfeed at least 12 months.
- Only Oregon has achieved an exclusive breastfeeding rate of 25% at 6 months.
- Six states have achieved all of the Healthy People 2010 objectives on breastfeeding; Hawaii, Idaho, Oregon, Utah, Vermont, and Washington.
- Non-Hispanic blacks and socio-economically disadvantaged groups have consistently lower breastfeeding rates.

The entire report can be found at www.cdc.gov

Ask Amy

Q. If I breastfeed can I still get pregnant?

Yes, women who breastfeed can still get pregnant. However, mothers who breastfeed exclusively are less likely to get pregnant during the first six months after their babies are born. The more often your baby breastfeeds (suckles) the less likely you are to ovulate (release an egg) and menstruate (bleed monthly). When you give your baby formula, water, or other foods or use a pacifier, your baby breastfeeds less often and you are more likely to get pregnant. Breastfeeding can be an effective, temporary method of birth control but ONLY under the following conditions:

- Your baby is less than 6 months of age.
- You are breastfeeding exclusively (at least 85-90% of your baby's feedings are breastfeedings).
- You have not had a menstrual period (monthly bleeding) since birth.

Discuss the different types of birth control with your doctor, midwife, lactation consultant, or nurse and choose one that is best for you and your baby.

Can I get the flu vaccine if I am breastfeeding?

According to the Advisory Committee on Immunization Practices:

"Influenza vaccine does not affect the safety of mothers who are breastfeeding or their infants. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination."

For additional information visit: www.cdc.gov

- In addition to its gastrokinetic and anti-emetic activity, domperidone affects the pituitary gland, causing an increase in prolactin secretion. Subsequently, domperidone is used "off-label" i.e.

for indication, dosage form, dose regimen, population, or other use parameter not mentioned in the approved labeling, to enhance milk production in lactating women.

- Domperidone is currently approved for use in over 80 countries including European Union Member States, Australia, New Zealand, Argentina, Mexico, South Africa, Hong Kong, Singapore, and Thailand.

- Domperidone is available without a prescription (over-the-counter) in several countries, including Belgium, Ireland, Italy, Netherlands, United Kingdom, Switzerland, and South Africa.

- Domperidone is not approved for use in the U.S. for any purpose and it is not approved for use in any country for the purpose of enhancing milk production in lactating women.

- The manufacturers of domperidone caution against the use of domperidone in lactating women.

- The American Academy of Pediatrics lists domperidone among those drugs thought to be compatible with breastfeeding.

What are the pharmacokinetics of domperidone?

- Domperidone is a dopamine-receptor blocking agent that produces an anti-emetic effect.
- Domperidone does not cross the blood-brain barrier to any appreciable degree and so exerts relatively little ef-

fect on cerebral dopaminergic receptors.

- Domperidone has been shown to increase the duration of antral and duodenal contractions to increase gastric emptying.

- Domperidone is rapidly absorbed, with peak plasma concentrations at approximately one hour after oral administration.

- Domperidone has low bio-availability (approximately 15 percent) due to first-pass hepatic and intestinal metabolism.

- Domperidone is 91 to 93 percent bound to plasma proteins. 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.

- The recommended oral dose for controlling gastrointestinal symptoms is 10-20mg

Elimination of Health Disparities a U.S. Priority

Eliminating health disparities between different racial/ethnic subgroups is a U.S. priority. Even at the earliest stages of pregnancy, disparities in health are evident. A new study of California women documents persistent disparities in rates of unintended pregnancy, prenatal care, and breastfeeding between women of different incomes, educational levels, and racial/ethnic groups. While, overall, the state experienced an improvement in these maternal and infant health measures, the aggregate improvements masked persistent gaps between different groups of women.

A new issue brief prepared by researchers at the University of California at San Francisco and the Kaiser Family Foundation, "Social and Economic Disparities in Maternal and Infant Health," analyzes changes in racial/ethnic and socioeconomic disparities in maternal and infant health in California in 1994/1995 and 1999/2001. This issue brief also reviews the policy implications of these differences and offers general recommendations for health care policymakers to consider in addressing health disparities. This issue brief can be found online at: www.kff.org

Institute of Medicine to Study Effect of Food Marketing on Diet and Health of Children and Youth

The Institute of Medicine, through the Food and Nutrition Board and the Board on Children, Youth, and Families, will undertake a comprehensive study of the science-based effects of food marketing on the diets and health of children and youth in the United States. This work is funded by the Centers for Disease Control and Prevention (CDC), in response to a Congressional directive.

An interdisciplinary committee has been convened to complete the study. Committee members have expertise in the areas of child and adolescent development, child and adolescent nutrition, psychology and behavioral economics, media and advertising, consumer marketing and behavior, social marketing and evaluation, education, public health and policy, food and beverage industries, entertainment industry, causal reasoning, constitutional law, and business ethics. The study will use information obtained from literature reviews, analyses of available surveys and other reports, existing compilations of research and data related to the issues under study, and input from a broad range of stakeholders.

The final product will be a comprehensive report, to be published by the National Academies Press, after it has undergone an independent and comprehensive review that is a hallmark of the National Academies process. This report will:

- Describe the state of food and beverage marketing to children and youth and the impact of this exposure on their diets and health;
- Develop a framework and indicators for various stakeholders to guide the development of effective marketing and advertising strategies that foster healthy food choices among children and youth; and
- Provide estimated costs of implementation strategies and benchmarks to guide future evaluation.

For additional information please visit www.iom.edu

AAP Releases Guidelines on Management of Hyperbilirubinemia

The American Academy of Pediatrics (AAP) has issued a clinical practice guideline on the management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. A key element of the guideline is the promotion and support of successful breastfeeding. The following recommendations appear in the guidelines:

RECOMMENDATION 1.0: Clinicians should advise mothers to nurse their infants at least 8 to 12 times per day for the first several days.

RECOMMENDATION 1.1: The AAP recommends against routine supplementation of non-dehydrated breastfed infants with water or dextrose water.

RECOMMENDATION 7.3: In breastfed infants who require phototherapy, the AAP recommends that, if possible, breastfeeding should be continued. In breastfed infants receiving phototherapy, supplementation with expressed breastmilk or formula is appropriate if the infant's intake seems inadequate, weight loss is excessive, or the infant seems dehydrated.

Among the list of risk factors for the development of severe hyperbilirubinemia is exclusive breastfeeding, particularly if breastfeeding is not going well and weight loss is excessive.

It's the Law

Scotland Protects Public Breastfeeding

September 24, 2004, Scotland's parliament approved a bill to protect a mother's right to breastfeed in public. Members of the Scottish Parliament voted overwhelmingly in favor of a bill that makes it a criminal offense to harass or discriminate against a mother who breastfeeds her baby in public. The bill is expected to become a law by the end of 2005. According to Elaine Smith, sponsor of the bill, "Asking a mother to desist from normal, everyday, natural and nurturing behavior is the crime." Liz Goudie of the National Childbirth Trust in Scotland supported the legislation stating, "Research has demonstrated that the perceived and, sadly, in some places, the real lack of social acceptability of breastfeeding is a major barrier to initiation and continuation rates among new mums."

three to four times daily although for nausea and vomiting the dose can be higher (up to 40 mg).

- The recommended oral dose for enhancing milk production is 10-20 mg three to four times a day, but there are reports of women taking up to 40 mg four times a day.

Does domperidone increase milk production?

Despite an abundance of anecdotal reports, there is very little scientific data demonstrating the effectiveness of domperidone as a galactagogue. The few studies that have been completed were done on relatively small samples. For example, in a study by da Silva et al, sixteen mothers with premature infants and low milk production were randomly chosen to receive placebo (n=9) or domperidone 10mg three times a day (n=7) for seven days. Milk volume increased from 112.8 to 162.2 mL/d in the domperidone group and 48.2 to 56.1 mL/d

in the placebo group. Prolactin levels increased from 12.9 to 119.3 ug/L in the domperidone group and 15.6 to 18.1 ug/L in the placebo group. No adverse effects were reported in infants or mothers.

Is domperidone safe?

According to the manufacturers, adverse side effects include very rare allergic reactions; very rare extrapyramidal side effects; rare gastro-intestinal disorders, including very rare transient intestinal cramps; rare galactorrhea, gynecomastia, and amenorrhea. There have been several published reports and case studies of cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of domperidone. Subsequently the intravenous form was removed from the market some time ago. There are no reports of cardiotoxicity for the oral form of domperidone. There are two unpublished cases of seizures in infants whose mothers took 20 mg four times a day for more than six months. And one published report of seizures in adults taking high doses of domperidone.

In those countries where the oral form of domperidone continues to be available, product labels contain a specific warning against the use of domperidone by breastfeeding women and note that the drug is excreted in breastmilk and could expose a breastfeeding infant to unknown risks. Of particular concern is the potential for interaction with other drugs, specifically ketoconazole. Theoretically, ketoconazole can interfere with the metabolism of domperi-

done which can lead to a marked increase in the serum level of domperidone.

The amount of domperidone excreted in human milk is estimated to be less than 7ug per day when administered at the highest recommended dose. Effects on the newborn are not well established, but the drug's known safety profile in infants makes it unlikely that domperidone poses a significant risk at the recommended dose.

What is the rationale behind the FDA warning?

The United States Breastfeeding Committee (USBC), in an effort to better understand the rationale behind the FDA warning, facilitated a conference call on July 29, 2004 between representatives of the FDA and representatives of the health care community. A summary of the issues discussed and the questions raised follows.

Issue

FDA authority over cross border importation of drugs, internet distribution of drugs, and compounding of drugs by U.S. pharmacists.

- If the FDA limits the ability of U.S. physicians to prescribe and U.S. pharmacists to compound domperidone, will a greater number of women attempt to purchase domperidone via the internet, wherein concerns about quality control have already been raised?

- Does the FDA have jurisdiction over the importation and/or compounding of drugs?

Comment

- The sale of drugs via the internet and the importation of drugs from other countries is re-

portedly the primary concern of the FDA.

- The FDA stated that prescriptions written by an informed and educated physician, for his/her specific patient, for an FDA approved drug provided by a legitimate U.S. compounding pharmacy is not the issue. Of concern is the importation of drugs by individuals wherein there is no oversight by a qualified physician or pharmacist who would normally direct, dosage, administration, and duration of therapy. The concern is even greater for drugs not approved for use in the U.S. such as domperidone. The FDA cited reports that some women were taking twice the maximum recommended dose of domperidone [40 mg or more four times a day]. The FDA theorized that the maternal serum level of domperidone might approach the dangerous levels seen in women taking the intravenous form particularly if drug-drug interactions were to occur.

- According to representatives of the FDA, the FDA does have jurisdiction over the importation and compounding of drugs but in the past has chosen not to pursue enforcement. The International Academy of Compounding Pharmacists [IACP] disputes the FDA's jurisdiction over this matter. According to the IACP, the FDA regulates but does not approve compounded drugs; that authority rests with the states. The IACP also disagrees with the FDA statements that compounded medications are new drugs subject to the provisions of the Food Drug Cosmetic Act [FDAC]. Congress clarified in 1997 that compounded drugs are exempt from the new drug approval process and from good manufacturing practices.

Traditionally, the FDA regulates the manufacturing of drugs and State Boards of Pharmacy regulate the practice of pharmacy compounding. Compounding differs from manufacturing in that a compounded drug is prepared and dispensed pursuant to a valid prescription order from a physician for a specific patient. Manufactured drugs are mass marketed and distributed through wholesalers and eventually dispensed through pharmacies to patients unknown to the manufacturer. Domperidone is not a component of an FDA-approved product nor does it have a USP/NF monograph. However, domperidone would have been a likely candidate for addition to the list of products allowed for use in compounding based on its chemical characterizations, safety, historical use, and evidence of effectiveness as demonstrated in its broad approval by other developed countries.

Issue

- In the absence of an immediate public health concern, does the law require that the FDA convene an advisory panel before issuing a warning/alert relative to a particular drug?
- Are there drugs under investigation that have the potential for increasing mothers' milk supply and meeting the need currently met by domperidone?

Comment

- There are no legal requirements concerning advisory panels. In the event an advisory panel is formed, the FDA is under no obligation to comply with the recommendations of the advisory panel.
- Under the laws governing intellectual property, the FDA may not disclose any information con-

cerning drugs that are currently in the research and development stage.

Issue

- Despite approval by the FDA's own division of gastrointestinal drugs, approval of domperidone for gastrointestinal symptoms / conditions has not been recommended by the FDA.
- Given the safety profile of domperidone versus metoclopramide, why has metoclopramide been approved for use in the U.S. but domperidone rejected?

Comment

- Representatives of Janssen Pharmaceutica Products reported that all U.S. clinical trials related to domperidone have been halted and there is no plan for future research. Industry representatives gave no reason for their decision to halt the trials.

Issue

- Representatives of the USBC suggested that perhaps a better understanding of lactation physiology on the part of the FDA might serve to alleviate FDA concerns regarding the potential impact of domperidone on the breastfed infant and the breastfeeding mother.

Comment

- The FDA expressed concern over the absence of credible scientific data to establish the safety and efficacy of domperidone as a galactagogue.

- The FDA indicated that there are approximately 1000 reports of adverse events subsequent to the use of domperidone; however these reports have not been released. Because the mechanism for reporting adverse events requires that the drug be approved for use in the U.S., the FDA has theorized that because domperidone has not been approved for use in the U.S. there is the possibility that an even greater number of adverse events are taking place but are not being reported. When the IACP asked the FDA for more specific information on the safety concerns, it was told that no further information was being made available at this time.

Issue

- What is the accepted standard regarding the off label use of a drug?

Comment

- The drug must be approved for use in the U.S. and must be generally recognized as safe (GRAS) as determined by a consensus of many studies.

Issue

Therapeutic alternatives:

- Metoclopramide is approved by the FDA. However, metoclopramide readily crosses the blood brain barrier and is associated with significant central nervous system side effects including depression, restlessness, and extrapyramidal symptoms.

- Anecdotal reports suggest that fenugreek and other herbs may be effective galactagogues, however health professionals are reluctant to recommend herbal preparations given the lack of quality scientific data and the absence of quality control.

Comment

- The FDA stated a willingness to work with sponsor(s) to assist in testing drugs that enhance milk production in lactating women. Domperidone has not been studied in any large clinical trial. Only one small randomized controlled trial compared the effects of domperidone on prolactin levels and milk volume.

- Discussion was held regarding the feasibility of contacting Janssen Pharmaceutica Products or its parent company, Johnson & Johnson, to ascertain their interest in pursuing a New Drug Application (NDA) or Orphan Drug Status. The FDA expressed a willingness to assist in any way possible.

Summary

- The FDA warning was prompted by an apparent increase in both cross-border importation and internet sales. Both of which merit concern.

- Reports of adverse events reportedly accumulated over twenty years in more than thirty countries have not been released. Therefore the seriousness of the events is not known i.e. cardiotoxicity as opposed to gynecomastia or galactorrhea, or the population affected i.e. men, non-lactating women, lactating women, or breastfed infants. There

are no reports of serious side effects when domperidone was administered orally at the recommended dose of 20-40 mg per day.

- The theoretical infant dose is 0.18 micrograms/kg/day or 7 micrograms per day assuming a maternal dose of 80 mg/day.
- The relative infant dose is 0.042 percent of the maternal dose.
- The risk-benefit assessment of domperidone is favorable given its large molecular weight (426 daltons), high protein binding (93 percent), and low oral bioavailability (15 percent).
- Domperidone has been shown to be effective in the treatment of gastrointestinal conditions. Prior attempts on the part of the manufacturer (Janssen Pharmaceutica Products) to secure FDA approval have been rejected. In order to gain approval the manufacturer must pursue a New Drug Application (NDA), license domperidone to another manufacturer that is willing to pursue a NDA, or pursue an Investigational New Drug application (IND) i.e. a request for exemption from the federal statute that prohibits an unapproved drug from being shipped in interstate commerce and authorizes the shipment of an unapproved drug across state lines.

Health care professionals in the gastro-intestinal community are communicating with members of the FDA in an effort to secure approval for the use of domperidone in treating patients with gastro-intestinal conditions. If domperidone is approved by the FDA for use in the U.S., for any condition, then consideration of off-label use i.e. as a galactagogue, might be feasible. The support and patience of the lactation community throughout this process is essential to its success. Future updates will follow.

For additional information please visit www.fda.gov

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3. Cheales-Siebenaler NJ. Induced lactation in an adoptive mother. *J Hum Lact* 1999;15(1):41-3.

4. da Silve OP et al. Effect of domperidone on milk production in mothers of premature newborns: a randomized, double-blind, placebo-controlled trial. *Can Med Assoc J* 2001;164(1):17-21.

5. Drolet B et al. Domperidone should not be considered a no-risk alternative to Cisapride in the treatment of gastrointestinal motility disorders. *Circulation* 2000; 102:1883-5.

6. Guidelines for Off-label Communications, Pharma Marketing News, Vol. 2, #11; REPRINT #211-05.

7. Hale T. http://neonatal.ama.ttuhscc.edu/lact/html/fda_warning_on_domperidone.html. June 2004.

8. Janssen Pharmaceutica Products. <http://home.intekom.com/pharm/janssen/motilium.html>

9. Joss RA et al. Sudden death in cancer patient on high-dose domperidone. *Lancet* 1985;I:1019.

SCIENCE OR SCIENCE FICTION ***Sudden Infant Death Syndrome (SIDS) Re-defined***

In an effort to facilitate research into sudden infant death, an expert panel of pediatric and forensic pathologists have redefined sudden infant death syn-

drome as the sudden unexpected death of an infant less than one year of age, with onset of the fatal episode occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history. In the future all sudden infant deaths will be assigned to one of the following categories:

- Category IA SIDS: Classic features of SIDS present and completely documented.
- Category IB SIDS: Classic features of SIDS present but incompletely documented.
- Category II SIDS: Infant deaths that meet category I criteria with one or more exceptions.
- Unclassified Sudden Infant Death.

Researchers hope that these new categories will facilitate more accurate investigation and diagnosis of unexpected sudden infant death. It is important to note that the proposed framework is a work in progress that will need to be reformulated and refined as more knowledge becomes available and the understanding of unexpected sudden infant death increases.

Pediatrics 2004; 114: 234-238; SIDS

Breastfeeding and Breast Cancer

Researchers in Sweden conducted a case-control study of women with breast cancer all of whom had gene mutations in either the BRCA1 [685] or BRCA2 [280] gene. Study participants were matched with 965 control subjects. Information on pregnancies and breastfeeding practices was derived from a questionnaire administered to the women during the course of genetic counseling. Women with BRCA1 gene mutations

who breastfed for more than 1 year were less likely to have breast cancer than those who never breastfed. No reduction in risk was identified for women with BRCA2 gene mutations. In the U.S. about 180,000 women develop breast cancer each year, and about 70% of women who develop breast cancer have one of these two gene mutations.

Journal of the National Cancer Institute
2004;96:1094-8.

WHAT'S NEW

Amy's Baby Company Releases Two New Products

Breastfeeding, Keep It Simple—the ideal breastfeeding book for parents and their families. *Breastfeeding, Keep It Simple* is clear, concise, easy-to-read, and affordable! It answers the breastfeeding questions asked most often and contains useful information for WIC clients and staff.

Breastfeeding Poster Series—A series of four colorful posters highlights the benefits of breastfeeding for mothers and babies. Two posters display an image of a breastfeeding baby and two posters display an image of a mother and baby. Each 16 x 20 inch poster has a protective coating for enhanced durability.

For additional information or to obtain a sample of *Breastfeeding, Keep It Sim-*

ple please contact
amyspangler@amysbabycompany.com or call
(770) 913.9332.

Pharmasoft Publishing Launches Newsletter

Medications and More a quarterly newsletter produced by Pharmasoft Publishing is now available online at www.ibreastfeeding.com. Features include:

- News and commentary by Thomas Hale, Ph.D., author of Medications and Mother's Milk
- FDA drug alerts/warnings that impact breastfeeding mothers and/or their babies
- Breastfeeding research updates
- A schedule of upcoming breastfeeding conferences
- Announcements of new books and materials available through Pharmasoft Publishing

To subscribe to the newsletter or to view previous issues please visit www.ibreastfeeding.com

EDUCATIONAL EVENTS

*An asterisk indicates those events where Amy Spangler will be speaking.

October 20, 2004*
Hamilton Memorial Hospital
Dalton, GA USA
Carol Syrmanse
800.289.7406

October 22-23, 2004
Emory University Annual Breastfeeding Conference

Emory Conference Center
Atlanta, Georgia USA
Linda McCollum
Linda_McCollum@oz.ped.emory.edu

November 12-13, 2004
Northeast Florida Breastfeeding Coalition
Impact of Birth Practices on Breastfeeding
Jacksonville, FL USA
Judy Neff
904.393.6937

April 11-14, 2005
Lactation Consultant Comprehensive Update
Raleigh, NC USA
www.wakeahec.org

PROFESSIONAL OPPORTUNITIES

Are you looking for a new employee, or new job opportunity? Use our Professional Opportunities column to streamline your search. Your advertisement will be read by hundreds of qualified professionals in the maternal and child health field and by more than 10,000 visitors during its 60 day flight. For additional information, contact us at info@amysbabycompany.com

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