

# Manometry Offers Useful Diagnostic Information

BY SHARON WORCESTER  
Tallahassee Bureau

FORT LAUDERDALE, FLA. — Anal manometry is a useful tool for the evaluation of patients with abnormal anorectal physiology, including those presenting with constipation, fecal incontinence, proctalgia, or rectal prolapse, according to Dana R. Sands, M.D.

Manometry provides information about the functional status of the anal sphincter

and distal rectum, and often is used with other tests such as anal ultrasound, anal sphincter EMG, pudendal nerve terminal motor latency assessment, and defecography, said Dr. Sands of the Cleveland Clinic Florida, Weston.

In patients with fecal incontinence, for example, anal ultrasound is the cornerstone of treatment, but anal manometry, EMG, and pudendal nerve assessment “round out the evaluation,” she said at a symposium on pelvic floor disorders spon-

sored by the Cleveland Clinic Florida.

Anal manometry, however, is not well standardized, Dr. Sands said, noting that different facilities have different protocols and normal values.

Some manometry devices include a microtransducer, some use air-filled balloon systems, and still others use continuously perfused probes. The Cleveland Clinic uses a balloon-tip catheter system that is perfused with water. The device measures rectal sensation, resting and squeezing

pressures at different levels in the anal canal, and rectal compliance, all of which can play a role in fecal incontinence.

Although some surgeons say their index finger is the best device for identifying anal sphincter pathology, manometry provides a higher level of information than that achieved via digital rectal exam, she said.

In one study of 64 patients, digital rectal exam performed by an experienced colorectal surgeon yielded 63% sensitivity and 57% specificity for internal anal sphincter pathology, and 84% sensitivity and 57% specificity for external anal sphincter pathology.

“I think we can be a little more sophisticated than that with the manometry machine,” she said, adding that manometry also provides insight into the etiology of conditions such as fecal incontinence and can aid in discussions with patients about expected outcomes and prognosis. ■

## Patients Need Not Stop Clopidogrel Before Surgery

WASHINGTON — Patients on long-term clopidogrel treatment don't need to stop the drug before surgery, Richard E. Kuntz, M.D., said at a meeting that was sponsored by the Cardiovascular Research Institute at Washington Hospital Center.

“There is growing experience that it's safe to perform surgery on a patient taking clopidogrel. At our institution, surgeons will operate on these patients. There is no significant difference in morbidity and mortality” during surgery, said Dr. Kuntz, who is a cardiologist at Brigham and Women's Hospital in Boston.

“Surgeons make more of a big deal about clopidogrel than they need to,” he added.

This approach to dealing with patients on long-term treatment with the antiplatelet drug clopidogrel (Plavix) was endorsed also by Ron Waksman, M.D., of the division of cardiology at the Washington Hospital Center.

“If we push our surgeons, they'll do surgery without waiting to stop clopidogrel,” said Dr. Waksman, who chaired the meeting.

The issue of when to stop clopidogrel recently became critical for patients who take the drug after they have received drug-eluting coronary stents. A report last year detailed four anecdotal cases of patients who developed clinically significant coronary thrombosis within a drug-eluting stent after their clopidogrel and aspirin regimens were stopped (Lancet 2004;364:1519-21).

In three of these cases, patients had stopped their antiplatelet medications before surgery.

These reports have made experts wary about stopping aspirin and clopidogrel in their patients.

—Mitchel L. Zoler

### BRIEF SUMMARY

#### ZOFRAN® (ondansetron hydrochloride) Tablets ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets ZOFRAN® (ondansetron hydrochloride) Oral Solution

The following is a brief summary only; see full prescribing information for complete product information.

#### CONTRAINDICATIONS

ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are contraindicated for patients known to have hypersensitivity to the drug.

#### WARNINGS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT<sub>3</sub> receptor antagonists.

#### PRECAUTIONS

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension.

**Information for Patients: Phenylethanolamines:** Phenylethanolamine patients should be informed that ZOFRAN ODT Orally Disintegrating Tablets contain phenylethanolamine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains <0.03 mg phenylethanolamine.

Patients should be instructed not to remove ZOFRAN ODT Tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

**Drug Interactions:** Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver (see CLINICAL PHARMACOLOGY, Pharmacokinetics in full prescribing information).

Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of available data, no dosage adjustment is recommended for patients on these drugs. **Phenylethanolamine, Carbamazepine, and Rifampicin:** In patients treated with potent inducers of CYP3A4 (i.e., phenylethanolamine, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs. **Tramadol:** Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol. **Chemotherapy:** Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of high-dose methotrexate.

**Use in Surgical Patients:** The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

**Carcinogenicity, Mutagenesis, Impairment of Fertility:** Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.

**Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

**Pediatric Use:** Little information is available about dosage in pediatric patients 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections of full prescribing information for use in pediatric patients 4 to 18 years of age).

**Geriatric Use:** Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY section of full prescribing information).

#### ADVERSE REACTIONS

The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ZOFRAN. A causal relationship to therapy with ZOFRAN has been unclear in many cases.

**Chemotherapy-Induced Nausea and Vomiting:** The adverse events in Table 1 have been reported in ~5% of adult patients receiving a single 24-mg ZOFRAN Tablet in 2 trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ~60 mg/m<sup>2</sup>).

Table 1. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFRAN Tablets (Highly Emetogenic Chemotherapy)

Event	Ondansetron 24 mg q.d. n = 300	Ondansetron 8 mg b.i.d. n = 124	Ondansetron 32 mg q.d. n = 117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in Table 2 have been reported in ~5% of adults receiving either 8 mg of ZOFRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Table 2. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFRAN Tablets (Moderately Emetogenic Chemotherapy)

Event	Ondansetron 8 mg b.i.d. n = 242	Ondansetron 8 mg t.i.d. n = 415	Placebo n = 262
Headache	58 (24%)	113 (27%)	34 (13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

**Central Nervous System:** There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.

**Hepatic:** In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1% to 2% of patients receiving ZOFRAN Tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.

There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

**Integumentary:** Rash has occurred in approximately 1% of patients receiving ondansetron.

**Other:** Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to ZOFRAN was unclear.

**Radiation-Induced Nausea and Vomiting:** The adverse events reported in patients receiving ZOFRAN Tablets and concurrent radiotherapy were similar to those reported in patients receiving ZOFRAN Tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.

**Postoperative Nausea and Vomiting:** The adverse events in Table 3 have been reported in ~5% of patients receiving ZOFRAN Tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 3. Frequency of Adverse Events From Controlled Studies With ZOFRAN Tablets (Postoperative Nausea and Vomiting)

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

Preliminary observations in a small number of subjects suggest a higher incidence of headache when ZOFRAN ODT Orally Disintegrating Tablets are taken with water, when compared to without water.

**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of ZOFRAN. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ZOFRAN.

**General:** Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

**Hepatobiliary:** Liver enzyme abnormalities

**Lower Respiratory:** Hiccups

**Neurology:** Oculogyric crisis, appearing alone, as well as with other dystonic reactions

**Skin:** Urticaria

#### DRUG ABUSE AND DEPENDENCE

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

#### OVERDOSAGE

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily intravenous doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: “Sudden blindness” (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of ZOFRAN Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.

 GlaxoSmithKline

GlaxoSmithKline  
Research Triangle Park, NC 27709

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GlaxoSmithKline  
Research Triangle Park, NC 27709

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