

Santa Barbara County
PUBLIC Health
DEPARTMENT

Emergency Medical Services Agency

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August 21, 2008

Steve Tharratt, MD, Director
Emergency Medical Services Authority
1930 Ninth Street, Suite 100
Sacramento, CA 95814-7043

Dear Dr. Tharratt:

Enclosed is a trial study application for the use of ondansetron by paramedics in Santa Barbara County.

Coastal Valleys EMS and Inland Counties EMS are considering joining this trial, and if they decide to so you will receive letters from them.

Please let me know if you need additional information.

Sincerely,


Angelo Salvucci, MD
Medical Director

Santa Barbara County
PUBLIC Health
DEPARTMENT

EMERGENCY MEDICAL SERVICES AGENCY

300 North San Antonio Road
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Ondansetron

Prehospital and Interfacility Transfer Clinical Trial Study

Submitted by:
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Marc Burdick, EMT-P

Emergency Medical Services Authority

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**REQUEST FOR APPROVAL
UNDEFINED SCOPE OF PRACTICE**

EMS MEDICAL DIRECTOR: Angelo Salvucci, MD

DATE: 8/21/2008

LOCAL EMS AGENCY: Santa Barbara County

NAME OF PROPOSED PROCEDURE OR MEDICATION: Ondansetron hydrochloride

1. DESCRIPTION OF THE PROCEDURE OR MEDICATION REQUESTED:

Antiemetic medication used to treat severe nausea and vomiting in the prehospital and interfacility transport environment (see complete packet for full details).

2. DESCRIPTION OF THE MEDICAL CONDITIONS FOR WHICH THEY WILL BE UTILIZED:

1) Intractable vomiting and 2) severe nausea (see complete packet for full details).

3. ALTERNATIVES(Please describe any alternate therapies considered for the same conditions and any advantages and disadvantages): None. (see complete packet for full details).

4. PATIENT POPULATION THAT WOULD BENEFIT, INCLUDING AN ESTIMATE OF FREQUENCY OF UTILIZATION:

It is estimated that approximately 500-1000 EMS patients a year will benefit from treatment with ondansetron in Santa Barbara County (see complete packet for full details).

5. OTHER FACTORS OR EXCEPTIONAL CIRCUMSTANCES:

See Attached

PLEASE ATTACH:

6. ANY SUPPORTING DATA, INCLUDING RELEVANT STUDIES AND MEDICAL LITERATURE.

See Attached

7. RECOMMENDED POLICIES/PROCEDURES TO BE INSTITUTED REGARDING USE, MEDICAL CONTROL, TREATMENT PROTOCOLS, AND QUALITY ASSURANCE OF THE PROCEDURE OR MEDICATION.

See Attached

8. DESCRIPTION OF THE TRAINING AND COMPETENCY TESTING REQUIRED TO IMPLEMENT THE PROCEDURE OR MEDICATION.

See Attached

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Appendix A: Zofran® Prescribing Information

Appendix B: Warden et al, Prehospital Emergency Care, Feb 2008

Appendix C: Zuver et al, Ann Emerg Med, Sep 2007

2. Overview of Local EMS System

Santa Barbara County lies approximately 85 – 150 miles north of Los Angeles along the central coast of California. The population is currently estimated at 414,000 persons over 2745 square miles. There are eight incorporated cities.

Annually there are 35,000 requests for EMS services, including both 9-1-1 calls and interfacility transports. The EMS System is served by a mixture of BLS, BLS-Optional Skills, and ALS first responders and three (3) ALS ambulance services. The largest provider, American Medical Response (AMR) responds to 90% of the calls for service. Santa Barbara County Fire and University of California-Santa Barbara also provide ambulance services.

There are five hospitals in Santa Barbara County and all function as base hospitals. Santa Barbara Cottage Hospital (Santa Barbara) is designated as Level II Trauma Center and serves as the regional trauma, pediatric, and neurointerventional referral center.

3. Description of Medication Requested:

The Santa Barbara County EMS Agency is requesting approval for the use of ondansetron hydrochloride for an 18-month trial study (October 2008 – March 2010) to evaluate the safety, efficacy, and clinical value in the prehospital and interfacility transport settings.

This medication is being requested for use by California –licensed and Santa Barbara County Accredited paramedics who work for approved ALS providers.

The initial training program is 90 minutes and includes a written and skill evaluations. (see Training Program for full description). Management of the trial study will include 100% case evaluation by the provider's CQI Program Coordinator and Medical Director. The EMS Agency will review all data and evaluate system-wide data. The EMS Agency will submit a report to the EMS Authority at the 18-month point.

4. Indications For Use:

The protocol (see page 6) for the use of ondansetron includes the following community-standard indications.

- Intractable vomiting
- Severe nausea

Ondansetron will be used for the treatment of nausea or vomiting of any cause, including gastritis/gastroenteritis, post-operative, medication reaction (including EMS-administered medications (e.g., morphine), motion sickness, headache, and abdominal pain (including suspected bowel obstruction).

5. Alternatives

Currently, Santa Barbara County paramedics have no antiemetic therapy available in the scope of practice. Patients with severe nausea and vomiting are managed in the prehospital setting using positioning and routine airway management. For interfacility transports patients may be given antiemetic therapy (as a treatment or prophylactic measure) prior to departure from the sending facility. Addition of antiemetic therapy would significantly improve the care and comfort of these patients who would otherwise need to wait for treatment in the emergency department.

6. Estimated Frequency

The annual EMS volume in Santa Barbara County is approximately 35,000 calls for service. These include both 9-1-1 and interfacility transports (IFT). Based on a review of patient care reports and the Warden et al report (attached), it estimated that 500-1000 patients may benefit annually from antiemetic therapy.

7. Other Factors

Like many other EMS systems in the State of California, Santa Barbara County has smaller community hospitals and larger specialty care facilities. As such, interfacility transport of patients requiring definitive care (e.g., stroke, STEMI, trauma, pediatrics) are increasingly common. Ground transport times range from fifteen to over sixty minutes. The roadways used to affect these transports are often winding, and in some cases mountainous. Travel, in combination with the patient's condition, frequently contributes to motion sickness, decreasing patient comfort and potentially affecting airway patency.

8. Relevant Supporting Literature and Clinical Studies

Ondansetron injection is the community-standard treatment for all causes of nausea or vomiting. The routine adult dose is 4 mg IV/IM and doses up to at least 32 mg are well tolerated. Pediatric dosing is 0.1 mg/kg up to 4 mg. Although clearance is reduced in patients with hepatic failure, within the range used in this study the dose does not need to be limited. The dose does not need to be adjusted for the elderly, in renal failure (5% clearance), or for other causes. Ondansetron does not cause akathisia or dystonic reactions commonly seen in other antiemetics.

We were able to find two reports of the prehospital use of ondansetron and five for use in the emergency department. Warden, et al, (attached) reported the use of ondansetron in 952 (of 20,054 total transported patients, 5%) adults and children. “For the 198 patients with paired before and after quantitative “nausea scales” recorded, the averages and standard deviations were 7.6 ± 2.4 and 4.6 ± 3.1 , respectively showing a clinically significant change. There were 447 charts with a qualitative change in nausea level with 2 (0.4%) reporting to be “a lot worse,” 6 (1.3%) “a little worse,” 150 (34%) “unchanged,” 178 (40%) “a little better,” and 111 (25%) “a lot better.” There were no reported adverse effects. Zuver, et al, (attached) reported that 128 of 196 patients had symptomatic improvement, with no adverse effects.

Ondansetron appears to be effective and without significant risk of adverse effects.

1. Warden CR, Moreno R, Daya M: Prospective evaluation of ondansetron for undifferentiated nausea and vomiting in the prehospital setting. *Prehosp Emerg Care*. 2008 Jan-Mar;12(1):87-91.
2. Zuver C, Silvestri S, Ralls GA, et al: Out-of-hospital use of intravenous ondansetron. *Ann Emerg Med*. 2007;50(3):S57.
3. Leman P. Utility of ondansetron in children with vomiting. *Ann Emerg Med*. 2002;40(3):366-7.
4. Reeves JJ, Shannon MW, Fleisher GR: Ondansetron decreases vomiting associated with acute gastroenteritis: a randomized, controlled trial. *Pediatrics*. 2002;109(4):e62.
5. Freedman SB, Adler M, Seshadri R, Powell EC: Oral ondansetron for gastroenteritis in a pediatric emergency department. *NEJM*. 2006;354(16):1698-705.
6. Ramsook C, Sahagun-Carreón I, Kozinetz CA, Moro-Sutherland D: A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. *Ann Emerg Med*. 2002;39(4):397-403.
7. Stork CM, Brown KM, Reilly TH, Secreti L, Brown LH: Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children. *Acad Emerg Med*. 2006.

9. Prehospital Treatment Protocol

SEVERE NAUSEA/VOMITING PARAMEDIC TRIAL STUDY

Indications:

1. Intractable vomiting
2. Severe nausea

Contraindications:

1. Known sensitivity to ondansetron or other 5-HT₃ antagonists:
 - Granisetron (Kytril)
 - Dolasetron (Anzemet)
 - Palonosetron (Aloxi)

Objective information:

1. Vital signs
2. Airway Patency
3. Need for antiemetic therapy

Treatment:

Procedure	ALS
Position of Comfort	x
Oxygen	x
Airway Management Protocol	x
Ondansetron: 4 mg IM or slow IV/IO (over > 30 sec)	x
Peds (age > 6 mo): 0.1 mg/kg (max 4 mg) IM/IV/IO	x

x = standing order BH/CF = Base Order or Communication Failure

10. Medical Control

This medication will be given under standing orders or by base hospital orders. Online, direct medical control is always available. The protocol (like all ALS protocols in Santa Barbara County) also includes allowance for paramedics to administer the medication when communication with the base is not possible (“communication failure”).

All uses of ondansetron will be reviewed by the ALS provider’s medical director using the established format and form. Sentinel and other adverse events will be reported to the EMS Agency immediately as per existing policy.

11. Quality Improvement/Tracking Process

Ondansetron Trial Study

****Continuous Quality Improvement Form****

Part I: To be completed by treating paramedic

Date: _____ Incident #: _____
Call Type (circle): 911 Interfacility Transport Other
Paramedic: _____ Unit: _____ Base Hosp: _____
Pt Age: _____ Gender: _____ Chief Complaint: _____
Indication (circle): Vomiting Nausea
doses given: _____ Distress prior: MODERATE SEVERE
Dose #1: _____ mg Route: IV IM Effect: WORSE (SM/LG) NO CHG BETTER (SM/MOD/LG)
Dose #2: _____ mg Route: IV IM Effect: WORSE (SM/LG) NO CHG BETTER (SM/MOD/LG)
Adverse Effect? Y/N Explain: _____
Comments: _____

Part II: To be completed by Provider CQI Coordinator

Reviewed by: _____ Date: _____
Use indicated by protocol? Y N Explain: _____
VS prior/after each dose? Y N Explain: _____
Correct dose? Y N Explain: _____
Correct route? Y N Explain: _____
Effect documented? Y N Explain: _____
Any adverse effects? Y N Explain: _____
Comments: _____

Medical Director comments: _____

Part III: To be completed by EMS Agency CQI Coordinator

Reviewed by: _____ Date: _____
Use indicated by protocol? Y N Explain: _____
All documentation completed? Y N
Agree with Provider CQI Coordinator? Y N
Comments: _____

Medical Director comments: _____

12. Training Program

The training program for paramedics on this trial study will include:

1. Overview and description of the trial study
2. Description, use, indications and contraindications of the medication.
3. Medication safety
4. ALS Protocol
5. CQI Process
6. Written Evaluation

All paramedics will be required to complete this program.

Base Station Prehospital Care Coordinators will educate ED and hospital staff on the existence of this study and addition of the medication into the ALS scope of practice.

Medication Fact Sheet

Ondansetron Hydrochloride

Classification: Antiemetic

Mechanism of Action: Serotonin receptor antagonist.

SB EMS Use: Treatment of nausea/vomiting

How Supplied: Generally 2mg/ml

Contraindications: Known sensitivity to ondansetron or other 5-HT₃ antagonists:

Granisetron (Kytril)

Dolasetron (Anzemet)

Palonosetron (Aloxi)

Precautions: none

Side Effects: May cause tachycardia, hypotension

Dose: Adult 4 mg IM/IV/IO.

Peds (Age > 6 months): 0.1 mg/kg IM/IV/IO to a maximum dose of 4 mg.

Contact base hospital if repeat dosing needed.

Suggested References

- Spratto, G., et al. PDR Nurse's Drug Handbook 2007 Ed. Delmar/Thompson Learning Inc. Clifton Park, NY, 2006
- Beck, R., et al. Drug Reference for EMS Providers. Delmar/Thompson Learning Inc. Clifton Park, NY, 2002
- Lehne, R. Pharmacology for Nursing Care 6th Ed. Elsevier. St Louis, MO, 2007

APPENDIX A

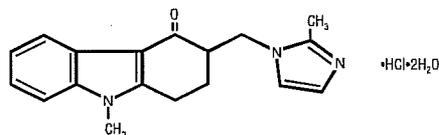
PRESCRIBING INFORMATION

ZOFRAN[®]
(ondansetron hydrochloride)
Injection

ZOFRAN[®]
(ondansetron hydrochloride)
Injection Premixed

DESCRIPTION

The active ingredient in ZOFRAN Injection and ZOFRAN Injection Premixed is ondansetron hydrochloride (HCl), the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT₃ receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has the following structural formula:



The empirical formula is C₁₈H₁₉N₃O•HCl•2H₂O, representing a molecular weight of 365.9.

Ondansetron HCl is a white to off-white powder that is soluble in water and normal saline.

Sterile Injection for Intravenous (I.V.) or Intramuscular (I.M.) Administration: Each 1 mL of aqueous solution in the 2-mL single-dose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 9.0 mg of sodium chloride, USP; and 0.5 mg of citric acid monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers in Water for Injection, USP.

Each 1 mL of aqueous solution in the 20-mL multidose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 8.3 mg of sodium chloride, USP; 0.5 mg of citric acid monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers; and 1.2 mg of methylparaben, NF and 0.15 mg of propylparaben, NF as preservatives in Water for Injection, USP.

ZOFRAN Injection is a clear, colorless, nonpyrogenic, sterile solution. The pH of the injection solution is 3.3 to 4.0.

Sterile, Premixed Solution for Intravenous Administration in Single-Dose, Flexible Plastic Containers: Each 50 mL contains ondansetron 32 mg (as the hydrochloride dihydrate); dextrose 2,500 mg; and citric acid 26 mg and sodium citrate 11.5 mg as buffers in Water for Injection, USP. It contains no preservatives. The osmolarity of this solution is 270 mOsm/L (approx.), and the pH is 3.0 to 4.0.

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out

certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Ondansetron is a selective 5-HT₃ receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT₃ type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action in chemotherapy-induced nausea and vomiting is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of vomiting. The released serotonin may stimulate the vagal afferents through the 5-HT₃ receptors and initiate the vomiting reflex.

In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT₃ receptor antagonist.

In normal volunteers, single I.V. doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in six normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

In a gender-balanced pharmacodynamic study (n = 56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of nausea and vomiting using the ipecacuanha model of emesis.

Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

Pharmacokinetics: Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by glucuronide or sulfate conjugation.

Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and T_{1/2} of ondansetron was observed.¹ This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended (see PRECAUTIONS: Drug Interactions).

In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In normal adult volunteers, the following mean pharmacokinetic data have been determined following a single 0.15-mg/kg I.V. dose.

Table 1. Pharmacokinetics in Normal Adult Volunteers

Age-group (years)	n	Peak Plasma Concentration (ng/mL)	Mean Elimination Half-life (h)	Plasma Clearance (L/h/kg)
19-40	11	102	3.5	0.381
61-74	12	106	4.7	0.319
≥75	11	170	5.5	0.262

A reduction in clearance and increase in elimination half-life are seen in patients over 75 years of age. In clinical trials with cancer patients, safety and efficacy were similar in patients over 65 years of age and those under 65 years of age; there was an insufficient number of patients over 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended in the elderly.

In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh² score of 10 or greater), clearance is reduced 2-fold to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe renal impairment (creatinine clearance <30 mL/min). This reduction in clearance is variable and was not consistent with an increase in half-life. No reduction in dose or dosing frequency in these patients is warranted.

In adult cancer patients, the mean elimination half-life was 4.0 hours, and there was no difference in the multidose pharmacokinetics over a 4-day period. In a study of 21 pediatric cancer patients (4 to 18 years of age) who received three I.V. doses of 0.15 mg/kg of ondansetron at 4-hour intervals, patients older than 15 years of age exhibited ondansetron pharmacokinetic parameters similar to those of adults. Patients 4 to 12 years of age generally showed higher clearance and somewhat larger volume of distribution than adults. Most pediatric patients younger than 15 years of age with cancer had a shorter (2.4 hours) ondansetron plasma half-life than patients older than 15 years of age. It is not known whether these differences in ondansetron plasma half-life may result in differences in efficacy between adults and some young pediatric patients (see CLINICAL TRIALS: Pediatric Studies).

Pharmacokinetic samples were collected from 74 cancer patients 6 to 48 months of age, who received a dose of 0.15 mg/kg of I.V. ondansetron every 4 hours for 3 doses during a safety and efficacy trial. These data were combined with sequential pharmacokinetics data from 41 surgery patients 1 month to 24 months of age, who received a single dose of 0.1 mg/kg of I.V. ondansetron prior to surgery with general anesthesia, and a population pharmacokinetic analysis was performed on the combined data set. The results of this analysis are included in Table 2 and are compared to the pharmacokinetic results in cancer patients 4 to 18 years of age.

Table 2. Pharmacokinetics in Pediatric Cancer Patients 1 Month to 18 Years of Age

Subjects and Age Group	N	CL (L/h/kg)	V _{d_{ss}} (L/kg)	T _{1/2} (h)
		Geometric Mean		Mean
Pediatric Cancer Patients 4 to 18 years of Age	N = 21	0.599	1.9	2.8
Population PK Patients* 1 month to 48 months of Age	N = 115	0.582	3.65	4.9

* Population PK (Pharmacokinetic) Patients: 64% cancer patients and 36% surgery patients

Based on the population pharmacokinetic analysis, cancer patients 6 to 48 months of age who receive a dose of 0.15 mg/kg of I.V. ondansetron every 4 hours for 3 doses would be expected to achieve a systemic exposure (AUC) consistent with the exposure achieved in previous pediatric studies in cancer patients (4 to 18 years of age) at similar doses.

In a study of 21 pediatric patients (3 to 12 years of age) who were undergoing surgery requiring anesthesia for a duration of 45 minutes to 2 hours, a single I.V. dose of ondansetron, 2 mg (3 to 7 years) or 4 mg (8 to 12 years), was administered immediately prior to anesthesia induction. Mean weight-normalized clearance and volume of distribution values in these pediatric surgical patients were similar to those previously reported for young adults. Mean terminal half-life was slightly reduced in pediatric patients (range, 2.5 to 3 hours) in comparison with adults (range, 3 to 3.5 hours).

In a study of 51 pediatric patients (1 month to 24 months of age) who were undergoing surgery requiring general anesthesia, a single I.V. dose of ondansetron, 0.1 or 0.2 mg/kg, was administered prior to surgery. As shown in Table 3, the 41 patients with pharmacokinetic data were divided into 2 groups, patients 1 month to 4 months of age and patients 5 to 24 months of age, and are compared to pediatric patients 3 to 12 years of age.

Table 3. Pharmacokinetics in Pediatric Surgery Patients 1 Month to 12 Years of Age

Subjects and Age Group	N	CL (L/h/kg)	V _{d_{ss}} (L/kg)	T _{1/2} (h)
		Geometric Mean		Mean
Pediatric Surgery Patients 3 to 12 years of Age	N = 21	0.439	1.65	2.9
Pediatric Surgery Patients 5 to 24 months of Age	N = 22	0.581	2.3	2.9
Pediatric Surgery Patients 1 month to 4 months of Age	N = 19	0.401	3.5	6.7

In general, surgical and cancer pediatric patients younger than 18 years tend to have a higher ondansetron clearance compared to adults leading to a shorter half-life in most pediatric patients. In patients 1 month to 4 months of age, a longer half-life was observed due to the higher volume of distribution in this age group.

In normal volunteers (19 to 39 years old, n = 23), the peak plasma concentration was 264 ng/mL following a single 32-mg dose administered as a 15-minute I.V. infusion. The mean elimination half-life was 4.1 hours. Systemic exposure to 32 mg of ondansetron was not proportional to dose as measured by comparing dose-normalized AUC values to an 8-mg dose. This is consistent with a small decrease in systemic clearance with increasing plasma concentrations.

A study was performed in normal volunteers (n = 56) to evaluate the pharmacokinetics of a single 4-mg dose administered as a 5-minute infusion compared to a single intramuscular injection. Systemic exposure as measured by mean AUC was equivalent, with values of 156 [95% CI 136, 180] and 161 [95% CI 137, 190] ng•h/mL for I.V. and I.M. groups, respectively. Mean peak plasma concentrations were 42.9 [95% CI 33.8, 54.4] ng/mL at 10 minutes after I.V. infusion and 31.9 [95% CI 26.3, 38.6] ng/mL at 41 minutes after I.M. injection. The mean elimination half-life was not affected by route of administration.

Plasma protein binding of ondansetron as measured in vitro was 70% to 76%, with binding constant over the pharmacologic concentration range (10 to 500 ng/mL). Circulating drug also distributes into erythrocytes.

A positive lymphoblast transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting:

Adult Studies: In a double-blind study of three different dosing regimens of ZOFTRAN Injection, 0.015 mg/kg, 0.15 mg/kg, and 0.30 mg/kg, each given three times during the course of cancer chemotherapy, the 0.15-mg/kg dosing regimen was more effective than the 0.015-mg/kg dosing regimen. The 0.30-mg/kg dosing regimen was not shown to be more effective than the 0.15-mg/kg dosing regimen.

Cisplatin-Based Chemotherapy: In a double-blind study in 28 patients, ZOFTRAN Injection (three 0.15-mg/kg doses) was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin-based chemotherapy. Treatment response was as shown in Table 4.

Table 4. Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cisplatin Therapy* in Adults

	ZOFTRAN Injection	Placebo	P Value [†]
Number of patients	14	14	
Treatment response			
0 Emetic episodes	2 (14%)	0 (0%)	
1-2 Emetic episodes	8 (57%)	0 (0%)	
3-5 Emetic episodes	2 (14%)	1 (7%)	
More than 5 emetic episodes/rescued	2 (14%)	13 (93%)	0.001
Median number of emetic episodes	1.5	Undefined [‡]	
Median time to first emetic episode (h)	11.6	2.8	0.001
Median nausea scores (0-100) [§]	3	59	0.034
Global satisfaction with control of nausea and vomiting (0-100)	96	10.5	0.009

* Chemotherapy was high dose (100 and 120 mg/m²; ZOFTRAN Injection n = 6, placebo n = 5) or moderate dose (50 and 80 mg/m²; ZOFTRAN Injection n = 8, placebo n = 9). Other chemotherapeutic agents included fluorouracil, doxorubicin, and cyclophosphamide. There was no difference between treatments in the types of chemotherapy that would account for differences in

response.

† Efficacy based on "all patients treated" analysis.

‡ Median undefined since at least 50% of the patients were rescued or had more than five emetic episodes.

§ Visual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.

|| Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

Ondansetron was compared with metoclopramide in a single-blind trial in 307 patients receiving cisplatin ≥ 100 mg/m² with or without other chemotherapeutic agents. Patients received the first dose of ondansetron or metoclopramide 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours later, or five additional metoclopramide doses were administered 2, 4, 7, 10, and 13 hours later. Cisplatin was administered over a period of 3 hours or less. Episodes of vomiting and retching were tabulated over the period of 24 hours after cisplatin. The results of this study are summarized in Table 5.

Table 5. Prevention of Vomiting Induced by Cisplatin (≥ 100 mg/m²) Single-Day Therapy* in Adults

	ZOFRAN Injection	Metoclopramide	P Value
Dose	0.15 mg/kg x 3	2 mg/kg x 6	
Number of patients in efficacy population	136	138	
Treatment response			
0 Emetic episodes	54 (40%)	41 (30%)	
1-2 Emetic episodes	34 (25%)	30 (22%)	
3-5 Emetic episodes	19 (14%)	18 (13%)	
More than 5 emetic episodes/rescued	29 (21%)	49 (36%)	
Comparison of treatments with respect to			
0 Emetic episodes	54/136	41/138	0.083
More than 5 emetic episodes/rescued	29/136	49/138	0.009
Median number of emetic episodes	1	2	0.005
Median time to first emetic episode (h)	20.5	4.3	<0.001
Global satisfaction with control of nausea and vomiting (0-100) [†]	85	63	0.001
Acute dystonic reactions	0	8	0.005
Akathisia	0	10	0.002

* In addition to cisplatin, 68% of patients received other chemotherapeutic agents, including cyclophosphamide, etoposide, and fluorouracil. There was no difference between treatments in the types of chemotherapy that would account for differences in response.

† Visual analog scale assessment: 0 = not at all satisfied, 100 = totally satisfied.

In a stratified, randomized, double-blind, parallel-group, multicenter study, a single 32-mg dose of ondansetron was compared with three 0.15-mg/kg doses in patients receiving cisplatin

doses of either 50 to 70 mg/m² or ≥100 mg/m². Patients received the first ondansetron dose 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours later to the group receiving three 0.15-mg/kg doses. In both strata, significantly fewer patients on the single 32-mg dose than those receiving the three-dose regimen failed.

Table 6. Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Dose Therapy in Adults

	0.15 mg/kg x 3	Ondansetron Dose 32 mg x 1	P Value
High-dose cisplatin (≥100 mg/m²)			
Number of patients	100	102	
Treatment response			
0 Emetic episodes	41 (41%)	49 (48%)	0.315
1-2 Emetic episodes	19 (19%)	25 (25%)	
3-5 Emetic episodes	4 (4%)	8 (8%)	
More than 5 emetic episodes/rescued	36 (36%)	20 (20%)	0.009
Median time to first emetic episode (h)	21.7	23	0.173
Median nausea scores (0-100)*	28	13	0.004
Medium-dose cisplatin (50-70 mg/m²)			
Number of patients	101	93	
Treatment response			
0 Emetic episodes	62 (61%)	68 (73%)	0.083
1-2 Emetic episodes	11 (11%)	14 (15%)	
3-5 Emetic episodes	6 (6%)	3 (3%)	
More than 5 emetic episodes/rescued	22 (22%)	8 (9%)	0.011
Median time to first emetic episode (h)	Undefined [†]	Undefined	
Median nausea scores (0-100)*	9	3	0.131

* Visual analog scale assessment: 0 = no nausea, 100 = nausea as bad as it can be.

† Median undefined since at least 50% of patients did not have any emetic episodes.

Cyclophosphamide-Based Chemotherapy: In a double-blind, placebo-controlled study of ZOFTRAN Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500 to 600 mg/m²) chemotherapy, ZOFTRAN Injection was significantly more effective than placebo in preventing nausea and vomiting. The results are summarized in Table 7.

Table 7. Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cyclophosphamide Therapy* in Adults

	ZOFTRAN Injection	Placebo	P Value [†]
Number of patients	10	10	
Treatment response			
0 Emetic episodes	7 (70%)	0 (0%)	0.001
1-2 Emetic episodes	0 (0%)	2 (20%)	
3-5 Emetic episodes	2 (20%)	4 (40%)	
More than 5 emetic episodes/rescued	1 (10%)	4 (40%)	0.131
Median number of emetic episodes	0	4	0.008
Median time to first emetic episode (h)	Undefined [‡]	8.79	
Median nausea scores (0-100) [§]	0	60	0.001
Global satisfaction with control of nausea and vomiting (0-100)	100	52	0.008

* Chemotherapy consisted of cyclophosphamide in all patients, plus other agents, including fluorouracil, doxorubicin, methotrexate, and vincristine. There was no difference between treatments in the type of chemotherapy that would account for differences in response.

[†] Efficacy based on "all patients treated" analysis.

[‡] Median undefined since at least 50% of patients did not have any emetic episodes.

[§] Visual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.

^{||} Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

Re-treatment: In uncontrolled trials, 127 patients receiving cisplatin (median dose, 100 mg/m²) and ondansetron who had two or fewer emetic episodes were re-treated with ondansetron and chemotherapy, mainly cisplatin, for a total of 269 re-treatment courses (median, 2; range, 1 to 10). No emetic episodes occurred in 160 (59%), and two or fewer emetic episodes occurred in 217 (81%) re-treatment courses.

Pediatric Studies: Four open-label, noncomparative (one US, three foreign) trials have been performed with 209 pediatric cancer patients 4 to 18 years of age given a variety of cisplatin or noncisplatin regimens. In the three foreign trials, the initial ZOFTRAN Injection dose ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the oral administration of ondansetron ranging from 4 to 24 mg daily for 3 days. In the US trial, ZOFTRAN was administered intravenously (only) in three doses of 0.15 mg/kg each for a total daily dose of 7.2 to 39 mg. In these studies, 58% of the 196 evaluable patients had a complete response (no emetic episodes) on day 1. Thus, prevention of vomiting in these pediatric patients was essentially the same as for patients older than 18 years of age.

An open-label, multicenter, noncomparative trial has been performed in 75 pediatric cancer patients 6 to 48 months of age receiving at least one moderately or highly emetogenic chemotherapeutic agent. Fifty-seven percent (57%) were females; 67% were white, 18% were American Hispanic, and 15% were black patients. ZOFTRAN was administered intravenously over 15 minutes in three doses of 0.15 mg/kg. The first dose was administered 30 minutes before the start of chemotherapy, the second and third doses were administered 4 and 8 hours after the first dose,

respectively. Eighteen patients (25%) received routine prophylactic dexamethasone (i.e., not given as rescue). Of the 75 evaluable patients, 56% had a complete response (no emetic episodes) on day 1. Thus, prevention of vomiting in these pediatric patients was comparable to the prevention of vomiting in patients 4 years of age and older.

Postoperative Nausea and Vomiting: Prevention of Postoperative Nausea and Vomiting:

Adult Studies: Adult surgical patients who received ondansetron immediately before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving 554 patients. ZOFTRAN Injection (4 mg) I.V. given over 2 to 5 minutes was significantly more effective than placebo. The results of these studies are summarized in Table 8.

Table 8. Prevention of Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg I.V.	Placebo	P Value
Study 1			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period	136	139	
0 Emetic episodes	103 (76%)	64 (46%)	<0.001
1 Emetic episode	13 (10%)	17 (12%)	
More than 1 emetic episode/rescued	20 (15%)	58 (42%)	
Nausea assessments: Number of patients No nausea over 24-h postoperative period	134 56 (42%)	136 39 (29%)	
Study 2			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period	136	143	
0 Emetic episodes	85 (63%)	63 (44%)	0.002
1 Emetic episode	16 (12%)	29 (20%)	
More than 1 emetic episode/rescued	35 (26%)	51 (36%)	
Nausea assessments: Number of patients No nausea over 24-h postoperative period	125 48 (38%)	133 42 (32%)	

The study populations in Table 8 consisted mainly of females undergoing laparoscopic procedures.

In a placebo-controlled study conducted in 468 males undergoing outpatient procedures, a single 4-mg I.V. ondansetron dose prevented postoperative vomiting over a 24-hour study period in 79% of males receiving drug compared to 63% of males receiving placebo ($P<0.001$).

Two other placebo-controlled studies were conducted in 2,792 patients undergoing major abdominal or gynecological surgeries to evaluate a single 4-mg or 8-mg I.V. ondansetron dose for prevention of postoperative nausea and vomiting over a 24-hour study period. At the 4-mg dosage, 59% of patients receiving ondansetron versus 45% receiving placebo in the first study ($P<0.001$) and 41% of patients receiving ondansetron versus 30% receiving placebo in the second study ($P=0.001$) experienced no emetic episodes. No additional benefit was observed in patients who received I.V. ondansetron 8 mg compared to patients who received I.V. ondansetron 4 mg.

Pediatric Studies: Three double-blind, placebo-controlled studies have been performed (one US, two foreign) in 1,049 male and female patients (2 to 12 years of age) undergoing general anesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or without adenoidectomy, strabismus surgery, herniorrhaphy, and orchidopexy. Patients were randomized to either single I.V. doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo. Study drug was administered over at least 30 seconds, immediately prior to or following anesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarized in Table 9.

Table 9. Prevention of Postoperative Nausea and Vomiting in Pediatric Patients 2 to 12 Years of Age

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	P Value
Study 1			
Number of patients	205	210	
0 Emetic episodes	140 (68%)	82 (39%)	≤ 0.001
Failure*	65 (32%)	128 (61%)	
Study 2			
Number of patients	112	110	
0 Emetic episodes	68 (61%)	38 (35%)	≤ 0.001
Failure*	44 (39%)	72 (65%)	
Study 3			
Number of patients	206	206	
0 Emetic episodes	123 (60%)	96 (47%)	≤ 0.01
Failure*	83 (40%)	110 (53%)	
Nausea assessments [†] :			
Number of patients	185	191	
None	119 (64%)	99 (52%)	≤ 0.01

* Failure was one or more emetic episodes, rescued, or withdrawn.

† Nausea measured as none, mild, or severe.

A double-blind, multicenter, placebo-controlled study was conducted in 670 pediatric patients 1 month to 24 months of age who were undergoing routine surgery under general anesthesia. Seventy-five percent (75%) were males; 64% were white, 15% were black, 13% were American Hispanic, 2% were Asian, and 6% were "other race" patients. A single 0.1-mg/kg I.V. dose of ondansetron was administered within 5 minutes following induction of anesthesia. Ondansetron was statistically significantly more effective than placebo in preventing vomiting. In the placebo group, 28% of patients experienced vomiting compared to 11% of subjects who received ondansetron ($P \leq 0.01$). Overall, 32 (10%) of placebo patients and 18 (5%) of patients who received ondansetron received antiemetic rescue medication(s) or prematurely withdrew from the study.

Prevention of Further Postoperative Nausea and Vomiting:

Adults Studies: Adult surgical patients receiving general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) who received no prophylactic antiemetics and who experienced nausea and/or vomiting within 2 hours postoperatively were evaluated in two double-blind US studies involving 441 patients. Patients who experienced an episode of postoperative nausea and/or vomiting were given ZOFTRAN Injection (4 mg) I.V. over 2 to 5 minutes, and this was significantly more effective than placebo. The results of these studies are summarized in Table 10.

Table 10. Prevention of Further Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg I.V.	Placebo	<i>P</i> Value
Study 1			
Emetic episodes: Number of patients	104	117	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (47%)	19 (16%)	<0.001
1 Emetic episode	12 (12%)	9 (8%)	
More than 1 emetic episode/rescued	43 (41%)	89 (76%)	
Median time to first emetic episode (min)*	55.0	43.0	
Nausea assessments:			
Number of patients	98	102	
Mean nausea score over 24-h postoperative period [†]	1.7	3.1	
Study 2			
Emetic episodes: Number of patients	112	108	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (44%)	28 (26%)	0.006
1 Emetic episode	14 (13%)	3 (3%)	
More than 1 emetic episode/rescued	49 (44%)	77 (71%)	
Median time to first emetic episode (min)*	60.5	34.0	
Nausea assessments:			
Number of patients	105	85	
Mean nausea score over 24-h postoperative period [†]	1.9	2.9	

* After administration of study drug.

[†] Nausea measured on a scale of 0-10 with 0 = no nausea, 10 = nausea as bad as it can be.

The study populations in Table 10 consisted mainly of women undergoing laparoscopic procedures.

Repeat Dosing in Adults: In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron 4 mg, administration of a second I.V. dose of ondansetron 4 mg postoperatively does not provide additional control of nausea and vomiting.

Pediatric Study: One double-blind, placebo-controlled, US study was performed in 351 male and female outpatients (2 to 12 years of age) who received general anesthesia with nitrous oxide and no prophylactic antiemetics. Surgical procedures were unrestricted. Patients who experienced two or more emetic episodes within 2 hours following discontinuation of nitrous oxide were randomized to either single I.V. doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo administered over at least 30 seconds.

Ondansetron was significantly more effective than placebo in preventing further episodes of nausea and vomiting. The results of the study are summarized in Table 11.

Table 11. Prevention of Further Postoperative Nausea and Vomiting in Pediatric Patients 2 to 12 years of Age

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	<i>P</i> Value
Number of patients	180	171	≤0.001
0 Emetic episodes	96 (53%)	29 (17%)	
Failure*	84 (47%)	142 (83%)	

* Failure was one or more emetic episodes, rescued, or withdrawn.

INDICATIONS AND USAGE

1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Efficacy of the 32-mg single dose beyond 24 hours in these patients has not been established.
2. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ZOFTRAN Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic ZOFTRAN Injection and experience nausea and/or vomiting postoperatively, ZOFTRAN Injection may be given to prevent further episodes (see CLINICAL TRIALS).

CONTRAINDICATIONS

ZOFTRAN Injection and ZOFTRAN Injection Premixed 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-HT₃ 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 distention.

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). 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 limited available data, no dosage adjustment is recommended for patients on these drugs.

Phenytoin, Carbamazepine, and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, 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.^{1,3}

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.^{4,5}

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.

Carcinogenesis, 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 per day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg per 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 I.V. doses up to 4 mg/kg per day 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 the use of ondansetron in pediatric surgical patients younger than 1 month of age. (See CLINICAL TRIALS section for studies of ondansetron in prevention of post-operative nausea and vomiting in patients 1 month of age and older.) Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months of age. (See CLINICAL TRIALS section for studies of ondansetron in chemotherapy-induced nausea and vomiting in pediatric patients 6 months of age and older.) (See DOSAGE AND ADMINISTRATION.)

The clearance of ondansetron in pediatric patients 1 month to 4 months of age is slower and the half-life is ~2.5 fold longer than patients who are >4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored. (See CLINICAL PHARMACOLOGY: Pharmacokinetics).

The frequency and type of adverse events reported in pediatric patients receiving ondansetron were similar to those in patients receiving placebo. (See ADVERSE EVENTS.)

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, 862 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).

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting: The adverse events in Table 12 have been reported in adults receiving ondansetron at a dosage of three 0.15-mg/kg doses or as a single 32-mg dose in clinical trials. These patients were receiving concomitant chemotherapy, primarily cisplatin, and I.V. fluids. Most were receiving a diuretic.

Table 12. Principal Adverse Events in Comparative Trials in Adults

	Number of Adult Patients With Event			
	ZOFTRAN Injection 0.15 mg/kg x 3 n = 419	ZOFTRAN Injection 32 mg x 1 n = 220	Metoclopramide n = 156	Placebo n = 34
Diarrhea	16%	8%	44%	18%
Headache	17%	25%	7%	15%
Fever	8%	7%	5%	3%
Akathisia	0%	0%	6%	0%
Acute dystonic reactions*	0%	0%	5%	0%

* See Neurological.

The following have been reported during controlled clinical trials:

Cardiovascular: Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported. In many cases, the relationship to ZOFTRAN Injection was unclear.

Gastrointestinal: Constipation has been reported in 11% of chemotherapy patients receiving multiday ondansetron.

Hepatic: In comparative trials in cisplatin chemotherapy patients with normal baseline values of aspartate transaminase (AST) and alanine transaminase (ALT), these enzymes have been reported to exceed twice the upper limit of normal in approximately 5% of patients. 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.

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

Neurological: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ZOFTRAN Injection, and rare cases of grand mal seizure. The relationship to ZOFTRAN was unclear.

Other: Rare cases of hypokalemia have been reported. The relationship to ZOFTRAN Injection was unclear.

Postoperative Nausea and Vomiting: The adverse events in Table 13 have been reported in $\geq 2\%$ of adults receiving ondansetron at a dosage of 4 mg I.V. over 2 to 5 minutes in clinical trials. 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 13. Adverse Events in $\geq 2\%$ of Adults Receiving Ondansetron at a Dosage of 4 mg I.V. over 2 to 5 Minutes in Clinical Trials

	ZOFRAN Injection 4 mg I.V. n = 547 patients	Placebo n = 547 patients
Headache	92 (17%)	77 (14%)
Dizziness	67 (12%)	88 (16%)
Musculoskeletal pain	57 (10%)	59 (11%)
Drowsiness/sedation	44 (8%)	37 (7%)
Shivers	38 (7%)	39 (7%)
Malaise/fatigue	25 (5%)	30 (5%)
Injection site reaction	21 (4%)	18 (3%)
Urinary retention	17 (3%)	15 (3%)
Postoperative CO ₂ -related pain*	12 (2%)	16 (3%)
Chest pain (unspecified)	12 (2%)	15 (3%)
Anxiety/agitation	11 (2%)	16 (3%)
Dysuria	11 (2%)	9 (2%)
Hypotension	10 (2%)	12 (2%)
Fever	10 (2%)	6 (1%)
Cold sensation	9 (2%)	8 (1%)
Pruritus	9 (2%)	3 (<1%)
Paresthesia	9 (2%)	2 (<1%)

*Sites of pain included abdomen, stomach, joints, rib cage, shoulder.

Pediatric Use: The adverse events in Table 14 were the most commonly reported adverse events in pediatric patients receiving ondansetron (a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered intravenously over at least 30 seconds. 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 14. Frequency of Adverse Events From Controlled Studies in Pediatric Patients 2 to 12 years of Age

Adverse Event	Ondansetron n = 755 Patients	Placebo n = 731 Patients
Wound problem	80 (11%)	86 (12%)
Anxiety/agitation	49 (6%)	47 (6%)
Headache	44 (6%)	43 (6%)
Drowsiness/sedation	41 (5%)	56 (8%)
Pyrexia	32 (4%)	41 (6%)

The adverse events in Table 15 were the most commonly reported adverse events in pediatric patients, 1 month to 24 months of age, receiving a single 0.1-mg/kg I.V. dose of ondansetron.

The incidence and type of adverse events were similar in both the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 15. Frequency of Adverse Events (Greater Than or Equal to 2% in Either Treatment Group) in Pediatric Patients 1 Month to 24 Months of Age

Adverse Event	Ondansetron n = 336 Patients	Placebo n = 334 Patients
Pyrexia	14 (4%)	14 (4%)
Bronchospasm	2 (<1%)	6 (2%)
Post-procedural pain	4 (1%)	6 (2%)
Diarrhea	6 (2%)	3 (<1%)

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of intravenous formulations of ZOFTRAN. 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 ZOFTRAN.

Cardiovascular: Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block and ST segment depression), palpitations, and syncope.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported.

Hepatobiliary: Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Local Reactions: Pain, redness, and burning at site of injection.

Lower Respiratory: Hiccups

Neurological: Oculogyric crisis, appearing alone, as well as with other dystonic reactions.

Skin: Urticaria

Special Senses: Transient blurred vision, in some cases associated with abnormalities of accommodation, and transient dizziness during or shortly after I.V. infusion.

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 doses as large as 150 mg and total daily dosages (three doses) as large as 252 mg have been administered intravenously 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 one patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took 48 mg of oral ondansetron. 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.

DOSAGE AND ADMINISTRATION

Prevention of Chemotherapy-Induced Nausea and Vomiting:

Adult Dosing: The recommended I.V. dosage of ZOFRAN for adults is a single 32-mg dose or three 0.15-mg/kg doses. A single 32-mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. The recommended infusion rate should not be exceeded (see OVERDOSAGE). With the three-dose (0.15-mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN.

ZOFRAN Injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form.

Vial: DILUTE BEFORE USE FOR PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING. ZOFRAN Injection should be diluted in 50 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

Flexible Plastic Container: REQUIRES NO DILUTION. ZOFRAN Injection Premixed, 32 mg in 5% Dextrose, 50 mL.

Pediatric Dosing: On the basis of the available information (see CLINICAL TRIALS: Pediatric Studies and CLINICAL PHARMACOLOGY: Pharmacokinetics), the dosage in pediatric cancer patients 6 months to 18 years of age should be three 0.15-mg/kg doses. The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy, subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN. The drug should be infused intravenously over 15 minutes. Little information is available about dosage in pediatric cancer patients younger than 6 months of age.

Vial: DILUTE BEFORE USE. ZOFRAN Injection should be diluted in 50 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

Flexible Plastic Container: REQUIRES NO DILUTION. ZOFRAN Injection Premixed, 32 mg in 5% Dextrose, 50 mL.

Geriatric Dosing: The dosage recommendation is the same as for the general population.

Prevention of Postoperative Nausea and Vomiting:

Adult Dosing: The recommended I.V. dosage of ZOFRAN for adults is 4 mg **undiluted** administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively, 4 mg **undiluted** may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied. In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron 4 mg, administration of a second I.V. dose of 4 mg ondansetron postoperatively does not provide additional control of nausea and vomiting.

Vial: REQUIRES NO DILUTION FOR ADMINISTRATION FOR POSTOPERATIVE NAUSEA AND VOMITING.

Pediatric Dosing: The recommended I.V. dosage of ZOFTRAN for pediatric surgical patients (1 month to 12 years of age) is a single 0.1-mg/kg dose for patients weighing 40 kg or less, or a single 4-mg dose for patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anesthesia induction, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Prevention of further nausea and vomiting was only studied in patients who had not received prophylactic Zofran.

Vial: REQUIRES NO DILUTION FOR ADMINISTRATION FOR POSTOPERATIVE NAUSEA AND VOMITING.

Geriatric Dosing: The dosage recommendation is the same as for the general population.

Dosage Adjustment for Patients With Impaired Renal Function: The dosage recommendation is the same as for the general population. There is no experience beyond first-day administration of ondansetron.

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic impairment (Child-Pugh² score of 10 or greater), a single maximal daily dose of 8 mg to be infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended. There is no experience beyond first-day administration of ondansetron.

ZOFTRAN Injection Premixed in Flexible Plastic Containers: Instructions for Use: To Open: Tear outer wrap at notch and remove solution container. Check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

Preparation for Administration: Use aseptic technique.

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of ZOFTRAN Injection Premixed.
6. Open flow control clamp to expel air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Perform venipuncture.
9. Regulate rate of administration with flow control clamp.

Caution: ZOFTRAN Injection Premixed in flexible plastic containers is to be administered by I.V. drip infusion only. ZOFTRAN Injection Premixed should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form. If used with a primary I.V. fluid system, the primary solution should be discontinued during ZOFTRAN Injection Premixed infusion.

Do not administer unless solution is clear and container is undamaged.

Warning: Do not use flexible plastic container in series connections.

Stability: ZOFTRAN Injection is stable at room temperature under normal lighting conditions for 48 hours after dilution with the following I.V. fluids: 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, and 3% Sodium Chloride Injection.

Although ZOFRAN Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative. After dilution, do not use beyond 24 hours.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Precaution: Occasionally, ondansetron precipitates at the stopper/vial interface in vials stored upright. Potency and safety are not affected. If a precipitate is observed, resolubilize by shaking the vial vigorously.

HOW SUPPLIED

ZOFRAN Injection, 2 mg/mL, is supplied as follows:

NDC 0173-0442-02 2-mL single-dose vials (Carton of 5)

NDC 0173-0442-00 20-mL multidose vials (Singles)

Store between 2° and 30°C (36° and 86°F). Protect from light.

ZOFRAN Injection Premixed, 32 mg/50 mL, in 5% Dextrose, contains no preservatives and is supplied as a sterile, premixed solution for I.V. administration in single-dose, flexible plastic containers (NDC 0173-0461-00) (case of 6).

Store between 2° and 30°C (36° and 86°F). Protect from light. Avoid excessive heat.

Protect from freezing.

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Research Triangle Park, NC 27709

ZOFRAN[®] Injection Premixed:

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Month YEAR

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APPENDIX B

PRELIMINARY REPORT

PROSPECTIVE EVALUATION OF ONDANSETRON FOR UNDIFFERENTIATED NAUSEA AND VOMITING IN THE PREHOSPITAL SETTING

Craig R. Warden, MD, MPH, Raymond Moreno, MD, Mohamud Daya, MD, MS

ABSTRACT

Objective. To evaluate the change in nausea scales and incidence of vomiting with the use of ondansetron in the treatment of nausea and vomiting in the prehospital setting. **Methods.** Data were prospectively collected on all emergency medical service patients who received ondansetron for undifferentiated nausea and vomiting during a 6-month study period. Added outcome measures for this study were verbal quantitative (scale of 1–10) and qualitative “nausea scales,” incidence of vomiting prior to and after administration of ondansetron, and adverse events. Patients who had this additional data collected and ones who did not were compared. Changes in the “nausea scales” and incidence of vomiting before and after administration and correlation among these measures were also compared. There was no control or placebo group. **Results.** Ondansetron was administered to 952 patients of 20,054 patients transported during this time period (5%); of these 472 had at least some of the outcome measures documented. There were minimal differences in the two cohorts; 198 patients had paired before and after quantitative “nausea scales” documented: 7.6 ± 2.4 and 4.6 ± 3.1 , respectively ($\Delta = 2.9$, 95% CI: 2.5–3.4); 447 patients had a qualitative change in nausea level documented: 0.4% “a lot worse,” 1.3% “a little worse,” 34% “unchanged,” 40% “a little better,” and 25% “a lot better”; 187 patients had all three measures documented with a Pearson correlation coefficient of 0.63 between the change in the quantitative scale and the qualitative scale (95% CI: 0.14–0.20, R^2 0.39). In 462 patients, vomiting decreased from 60% to 30% (Wilcoxon signed ranks test $p < 0.001$). The Pearson correlation coefficients for the change in vomiting incidence with the qualitative and quantitative “nausea scales” were poor:

0.012 (95% CI: -0.015 to 0.039 , R^2 0.00014) and 0.051 (95% CI: -0.032 to 0.118 , R^2 0.00026), respectively. There were no reported adverse events. **Conclusions.** Ondansetron appears to be moderately effective in decreasing nausea and vomiting in undifferentiated prehospital patients. Additional controlled trials may be needed to compare it with other antiemetics. **Key words:** ondansetron; prehospital; nausea; vomiting

PREHOSPITAL EMERGENCY CARE 2008;12:87–91

INTRODUCTION

Nausea and vomiting is thought to be common in the prehospital setting, but there is currently no study that documents its incidence. Etiologies include varied conditions such as motion sickness, gastrointestinal illness, medication side effects, and intracranial disorders.¹ Success at treating discomfort such as nausea and vomiting ranked second only to survival in desirable outcomes for both adults and children in the Emergency Medical Services Outcomes Project consensus document.² Emergency Medical Services (EMS) systems around the country have used agents such as droperidol, promethazine, and prochlorperazine to treat patients with nausea and vomiting. The FDA black box warning for droperidol,³ as well as intermittent nationwide shortages of agents such as prochlorperazine have caused a reevaluation of antiemetic use in emergency settings. As part of a Portland, Oregon, tricity emergency medical services (EMS) Protocol Development Committee review process, we evaluated the literature on antiemetic use and found only a few emergency department-based studies,^{4–6} and one prehospital study.¹ Although some indication of effectiveness can be drawn from the extensive anesthesia and oncology literature on antiemetics, the undifferentiated patient population encountered in the EMS setting demands that one select an agent that is safe and effective in a wide variety of patient presentations.

Given the current limited availability of alternatives, many EMS systems that want to treat nausea and vomiting are choosing between antiemetics, such as

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promethazine (an older agent with a significant side effect profile), and the newer 5-HT₃ receptor antagonists, such as ondansetron and granistron. Although the 5-HT₃ receptor antagonists have an excellent safety profile and are more effective than placebo in ED-based clinical trials,⁵⁻⁹ their safety and effectiveness in the prehospital setting will need to be demonstrated for EMS systems to invest in a drug that is more expensive than its alternatives. In the Portland tricounty area, we have instituted a systemwide change to our protocols (Appendices A and B) that incorporates intravenous (IV) or intramuscular (IM) administration of ondansetron as the primary antiemetic for the EMS system due to evidence demonstrating its effectiveness in other settings and favorable side effect profile. Previously, inapsine was used as the antiemetic, which was dropped because of the FDA black box warning. This presents us with a unique opportunity to evaluate the addition of a new drug into the prehospital setting.

METHODS

Study Design

This was a prospective, observational 6-month study attempting to evaluate the safety and effectiveness of IV or IM ondansetron in the prehospital setting to treat nausea and vomiting. There was no placebo or control group, as all patients meeting treatment criteria under the existing Portland tricounty prehospital nausea and vomiting and ondansetron protocols were entered into the study. The "History" and "Physical Findings" sections are used as cues for the medics and are not indications (except for nausea and vomiting) or contraindications for the use of ondansetron. This study was reviewed by the OHSU Institutional Review Board and deemed exempt from consent because there is no change in patient treatment for this study and no patient identifiers were available to researchers.

Setting

The study took place in the Multnomah County (including Portland) EMS system because it had the only comprehensive electronic data capture capability at the time of the study. It has one advanced life support (ALS) private transporting agency that is simultaneously dispatched with fire department apparatus that also have at least one paramedic, all under a unified county medical director and protocols. The county covers 465 square miles and had a population of 660,486 in the 2000 census.

Inclusion/Exclusion Criteria

All patients receiving ondansetron for nausea and vomiting between January 1, 2005, and June 30, 2005, were

included. In summary, paramedics may administer ondansetron to patients with undifferentiated nausea and vomiting over the age of 12 without contacting on-line medical control (OLMC). For individuals under 12 years old, paramedics are required to call OLMC for approval before drug administration. The only exclusion criterion in the protocol is a known allergy to ondansetron or other 5-HT₃ antagonists. The history and physical examination components are to be elicited for documentation but are not exclusion factors except as above. The dose was 4 mg IV or IM for adults and children >40 kg or 0.1 mg/kg for children <40 kg. Paramedics were inserviced initially in the "Nausea and Vomiting" and "Ondansetron" protocols when they were changed and again separately in the use of the study protocol with several reminders by e-mail and memo throughout the study period.

Definition of Clinical Endpoints

The primary outcome variable was the change in self-reported nausea on a quantitative 1-10 verbal scale before treatment and at hospital arrival. Secondary outcome variables were a qualitative "nausea scale" ("a lot better," "a little better," "unchanged," "a little worse," and "a lot worse"), and the occurrence of vomiting before treatment and during transport. Verbal scales were used because of the logistic difficulties of carrying and retaining paper copies of scales. In addition, verbal scales are found to be highly correlated with visual analogue scales, at least in the assessment of pain.¹⁰⁻¹² Additional data variables that were collected include demographic variables, primary clinical assessment, potential adverse effects (headache, rash, breathing difficulty, diarrhea, or chest pain), and treatment interventions. A "Physical Findings" section of the general patient care chart was added partly through the study period, and the data on "abdominal" and "neurological" exams were collected on these patients.

Data Collection

Data were collected from electronic download of the patient care records from the transporting agency that also consolidates the data from first-responding fire agencies. The cases were located by using a query on the administration of ondansetron. The paramedics do primary data entry electronically for patient care documentation. A special "procedure section" was added to the electronic chart for collecting additional data for the purposes of this study but because of programming constraints, these could not be made mandatory data collection fields. Demographic and clinical data including primary clinical impression (collapsed into major organ system categories), vital signs, and physical examination findings were collected. Unfortunately, certain variables could not be analyzed because of the

structure of the electronic chart as downloaded including patients' current medications and medical history, routes of administration, and other medications given. Patient data were downloaded into an Excel[®] spreadsheet (Microsoft, Inc., Redmond WA) and imported into SPSS[®] 14.0 (SPSS, Inc., Chicago IL) for analysis. Patient-identifying data were not transferred from the EMS agency database or able to be viewed by the investigators.

Statistical Analysis

A descriptive analysis of all patients receiving ondansetron was performed. Changes in the quantitative "nausea scale" were compared by using the paired samples *t*-test and the comparison of changes in the quantitative "nausea scale" with the qualitative "nausea scale," and occurrence of vomiting was made with the Pearson correlation coefficient. We compared the various nausea scales to attempt an internal validation of their performance and also with an eye for future clinical trials. The change in the qualitative "nausea scale" was compared to the change in the occurrence of vomiting using the Wilcoxon signed ranks test. Significance was set at $p < 0.05$.

RESULTS

During the 6-month study period 20,054 patients were transported, paramedics administered ondansetron to 952 (5%) patients of which 472 (50%) had at least part of the nausea and vomiting special procedure section completed. Of these, 454 had an initial quantitative "nausea scale" entered, and 215 had a subsequent nausea reassessment completed with 201 of these with a quantitative "nausea scale" entered. In the final analysis, there were 198 cases with paired values of both before and after ondansetron administration nausea scales documented. See Figure 1 for flowchart of availability of clinical outcome variables for patients.

Table 1 compares the "studied" and "not studied" cohorts of patients. Of note, only four patients who received ondansetron were less than 12 years old, and only 16 were less than 18 years old. Ondansetron was used in a wide cross section of EMS patients with a concentration in the general illness, gastrointestinal, and neurological categories (most commonly for headaches), as would be expected. Looking at two important physical findings, the distribution of abdominal and neurological findings ("normal," "abnormal," "not assessed," and "missing") did differ somewhat between the two cohorts. Surprisingly, in the paramedic assessment, 263 (32%) of 822 patients given ondansetron after the Physical Assessment portion of PCR was started did not have a documented abdominal assessment, and of the ones who did have an assess-

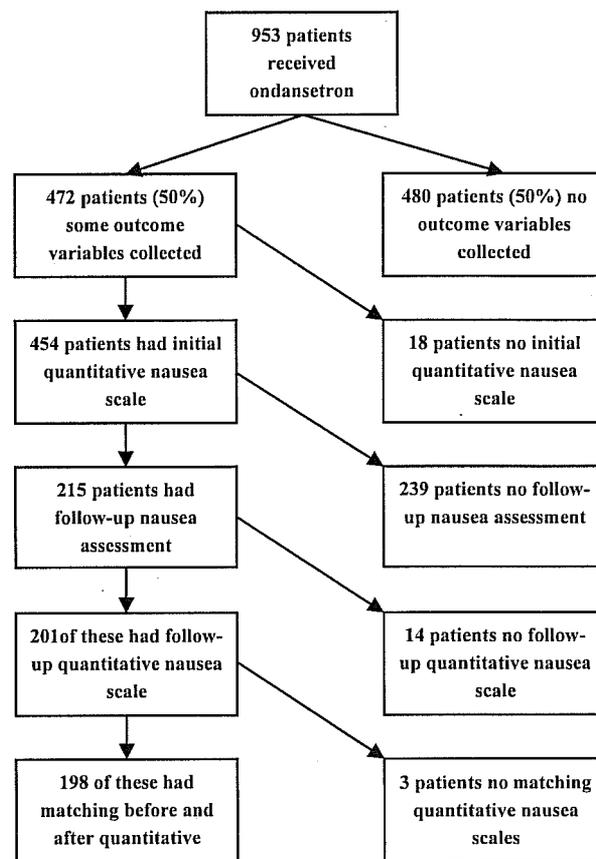


FIGURE 1. Flowchart of availability of outcome variables in study cohort.

ment fully 168 (30%) of 559 had an abnormal exam. For the neurological assessment, 187 (23%) of 822 were not evaluated, but of the remaining only 37 (6%) were abnormal. In the "Ondansetron" medication and the "Nausea and Vomiting" protocols, there are no specific physical finding contraindications, and many of these abnormalities could be mild consistent with gastroenteritis or other viral illnesses.

For the 198 patients with paired before and after quantitative "nausea scales" recorded, the averages and standard deviations were 7.6 ± 2.4 and 4.6 ± 3.1 , respectively ($\Delta = 2.9$, 95% CI: 2.5–3.4) showing a clinically significant change.^{13,14} There were 447 charts with a qualitative change in nausea level with 2 (0.4%) reporting to be "a lot worse," 6 (1.3%) "a little worse," 150 (34%) "unchanged," 178 (40%) "a little better," and 111 (25%) "a lot better." The Pearson correlation coefficient for the 187 patients who had both a change in the quantitative "nausea scale" and a qualitative "nausea scale" recorded was 0.63 (95% CI: 0.14–0.20 with R^2 of 0.39), showing moderately good correlation. Of 462 patients assessed, 60% had vomiting prior to administration of ondansetron, and 30% patients had vomiting afterwards (Wilcoxon signed ranks test $p < 0.001$).

TABLE 1. Comparison of Cohorts of Assessed Versus Nonassessed Patients

Characteristic	"Not Studied" Cohort n = 472 (50%)	"Studied" Cohort n = 480 (50%)
Age (average \pm SD, years)	55.6 \pm 21.3	55.3 \pm 21.4
Males	164 (34%)	155 (33%)
Total prehospital time (average \pm SD, minutes)	38.5 \pm 12.4	39.2 \pm 12.9
Primary impression*		
Behavioral	1 (17%)	5 (83%)
Cardiovascular	39 (53%)	35 (47%)
Diabetic	7 (44%)	9 (56%)
General illness	74 (43%)	99 (%)
Gastrointestinal	109 (49%)	113 (51%)
Urinary	18 (45%)	22 (55%)
Musculoskeletal	12 (60%)	8 (40%)
Neurological	73 (56%)	58 (44%)
Gynecological	3 (27%)	8 (73%)
Respiratory	11 (61%)	7 (39%)
Toxicological	32 (70%)	14 (30%)
Trauma	40 (50%)	40 (50%)
Other	61 (53%)	54 (47%)
Abdominal findings†		
Normal	182 (47%)	208 (53%)
Abnormal	74 (44%)	94 (53%)
Not assessed	150 (57%)	113 (43%)
Missing	74 (56%)	57 (44%)
Neurological findings†		
Normal	261 (44%)	336 (56%)
Abnormal	19 (51%)	18 (49%)
Not assessed	126 (67%)	61 (33%)
Missing	74 (56%)	57 (44%)
Vital signs		
Initial systolic BP (mmHg \pm SD)	130 \pm 27	131 \pm 29
Initial diastolic BP (mmHg \pm SD)	80 \pm 34	79 \pm 26
Initial heart rate	87 \pm 20	86 \pm 19
Initial respiratory rate	19 \pm 5	19 \pm 6
Initial pulse oximetry (% saturation)	97 \pm 3	98 \pm 2
Final systolic BP (mmHg \pm SD)	142 \pm 45	143 \pm 48
Final diastolic BP (mmHg \pm SD)	82 \pm 17	82 \pm 20
Final heart rate	89 \pm 20	87 \pm 19
Final respiratory rate	19 \pm 4	19 \pm 4
Final pulse oximetry (% saturation)	97 \pm 4	98 \pm 3

SD = standard deviation; *Percentages are split of each item between the two cohorts.

The Pearson correlation coefficients for the change in vomiting incidence with the qualitative and quantitative "nausea scales" were low: 0.012 (95% CI: -0.015 to 0.039, $R^2 = 0.00014$) and 0.051 (95% CI: -0.032 to 0.118, $R^2 = 0.00026$), respectively. The field for capturing potential adverse effects was so infrequently used that it was not analyzable. There were no anecdotal reports of any serious adverse effects during the study period.

DISCUSSION

During this study period, 5% of patients transported in this EMS system received ondansetron for nausea

and/or vomiting. Ondansetron was shown to be effective in treating a wide variety of patients with undifferentiated nausea and vomiting in this setting. These findings are congruent with other studies of ondansetron including ones in the emergency department setting.⁵⁻⁹ All of the ED-based studies involved children, primarily because of its favorable side effect profile. Surprisingly in our study, very few children and adolescents received ondansetron, possibly reflecting a hesitation to treat children's discomfort, the need to use OLMC for patients under 12 years old, or the lack of use of EMS for vomiting pediatric patients. In part due to this study and continued low reported adverse effects, the protocol has since been liberalized to allow non-OLMC use of ondansetron for children over 2 years of age. Parenteral ondansetron has favorable pharmacokinetics hours for prehospital use with a time to maximal plasma concentration of 5 minutes and an elimination half-life of 6 hours.^{15,16} Ondansetron showed a clinically significant change in both the quantitative and qualitative "nausea scales" but with only a moderate correlation between them.¹³ There is less validation of verbal scales in the literature. There was also a significant change in the occurrence of vomiting after administration of ondansetron, but this was not strongly correlated with the change in either of the "nausea scales." One reason may be these scales are not linear, or there was a systematic difference in how the scales were applied.

A logical next step would be to attempt a randomized controlled or a two-site comparison trial of ondansetron with another antiemetic to see if there is any difference in effectiveness comparing pre- and postadministration nausea levels and also to document any adverse effects. Key factors these trials should address are cost-effectiveness and risk of adverse events of various choices for antiemetics suitable for prehospital use.

The study suffered from poor compliance with the use of the embedded data collection instrument in the electronic patient care record with only 50% of the cases receiving any of the study section completed. The only significant differences in the "studied" and "not studied" cohorts were in the distribution of findings in the "Abdominal" and "Neurological" portions of the physical examination. Most importantly, there were high proportions of missing data and whether this would have an effect on the effectiveness or side effects of ondansetron is not clear because abnormal findings do not exclude its use in the current protocol. Even in the cases with outcome results, not all study data were documented for each patient, further degrading comparison of various outcomes. As with all health care providers, extra documentation meets resistance, and the only way to improve this for future studies is to offer rewards or make critical fields for study mandatory. For our study setting, it was not deemed possible to do a randomized controlled trial because ondansetron was added to the paramedics' scope of practice by a

protocol change necessitated by the black box warning for droperidol, the previous antiemetic in our EMS system.³ Few involved stakeholders thought it ethical to do a placebo-controlled trial since we had been using an antiemetic for years, and agencies were reluctant to deal with the complications of using two different medications during the study period. All of these factors illustrate the continued difficulty in trying to pursue controlled trials in the prehospital arena especially with limited funding. The study is also limited by the absence of hospital follow-up, which is also a challenge for most EMS studies. In the absence of hospital follow-up, we cannot know how well it worked in different diagnostic conditions.

CONCLUSION

In this prospective study, we were able to show that ondansetron was able to improve several "nausea scales" and the incidence of vomiting in prehospital patients with undifferentiated nausea and vomiting. The next step would be to do a randomized controlled trial of ondansetron versus other potentially appropriate antiemetics. In the meantime, EMS agencies may consider using ondansetron if they wish to treat nausea and vomiting.

We thank Pontine Rostek, EMT-P, Multnomah County American Medical Response, who steadfastly facilitated data collection for the duration of the study. This research was supported by an unrestricted grant from GlaxoSmithKline, the manufacturer of ondansetron (Zofran®). The authors have no other conflict of interest to report.

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APPENDIX C

179 Out-of-Hospital Use of Intravenous Ondansetron

Zuver C, Silvestri S, Ralls GA, Stalbaum T, Hawley D/

Orlando Regional Medical Center, Orlando, FL; Office of the Medical Director, Orange County Emergency Medical Services System, Orlando, FL

Study Objectives: Ondansetron is a commonly used antiemetic. Its safety and efficacy profile has been well established in the emergency department and in-patient setting. Out-of-hospital use has not yet been adequately reported in the literature. We evaluate the out-of-hospital use of intravenous ondansetron within a regional emergency medical services (EMS) system.

Methods: This is an observational cohort study of consecutive patients who were administered intravenous ondansetron in the out-of-hospital setting. The study took place in an urban, regional EMS system from October 2005 to December 2006. The regional EMS system consists of several different advanced life support agencies that collectively transport over 100,000 patients per year. The EMS system operates under unified medical direction and, prior to October 2005, established standing orders for the administration of intravenous ondansetron for severe persistent vomiting. EMS quality managers collected consecutive run reports of patients who received intravenous ondansetron in the out-of-hospital setting. Study investigators then extracted prehospital clinical care and patient demographic data. Emergency department records corresponding to each run report were reviewed and all information was then entered into a Microsoft Excel database. The primary outcome measures were symptomatic improvement and reported adverse effects. Symptomatic improvement was defined by: paramedic or emergency department documented improvement or no emergency department administration of an antiemetic within 4 hours of patient arrival. Descriptive statistics were used for analysis.

Results: During the study period, 190 patients received intravenous ondansetron. 62 (32.6%) of the patients were male and the mean age (\bar{x} / SD) was 45.4 (\bar{x} / 18.8). Of the 190 patients, 162 (85.2%) had complete data available for analysis. In this cohort, 149 (91.9%) patients received a 4 mg dose and 13 (8%) received a 2 mg dose. 151 (93.2%) patients were administered ondansetron under standing orders, while medical control was contacted for 11 patients. 128 patients (79%) had symptomatic improvement, and there were no reported adverse effects.

Conclusion: In our system, paramedics demonstrated safe and effective use of intravenous ondansetron in the out-of-hospital setting.

Research Forum Abstracts

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