Legal Briefs

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Do surgeons get sued when they work with anesthesiologists?

Key words: Malpractice, supervision, vicarious liability.

Because the majority of anesthesia accidents arise from a lack of vigilance, it seems fairly elementary that a surgeon looking for an anesthesia provider should look for someone vigilant, well-organized, and someone with whom the surgeon can work easily. The type of license the anesthetist holds, whether MD or CRNA, is irrelevant to the quality of care they render. Yet many surgeons have been told, and a surprising number actually believe, that whether the provider is a nurse anesthetist or an anesthesiologist affects the surgeon's liability. Some surgeons have been told that they are liable for the negligence of nurse anesthetists but do not need to worry about "what goes on at the head of the table" when they work with anesthesiologists.

This column has pointed out that the principles governing the liability of a surgeon for anesthesia are the same whether the surgeon works with a nurse anesthetist or an anesthesiologist. The liability of a surgeon for anesthesia is most often based on whether the surgeon controls the anesthesia provider which depends on the facts of the case not on the status of the anesthesia provider. In the past, we have highlighted cases which either clarify these principles or typify cases in which surgeons have *not* been held liable for the negligence of a nurse anesthetist.

CRNAs are human and therefore, not perfect, but anesthesiologists are also human and therefore, imperfect as well. Some months ago we highlighted cases involving mistakes made by anesthesiologists. We were not trying to make a blanket statement about anesthesiologist care. The point of the column was that it does not make sense for either nurse anesthetists or anesthesiologists to attempt to capitalize on the errors of the other. Anesthesia is very safe, and both professions should be trying to make it even safer.

Nonetheless, there continue to be efforts to make surgeons believe that there is some reason to prefer the services of one class of anesthesia provider to the other. Surgeons should understand that, unfortunately, there is risk associated with anesthesia, whether it is administered by nurse anesthetists or anesthesiologists.

There continues to be a double standard in anesthesia. Mistakes and lawsuits when anesthesiologists have given care are overlooked while an episode involving a CRNA may be followed by demands for a change in the manner anesthesia is administered. Not only can anesthesiologists make mistakes, but also surgeons can be sued when they work with an anesthesiologist just as easily as they can as when they work with a nurse anesthetist.

All of the following cases involve lawsuits against surgeons for anesthesia mishaps. No CRNA was involved in *any* of them. In every case, the administrator of anesthesia was an anesthesiologist.

Adams v Childrens Mercy Hospital

In *Adams v Childrens Mercy Hospital,* 848 SW 2d 535 (Missouri Court of Appeals, 1993), a child was severely burned by grease. The child was scheduled for skin grafting surgery. Anesthesia was provided by a resident supervised by two anesthesiologists. The resident had administered too much distilled salt water, and it caused substantial swelling of the bodily tissue. Following the surgery, an anesthesiologist removed the breathing tube. About 6 minutes after the extubation, the patient suffered a cardiopulmonary arrest as a result of the

closure of the airway because of the swollen tissue. The anesthesiologist reinserted the tube but, unfortunately, the tube was inserted into the esophagus rather than the trachea. The child was severely brain damaged, blind, and neurologically impaired.

The child brought suit against the hospital, the anesthesiologist, the resident, and the surgeon. Not only was the surgeon involved in this suit over an anesthesia mishap, but also the jury awarded 2% of the damages against the surgeon. The case was appealed by the hospital which claimed there was insufficient evidence for its liability, but a number of the physicians, including the surgeon, settled their awards prior to the appeal.

Costell v Toledo Hospital

In *Costell v Toledo Hospital,* 98 Ohio App.3d 586, 649 NE 2d 35, (1994), the patient entered the hospital for heart surgery. The surgery was complete and the surgeon had left the operating room when the patient had a heart attack. The patient's executor claimed that the anesthesiologist, who was still in the operating room, failed to respond to the emergency quickly enough. Although the surgeon returned to the operating room and was able to get the patient's heart beating again, the patient had suffered a loss of oxygen to his brain. The patient never recovered consciousness and died in the hospital several months later. The patient's family brought suit against the anesthesiologist, the hospital, and the surgeon. A trial court granted summary judgment for the hospital on the grounds that the physicians were not its agents, but the Court of Appeals of Ohio reversed because there were sufficient issues as to whether or not the anesthesiologist was the hospital's agent to permit the case to proceed.

Brown v Bozorgi

In *Brown v Bozorgi,* 234 Ill. App. 3d 972, 602 NE 2d 48, (1992), an anesthesiologist improperly inserted an endotracheal tube into the patient's esophagus. The patient brought suit against the anesthesiologist and the obstetrician. Although it was clear that the damage was caused by the negligent intubation, the patient sought, nonetheless, to hold the surgeon liable on the theory that the deceased would not have died if the surgeon had applied appropriate resuscitative measures. The jury was instructed that *"more than one person may be to blame for causing an injury. If you decide that the defendant* [surgeon] *was negligent and that the negligence was* [the] *approximate cause of injury to the plaintiff, it is not a defense that some third person* [one assumes the anesthesiologist] *who is not a party to the suit may also have been to blame."*

The anesthesiologist settled with the plaintiff. The jury returned a verdict in favor of the surgeon, but the patient appealed on the grounds that during closing testimony the surgeon's lawyer stated that *"Now, what's the case about? It's not just the death of* [the patient]. *You know who caused* [her] *death.* [The anesthesiologist] *caused her death, but he walks away from this."* The court let the judgment in favor of the surgeon stand.

Ruby Jones v Neuroscience Associates, Inc.

In *Ruby Jones v Neuroscience Associates, Inc.,* 250 Kan. 477, 827 P.2d 51 (1992), the patient was injured in an automobile accident. She was hospitalized for a cervical laminectomy to relieve pain in her *right* arm. After the surgery, she was unable to move her *left* hand. All of the fingers in her left hand were curled into a fist. The injury to her left hand was apparently the result of pressure against the radial nerve, a positioning problem related to the anesthesia. Both the surgeon and the anesthesiologist thought the condition would improve but it did not. Ultimately the patient was told by a neurologist that she should have had a procedure immediately after the operation. She sued both the surgeon and the anesthesiologist. The question was whether the statute of limitations had expired. The Supreme Court of Kansas ruled that there was sufficient question as to when the patient discovered the accident to permit the case to go forward.

Seneris v Haas

In *Seneris v Haas,* 45 Cal. 2d 811, 291 P.2d 915 (California, 1955), an anesthesiologist administered a spinal anesthetic to a patient who had a spontaneous and uncomplicated delivery. However, the following morning the patient could not move her legs and had pain in her back, neck, head, arms, and wrist. She regained the use of her right leg but at the time of trial was still suffering pain in her left hip and had limited use of her left leg. She brought suit against the anesthesiologist and the obstetrician claiming that they were liable under the doctrine of *res ipsa loquitur.* The trial court entered judgment in favor of the obstetrician, anesthesiologist, and hospital, but the California Supreme Court ruled that the case had to proceed at least against the anesthesiologist.

Szabo v Bryn Mawr Hospital

In *Szabo v Bryn Mawr Hospital,* 432 Pa. Super. 409, 638 A. 2d 1004, (1994), the patient advised an anesthesiologist that he had ingested 4 ounces of milk the morning of the operation. Nonetheless, the anesthesiologist made the decision to proceed with the surgery. Shortly after anesthesia began,

the patient vomited solid food particles and had to be treated for aspiration pneumonitis. The patient brought suit against the anesthesiologist and the surgeon. The suit against the surgeon was dismissed, but the appellate court reversed and sent the case back for a trial because it determined that there were insufficient facts for it to determine whether the anesthesiologist was subject to the control of the surgeon.

Tiburzio-Kelly v Montgomery

In *Tiburzio-Kelly v Montgomery,* 452 Pa. Super. 158, 681 A. 2d 757 (1996), the plaintiff experienced labor symptoms and went to the hospital. The plaintiff was placed in the delivery room for preparation while the obstetrician prepared for surgery. By the time the patient and doctor were prepared, no anesthesiologist had appeared. Initially, the obstetrician decided to wait for the anesthesiologist, but after a while, he began a cesarean surgery. The decision required him to cut into plaintiff while she was fully conscious and required him to anesthetize each progressive layer of the abdomen before each incision. Approximately 7 minutes after the baby was born, an anesthesiologist arrived and administered an anesthetic to permit the doctors to complete the operation on the plaintiff. The baby was born with complications. Testimony indicated that she had suffered from oxygen deprivation while in utero. As a consequence, she had a seizure disorder and a reduced mental capacity which bordered on mental retardation.

The baby and her parents brought suit against the obstetrician, the anesthesiologist, the hospital, and the anesthesiologist corporation. The jury returned a verdict absolving the obstetrician and the anesthesiologist group of all liability. Plaintiffs appealed, and the appellate court ordered a new trial against the anesthesiologist group, because the trial court had not permitted the plaintiff to assert its claims fully. The appellate court agreed with the plaintiff that it was negligence for the anesthesiologist group to fail to show up.

Bert v Meyer

In *Bert v Meyer,* 663 N.Y.S. 2d 99, (New York, 1997), the plaintiff's wife died following a cesarean section. The jury awarded damages in favor of the plaintiff against the anesthesiologist and the obstetricians. The obstetricians appealed on the grounds that the anesthesiologist was solely responsible. The appellate court upheld the verdict against both the anesthesiologist and obstetricians on the grounds that the plaintiff was not required to prove the precise nature of the negligence in order to establish a prima facie case.

Robertson v Hospital Corporation of America

In *Robertson v Hospital Corporation of America,* 653 So. 2d 1265 (Court of Appeal of Louisiana, 1995), a jury allocated fault for ulnar nerve injury sustained by the patient during the course of abdominal surgery as 70% for the anesthesiologist, 20% to the surgeon, and 10% to the circulating nurse.

Kerber v Sarles

In *Kerber v Sarles,* 542 NYS 2d 94, 151 Ad.2d 1031, (New York, 1989), the court held that *res ipsa loquitur* was applicable to a case where a patient's teeth were damaged during foot surgery. Expert testimony was presented that the injury to the teeth was caused by excess force administered by an anesthesiologist who was, arguably, not under the control of either the hospital or the podiatrist. Nonetheless, the patient proceeded with a lawsuit against the podiatrist and the hospital, but not against the anesthesiologist, on the theory of *res ipsa loquitur.*

The trial court had granted summary judgment in favor of the podiatrist because the trial court believed that evidence showed that the injury was caused by the anesthesiologist which was not "something in the exclusive control of the defendant" as required for the application of *res ipsa loquitur.* The appellate court reversed and held that the trial court's ruling was erroneous. The plaintiff had no way of knowing what had happened while she was anesthetized and she could maintain her suit under the doctrine of *res ipsa loquitur* against the podiatrist and hospital if she wished.

Menzie v Windom Community Memorial Hospital

In *Menzie v Windom Community Memorial Hospital,* 774 F.Supp. 91 (U.S.D.C. Conn., 1991), the patient was injured in a motorcycle accident. An orthopedic surgeon was called who examined the patient and after reviewing x-rays determined that the patient's life was in jeopardy and that surgery was immediately necessary. An anesthesiologist took the patient's medical history and obtained informed consent. The patient's blood pressure dropped after the anesthesiologist administered the spinal anesthetic but before surgery commenced and the patient suffered a cardiorespiratory arrest. The patient sued the surgeon, the anesthesiologist, and the hospital. The hospital was released as a defendant because neither the surgeon nor the anesthesiologist were its agents.

Thompson v Presbyterian Hospital

In *Thompson v Presbyterian Hospital,* 652 P.2d 260 (Okla., 1982), a patient desired a tubal ligation.

The surgeon discussed the procedure with her and on receiving her consent enlisted the aid of an anesthesiologist. The anesthesiologist was unable to meet with the patient to discuss her choice of anesthesia and the surgeon acted as a go-between. The surgeon reported to the anesthesiologist that the patient had agreed to a spinal anesthetic and that the surgeon would write the preoperative orders. The surgeon included a premedication prescription of 100 mg of Demerol®. The following morning the anesthesiologist administered the anesthetic, and the surgeon proceeded with the operation. During the procedure the patient suffered a cardiac arrest. Her administrator brought an action against the surgeon, the anesthesiologist, the anesthesiologist's professional corporation, and the hospital.

The plaintiff introduced testimony by a medical expert that the surgeon's act of prescribing Demerol was a deviation from the standard of care which, when combined with the later actions of the anesthesiologist, started a chain of events that led to the patient's hypoxic brain damage. The appellate court held that the surgeon could not foresee that the anesthesiologist would give an improper saddle block or fail to properly monitor the patient during surgery, therefore, the suit against the surgeon was dismissed.

Medvecz v Choi

In *Medvecz v Choi,* 569 F. 2d 1221 (US Ct. of App., 3d Cir., 1977), a patient received anesthesia while being x-rayed. The patient became paralyzed after the dye migrated from the blood vessels into the spinal cord. The plaintiff brought suit against the surgeon, the hospital, and the anesthesiologist. There had been a dramatic drop in the patient's blood pressure during the operation. The surgeon said that he had not been notified of the drop in blood pressure, and that if he had been notified he would have halted the surgical procedure. Why the dye migrated to the spinal column was disputed. The anesthesiologist claimed that the dye migrated to the spinal cord because too much had been used. Other testimony suggested that the drop in blood pressure was the cause.

During trial the anesthesiologist testified on cross-examination, for the first time, that he had left the operating room in the middle of the procedure although he could not remember why nor could he remember what he did or who, if anyone, replaced him. This directly contradicted testimony he had given during his deposition. Given the revelation, the patient had asked for an instruction to the jury on the issue of abandonment which had been refused. The appellate court held that this was an error and sent the case back to the trial court for a new trial.

Dunn v Maras

In *Dunn v Maras,* 182 Ariz. 412, 897 P.2d 714 (1995), the patient went to the hospital to deliver her fourth child. The obstetrician examined the plaintiff and left instructions that the plaintiff could receive an epidural anesthetic or other pain medication on request. He left the hospital for his office across the street. An anesthesiologist then administered an epidural injection. A second epidural was required because the first had provided an "unequal block," affecting only one side of the plaintiff's body. Hospital records show that the patient became "cold and jittery," short of breath, and needed oxygen. The fetal heart tone was recorded as weak, requiring the administration of several ephedrine injections to elevate the patient's blood pressure. The obstetrician was called at home, an emergency cesarean section was performed, and although the child was saved, the patient suffered severe brain damage.

The anesthesiologist claimed that the plaintiff's condition stemmed not from the mishandled epidural but from an unrelated malady known as amniotic fluid embolism syndrome. The jury verdict rendered against the plaintiff and in favor of the defendants was appealed because one of the jurors had learned of the terms of a settlement between the plaintiff and the hospital and, during jury deliberations, described the plaintiff as "greedy." The surgeon's position at trial had been that this was an anesthesia incident and that there was nothing that he could have done to save the plaintiff. Nonetheless, the appellate court ordered a new trial against both the surgeon and the anesthesiologist.

Conclusion

As these cases show, surgeons are not protected when they work with anesthesiologists. In our legal system, plaintiffs are entitled to sue anybody they wish as long as they reasonably believe that they have a claim. It is probably true that some surgeons have been sued for anesthesia incidents when anesthesia has been provided by a nurse anesthetist. But it is equally true that surgeons have also been sued and held liable when anesthesia was provided by an anesthesiologist. Anesthesia incidents are rare today and becoming rarer. Surgeons cannot prevent their involvement in cases arising from anesthesia incidents whether they work with nurse anesthetists or anesthesiologists. They would be far better advised to select competent, vigilant providers without regard to whether or not they have a nursing or medical license.

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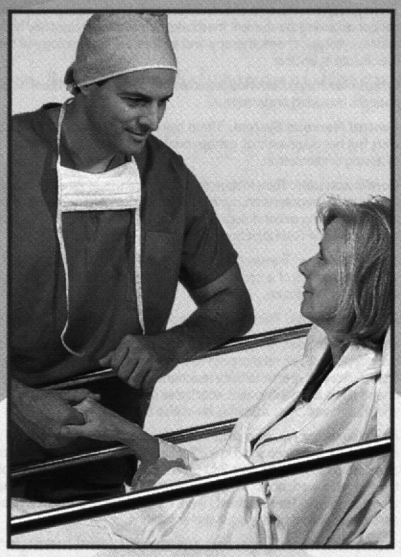

It's what ZOFRAN is all about too.

Rated high in patient satisfaction during surgical clinical trials[1]*

The most commonly reported adverse events in patients receiving ZOFRAN in clinical trials were headache (5% to 27%), diarrhea (<1% to 16%), constipation (<1% to 9%), fever (<1% to 8%), and malaise/fatigue (0% to 13%).[1]

- **Most used IV antiemetic for PONV[1†]**
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*** In a study of 2,061 adult patients (at high risk for PONV) undergoing surgery, patient satisfaction with IV antiemetic therapy was assessed on a 5-point scale ranging from "very satisfied" to "very dissatisfied." Eighty-four percent of patients receiving ZOFRAN Injection rated themselves as either "very satisfied" or "somewhat satisfied" with control of their postoperative nausea and vomiting.**

† Hospital Research Associates anesthesia audit (hospital and surgicenter audits June 1997).

Reference: 1. Data on file, Glaxo Wellcome Inc.

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BRIEF SUMMARY

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

CONTRAINDICATIONS:

ZOFRAN Injection, ZOFRAN Injection Premixed, ZOFRAN 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_3 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.

Drug Interactions: Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, 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. 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.

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

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 IV doses up to 4 mg/kg per day and at daily oral doses up to 15 and 30 mg/kg per 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: ***ZOFRAN Injection:*** Little information is available about dosage in pediatric patients under 2 years of age (see DOSAGE AND ADMINISTRATION section of full prescribing information for use in pediatric patients 4 to 18 years of age receiving cancer chemotherapy or for use in pediatric patients 2 to 12 years of age receiving general anesthesia).

ZOFRAN Tablets: Little information is available about dosage in children 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections of full prescribing information for use in children 4 to 18 years of age).

Use in Elderly Patients: Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY section of full prescribing information). Prevention of nausea and vomiting in elderly patients was no different than in younger age-groups.

ADVERSE REACTIONS:

ZOFRAN INJECTION:

Chemotherapy-Induced Nausea and Vomiting: The following adverse events have been reported in individuals 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 IV fluids. Most were receiving a diuretic.

Principal Adverse Events in Comparative Trials

	Number of Patients With Event			
	ZOFRAN® Injection		Metoclopramide	Placebo
	0.15 mg/kg x 3 n = 419	*32 mg x 1 n = 220*	*n = 156*	*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 Central Nervous System below.

The following have been reported during controlled clinical trials or in the routine management of patients. The percentage figures are based on clinical trial experience.

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.

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.

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

Cardiovascular: Rare instances of tachycardia, angina (chest pain), bradycardia, hypotension, syncope, and electrocardiographic alterations, including second degree heart block. In many cases the relationship to ZOFRAN Injection was unclear.

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

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

Other: Rare cases of hypokalemia and grand mal seizures have been reported. The relationship to ZOFRAN Injection was unclear. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria), have also been reported.

Postoperative Nausea and Vomiting: The following adverse events have been reported in ≥2% of adults receiving ondansetron at a dosage of 4 mg IV 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.

	ZOFRAN® Injection *4 mg IV 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 following 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.

Frequency of Adverse Events From Controlled Studies

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%)

ZOFRAN TABLETS:

Chemotherapy-Induced Nausea and Vomiting: The following adverse events have been reported in adults receiving either 8 mg of ZOFRAN Tablets two or three times a day for 3 days or placebo in four trials. These patients were receiving concurrent chemotherapy, primarily cyclophosphamide-based regimens.

Principal Adverse Events in US Trials: 3 Days of Therapy With ZOFRAN Tablets

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%)
Abdominal pain	3 (1%)	13 (3%)	1 (<1%)
Xerostomia	5 (2%)	6 (1%)	1 (<1%)
Weakness	0 (0%)	7 (2%)	1 (<1%)

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 following adverse events 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.

Frequency of Adverse Events From Controlled Studies

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%)

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 IV doses as large as 145 mg and total daily IV doses (three 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.

"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 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.

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Research Triangle Park, NC 27709

ZOFRAN® Injection:
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