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Official Publication of the Association of Veterans Administration Surgeons, New England Surgical Society, Pacific Coast Surgical Association, Society of Surgical Oncology, Surgical Infection Society, Western Surgical Association.

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- Who Should Be Responsible for Care of the Critically Ill Surgical Patient?** 1103
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- Diagnosis and Treatment of Pancreatic Injuries: An Analysis of Management Principles** 1109
David H. Wisner, MD; Rebekah L. Wold, MD; Charles F. Frey, MD, Davis, Calif
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- Percutaneous Cholecystolithotomy: A Minimally Invasive Alternative to Cholecystectomy and to Shock Wave Lithotripsy** 1114
Donald P. Griffith, MD; Malachy J. Gleeson, MD; Michael F. Appel, MD; Philip S. Bentlif, MD; F. Lyone Hochman, MD; Barry D. Toombs, MD; Mark D. Skolkin, MD, Houston, Tex
● Percutaneous cholecystolithotomy is applicable to all gallstones, and is a safe, practical alternative to cholecystectomy.

Invited Commentary: Donald E. Fry, MD, Albuquerque, NM

- Abdominal Pain in Neutropenic Patients** 1119
LCDR David S. Wade, MC, USN, Bethesda, Md; Harold Douglass, Jr, MD; Hector R. Nava, MD; Marion Piedmonte, MA, Buffalo, NY
● An algorithm for the evaluation and treatment of neutropenic patients with abdominal pain is presented.

Invited Commentary: Philip D. Schneider, MD, PhD, Sacramento, Calif

- Pediatric Trauma Score: Predictor of Hospital Resource Use?** 1128
Charles Aprahamian, MD; Richard P. Cattet, MD; Alonzo P. Walker, MD, Milwaukee, Wis; Harvey W. Gruchow, PhD, Greensboro, NC; Gary Seabrook, MD, Milwaukee, Wis
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- Level I and II Axillary Dissection in the Treatment of Early-Stage Breast Cancer: An Analysis of 259 Consecutive Patients** 1144
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 Paulo C. Cardoso de Almeida, MD, São Paulo, Brazil; Herbert C. Hoover, Jr, MD, Boston, Mass
 • Cystic teratomas of the pancreas are rare, requiring early diagnosis and surgical resection.

Primary Hypertrophic Pyloric Stenosis in the Adult **1219**
 Robert L. Quigley, MD, Dphil; Scott Pruitt, MD; Theodore N. Pappas, MD; Onye Akwari, MD, Durham NC
 • Adult primary hypertrophic pyloric stenosis is rare and its cause(s) remains unclear.

TECHNIQUE

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 Bruce S. Cutler, MD, Worcester, Mass; Lazar J. Greenfield, MD, Ann Arbor, Mich; Thomas J. Vander Salm, MD, Worcester, Mich
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TORADOL® (ketorolac tromethamine)

Brief Summary

TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 3% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%); independent of concentration. In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 µg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 µg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time.

There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with *S. typhimurium*, *S. cerevisiae*, or *E. coli* and did not cause chromosome breakage in the in vivo mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery. **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 73 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 79 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. **Pediatric Use:** TORADOL is not recommended for use in children. **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. **Incidence greater than 1%:** Body as a whole: edema, GI: nausea, dyspepsia, GI pain, diarrhea. Nervous system: drowsiness, dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). **Incidence of reported reaction 3% to 9%:** Reactions occurring in less than 3% are unmarked. **Incidence 1% or less:** Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥ 6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic activity. In vitro, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses > 100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others.

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 Bethesda, MD 20814



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