CME CREDIT

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should patients with documented or probable coronary artery disease routinely be placed on beta-blockers before noncardiac surgery?

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A: YES. Current evidence suggests that patients with either documented coronary disease or significant cardiac risk factors should routinely be started on beta-blockers before noncardiac surgery. Three lines of evidence support this recommendation: the frequency and severity of complications, the mechanism of action of beta-blockers, and data from randomized clinical trials.

SURGICAL COMPLICATIONS ARE FREQUENT AND SEVERE

Complications associated with noncardiac surgery are frequent, and many of these complications are cardiac. In a large Veterans Administration study,[1] the 30-day mortality rate was 3.1%, the cardiac complication rate was 4.5%, and the myocardial infarction rate was 0.7%.[1]

BETA-BLOCKERS REDUCE MYOCARDIAL OXYGEN DEMAND

Perioperative myocardial ischemia is thought to be caused by high levels of circulating catecholamines, an increased heart rate, and consequent increased oxygen demand. Beta-blockers reduce myocardial oxygen demand and so in theory should reduce the risk of myocardial ischemia and infarction.

In addition, beta-blockers are known to be beneficial in stable angina,[2] heart failure,[3] and after an acute myocardial infarction.[4] These observations provide further reason to think that beta-blockers may help decrease risk during the stress of surgery.

STUDIES OF BETA-BLOCKERS IN NONCARDIAC SURGERY

Direct evidence in favor of perioperative beta-blocker use comes from clinical intervention studies. Three of the most important are discussed below:

In a study at the San Francisco Veterans Affairs Medical Center,[5] 200 patients were randomized to receive either atenolol or placebo, starting before surgery and continuing until discharge. The atenolol group had significantly fewer deaths from cardiac causes both during the first 6 to 8 months and at 2 years of follow-up, and atenolol caused no significant adverse effects that could be detected. This study led to a recommendation that beta-blockers be given perioperatively to patients at high risk, which was included in a 1997 clinical guideline for preoperative assessment and management of patients at risk for coronary artery disease.[6] Patients undergoing vascular surgery were considered at especially high risk of cardiac complications because many have asymptomatic coronary disease.

Preoperative atenolol reduced postoperative cardiac mortality

In another study,[7] patients older than 65 years were randomly assigned to three protocols: one with no atenolol, one with atenolol before and after surgery, and one with atenolol during surgery only. Neither atenolol regimen significantly altered the hormonal stress response, but both improved hemodynamic stability during emergence from anesthesia, keeping the systolic blood pressure between 90 and 180 mm Hg and the heart rate between 40 and 100 beats/minute. In addition, the patients given atenolol required less postoperative analgesia.

A study of bisoprolol in patients at high risk who were undergoing vascular surgery also had favorable results.[8] In this study, 112 patients with abnormal dobutamine echocar-

diograms were randomized to receive standard care or bisoprolol starting at least 1 week before surgery and continuing for 30 days afterward. Patients who received bisoprolol had a 3.4% mortality rate, compared with 17% among those receiving standard care. Another 17% of the standard care group had nonfatal myocardial infarctions, whereas none of the bisoprolol group did. No serious side effects occurred in the bisoprolol group.

ARGUMENTS AGAINST ROUTINE BETA-BLOCKER USE

Some argue that more research is needed before the results of these studies can be applied to all patients. Furthermore, critics point to possible complications from the use of beta-blockers, including bronchospasm, myocardial depression, bradycardia, and conduction system abnormalities. However, as noted, studies to date have not found these complications to be a problem, provided that standard precautions are followed, such as withholding the beta-blocker if the heart rate is less than 55 or if the systolic blood pressure is less than 100 mm Hg.

WHICH PATIENTS WILL BENEFIT?

Vascular-surgery patients may benefit the most from beta-blockers

The patients who would appear to benefit the most from perioperative use of beta-blockers are those undergoing vascular surgery, who have a high likelihood of asymptomatic cardiac disease and a high risk of cardiac morbidity and mortality.

The potential benefits of beta-blockers probably also outweigh the risks for patients scheduled for nonvascular surgery who have a history of coronary disease or significant risk factors for coronary disease.

The benefit may be substantially less or negligible in patients undergoing minor procedures such as ophthalmologic surgery, especially procedures that do not require general anesthesia.

The optimum timing and duration of therapy remains to be determined. However, on the basis of available evidence, we conclude that beta-blockers should be started preoperatively and continued until discharge if no complications develop.

Atenolol is preferred because it was studied in the trials discussed earlier. If the heart rate is greater than 65 and the systolic blood pressure is greater than 100 mm Hg, give 100 mg daily. If the heart rate is 55 to 65 and the systolic blood pressure is greater than 100 mm Hg, give 50 mg. If the heart rate is less than 55 or the systolic blood pressure is less than 100, do not give atenolol.

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CME ANSWERS

Answers to the credit test on page 367 of this issue

1 **D** 2 **C** 3 **E** 4 **D** 5 **D** 6 **B** 7 **C** 8 **A** 9 **C** 10 **D** 11 **C** 12 **A**

ZOSYN® (Sterile Piperacillin Sodium and Tazobactam Sodium)
Brief Summary

See package insert for full prescribing information.

INDICATIONS AND USAGE

For the treatment of patients with moderate to severe infections caused by piperacillin-resistant, piperacillin/tazobactam-susceptible, β-lactamase producing strains of the designated microorganisms in the specified conditions listed below:

Appendicitis (complicated by rupture or abscess) and peritonitis caused by *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis, B. ovatus, B. thetaiotaomicron,* or *B. vulgatus.*

Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses, and ischemic/diabetic foot infections caused by *Staphylococcus aureus.*

Postpartum endometritis or pelvic inflammatory disease caused by *Escherichia coli.*

Community-acquired pneumonia (moderate severity only) caused by *Haemophilus influenzae.*

Nosocomial pneumonia (moderate to severe) caused by *Staphylococcus aureus.*

Infections caused by piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, are also amenable to ZOSYN treatment due to its piperacillin content. Treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, β-lactamase producing organisms susceptible to ZOSYN should not require the addition of another antibiotic.

ZOSYN is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms.

CONTRAINDICATIONS

ZOSYN is contraindicated in patients with a history of allergic reactions to any of the penicillins, cephalosporins, or β-lactamase inhibitors.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ZOSYN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, ZOSYN SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ZOSYN, and may range in severity from mild to life-threatening. Consider this diagnosis in patients who present with diarrhea after antibacterial agent administration.

After the diagnosis of pseudomembranous colitis has been established, initiate therapeutic measures. Mild cases usually respond to drug discontinuation alone. In moderate to severe cases, fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis may be necessary.

PRECAUTIONS

General: Bleeding manifestations have occurred in some patients receiving β-lactam antibiotics, including piperacillin. These reactions have sometimes been associated with coagulation test abnormalities such as clotting time, platelet aggregation, and prothrombin time and are more likely to occur in renal failure patients. If bleeding manifestations occur, discontinue ZOSYN and institute appropriate therapy.

The possibility of the emergence of resistant organisms that might cause superinfections should be kept in mind. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

ZOSYN is a monosodium salt of piperacillin and a monosodium salt of tazobactam, containing 2.35 mEq (54 mg) of Na+ per gram of piperacillin; consider this when treating patients requiring restricted salt intake. Perform periodic electrolyte determinations in patients with low potassium reserves; the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

As with other semisynthetic penicillins, piperacillin has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Laboratory Tests: Perform periodic assessment of hematopoietic function, especially with prolonged therapy, i.e., ≥21 days. (See **ADVERSE REACTIONS—Adverse Laboratory Events.**)

Drug Interactions: *Aminoglycosides*—The mixing of ZOSYN with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside. (See Full Prescribing Information—**Compatible Intravenous Diluent Solutions, DOSAGE AND ADMINISTRATION.**)

When ZOSYN was co-administered with tobramycin, the area under the curve, renal clearance, and urinary recovery of tobramycin were decreased by 11%, 32%, and 38%, respectively. Pharmacokinetic alterations of tobramycin when administered with ZOSYN may be due to *in vivo* and *in vitro* inactivation of tobramycin in the presence of piperacillin/tazobactam. The inactivation of aminoglycosides in the presence of penicillin-class drugs has been recognized. It has been postulated that microbiologically inactive penicillin-aminoglycoside complexes of unknown toxicity form. In patients with severe renal dysfunction (i.e., chronic hemodialysis patients), tobramycin pharmacokinetics are significantly altered when administered with piperacillin. The alteration of tobramycin pharmacokinetics and the potential toxicity of the penicillin-aminoglycoside complexes in patients with mild to moderate renal dysfunction who are administered an aminoglycoside with ZOSYN are unknown.

Probenecid—Probenecid administered with ZOSYN prolongs the half-life of piperacillin by 21% and of tazobactam by 71%.

Vancomycin—No pharmacokinetic interactions with ZOSYN have been noted.

Heparin—Coagulation parameters should be tested more frequently and monitored regularly during simultaneous administration of high doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.

Vecuronium—Piperacillin used with vecuronium has been implicated in the prolongation of the neuromuscular blockade of vecuronium. ZOSYN could produce the same phenomenon if given with vecuronium. Due to their similar mechanism of action, the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. (See package insert for vecuronium bromide.)

Drug/Laboratory Test Interactions: As with other penicillins, ZOSYN may result in a false-positive reaction for glucose in the urine using a copper-reduction method (CLINITEST®§). Glucose tests based on enzymatic glucose oxidase reactions (such as DIASTIX®§ or TES-TAPE®§) are recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term carcinogenicity studies in animals have not been conducted with piperacillin/tazobactam, piperacillin, or tazobactam. *Piperacillin/tazobactam* was negative in the following mutagenicity tests/assays up to the concentrations noted: microbial mutagenicity assay (14.84/1.86 μg/plate), unscheduled DNA synthesis (UDS) test (5689/711 μg/mL), mammalian point mutation (Chinese hamster ovary cell HPRT) assay (8000/1000 μg/mL), and a mammalian cell (BALB/c-3T3) transformation assay (8/1 μg/mL). *In vivo*, piperacillin/tazobactam did not induce chromosomal aberrations in rats dosed I.V. with 1500/187.5 mg/kg; this dose is similar to the maximum recommended human daily (MRHD) dose on a body-surface-area basis (BSA) (mg/m²).

Piperacillin was negative in the following mutagenicity tests/assays up to the concentrations noted: microbial mutagenicity assays (50 μg/plate), UDS test (10,000 μg/mL), and a cell (BALB/c-3T3) transformation assay (3000 μg/mL). There was no DNA damage in bacteria (Rec assay) exposed to piperacillin at concentrations up to 200 μg/disk. In a mammalian point mutation (mouse lymphoma cells) assay, piperacillin was positive at concentrations ≥2500 μg/mL. *In vivo*, piperacillin did not induce chromosomal aberrations in mice at I.V. doses up to 2000 mg/kg/day or rats at I.V. doses up to 1500 mg/kg/day. These doses are half (mice) or similar to (rats) the MRHD dose based on BSA (mg/m²). In another *in vivo* test, there was no dominant lethal effect when piperacillin was administered to rats at I.V. doses up to 2000 mg/kg/day, which is similar to the MRHD dose based on BSA (mg/m²). When mice were administered piperacillin at I.V. doses up to 2000 mg/kg/day, which is half the MRHD dose based on BSA (mg/m²), urine from these animals was not mutagenic when tested in a microbial mutagenicity assay. Bacteria injected into the peritoneal cavity of mice administered piperacillin at I.V. doses up to 2000 mg/kg/day did not show increased mutation frequencies.

Tazobactam was negative in the following mutagenicity assays up to the concentrations noted: microbial mutagenicity assays (333 μg/plate), UDS test (2000 μg/mL), mammalian point mutation (Chinese hamster ovary cell HPRT) (5000 μg/mL), a cell (BALB/c-3T3) transformation assay (900 μg/mL). In another mammalian point mutation (mouse lymphoma cells) assay, tazobactam was positive at concentrations ≥3000 μg/mL. In an *in vitro* cytogenetics (Chinese hamster lung cells) assay, tazobactam was negative at concentrations up to 3000 μg/mL. *In vivo*, tazobactam did not induce chromosomal aberrations in rats at I.V. doses up to 5000 mg/kg, which is 23 times the MRHD dose based on BSA (mg/m²).

Pregnancy: *Teratogenic effects—Pregnancy Category B:* Piperacillin/tazobactam: Reproduction studies in rats have revealed no evidence of impaired fertility due to piperacillin/tazobactam administered up to a dose which is similar to the MRHD dose based on BSA (mg/m²).

Teratology studies in mice and rats have revealed no evidence of harm to the fetus due to piperacillin/tazobactam administered up to a dose which is 1 to 2 times and 2 to 3 times the human dose of piperacillin and tazobactam, respectively, based on BSA (mg/m²).

Piperacillin: Reproduction and teratology studies in mice and rats have revealed no evidence of impaired fertility or fetal harm due to piperacillin administered up to a dose which is half (mice) or similar to (rats) the MRHD dose based on BSA (mg/m²).

Tazobactam: Reproduction studies in rats have revealed no evidence of impaired fertility due to tazobactam administered at doses up to 3 times the MRHD dose based on BSA (mg/m²).

Teratology studies in mice and rats have revealed no evidence of fetal harm due to tazobactam administered at doses up to 6 and 14 times, respectively, the human dose based on BSA (mg/m²). In rats, tazobactam crosses the placenta. Concentrations in the fetus are less than or equal to 10% of those found in maternal plasma.

There are no adequate and well-controlled studies with the piperacillin/tazobactam combination or with piperacillin or tazobactam alone in pregnant women. Use this drug during pregnancy only if clearly needed.

Nursing Mothers: Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Exercise caution when ZOSYN is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Patients over 65 years are **not** at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency.

ADVERSE REACTIONS

During the initial clinical investigations, 2621 patients worldwide were treated with ZOSYN in phase 3 trials. In the key North American clinical trials (n=830 patients), 90% of the adverse events reported were mild to moderate in severity and transient in nature. However, in 3.2% of the patients treated worldwide, ZOSYN was discontinued because of adverse events primarily involving the skin (1.3%), including rash and pruritus; the gastrointestinal system (0.9%), including diarrhea, nausea, and vomiting; and allergic reactions (0.5%). Adverse local reactions that were reported, irrespective of relationship to ZOSYN therapy, were phlebitis (1.3%), injection site reaction (0.5%), pain (0.2%), inflammation (0.2%), thrombophlebitis (0.2%), and edema (0.1%).

In the completed study of nosocomial lower respiratory tract infections, 155 patients received ZOSYN 3.375 g every 4 hours in combination with an aminoglycoside. In this trial, 88.5% of the adverse experiences reported were mild to moderate in severity and transient in nature. In this trial, ZOSYN was discontinued in four patients (2.6%) due to adverse experiences: thrombocytopenia and pancreatitis in one patient; fever in one patient; fever and eosinophilia in another patient; and diarrhea and elevated liver enzymes in the fourth patient.

Adverse Clinical Events: Based on patients from the North American trials (n=1063), the events with the highest incidence in patients, irrespective of relationship to ZOSYN therapy, were diarrhea (11.3%); headache (7.7%); constipation (7.7%); nausea (6.9%); insomnia (6.6%); rash (4.2%), including maculopapular, bullous, urticarial, and eczematoid; vomiting (3.3%); dyspepsia (3.3%); pruritus (3.1%); stool changes (2.4%); fever (2.4%); agitation (2.1%); pain (1.7%); moniliasis (1.6%); hypertension (1.6%); dizziness (1.4%); abdominal pain (1.3%); chest pain (1.3%); edema (1.2%); anxiety (1.2%); rhinitis (1.2%); and dyspnea (1.1%).

Based on patients in the completed study of nosocomial lower respiratory tract infections (n=155), using every-4-hour dosing and aminoglycoside therapy, the events with the highest incidence in patients, irrespective of relationship to ZOSYN and aminoglycoside therapy, were diarrhea (20%); constipation (8.4%); agitation (7.1%); nausea (5.8%); headache (4.5%); insomnia (4.5%); oral thrush (3.9%); erythematous rash (3.9%); anxiety (3.2%); fever (3.2%); pain (3.2%); pruritus (3.2%); hiccough (2.6%); vomiting (2.6%); dyspepsia (1.9%); edema (1.9%); fluid overload (1.9%); stool changes (1.9%); anorexia (1.3%); cardiac arrest (1.3%); confusion (1.3%); diaphoresis (1.3%); duodenal ulcer (1.3%); flatulence (1.3%); hypertension (1.3%); hypotension (1.3%); inflammation at injection site (1.3%); pleural effusion (1.3%); pneumothorax (1.3%); rash, not otherwise specified (1.3%); supraventricular tachycardia (1.3%); thrombophlebitis (1.3%); and urinary incontinence (1.3%).

Additional adverse systemic clinical events reported in 1.0% or less of the patients in the initial North American trials and/or in the patients administered ZOSYN 3.375 g every 4 hours plus an aminoglycoside in the nosocomial lower respiratory tract study are listed below within each body system (bracketed events occurred only in the nosocomial pneumonia trial): *Autonomic nervous system:* hypotension, ileus, syncope. *Body as a whole:* rigors, back pain, malaise, [asthenia, chest pain]. *Cardiovascular:* tachycardia, including supraventricular and ventricular; bradycardia; arrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction, [angina]. *Central nervous system:* tremor, convulsions, vertigo, [aggressive reaction (combative)]. *Gastrointestinal:* melena, flatulence, hemorrhage, gastritis, hiccough, ulcerative stomatitis, [fecal incontinence, gastric ulcer, pancreatitis]. Pseudomembranous colitis was reported in one patient during the clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See **WARNINGS**.) *Hearing and vestibular system:* tinnitus, [deafness, earache]. *Hypersensitivity:* anaphylaxis. *Metabolic and Nutritional:* symptomatic hypoglycemia, thirst, [gout, vitamin B_1, deficiency anemia]. *Musculoskeletal:* myalgia, arthralgia. *Platelets, Bleeding, Clotting:* mesenteric embolism, purpura, epistaxis, pulmonary embolism, [ecchymosis, hemoptysis] (See **PRECAUTIONS—General**). *Psychiatric:* confusion, hallucination, depression. *Reproductive, Female:* leukorrhea, vaginitis, [perineal irritation/pain]. *Reproductive, Male:* [balanoposthitis]. *Respiratory:* pharyngitis, pulmonary edema, bronchospasm, coughing, [atelectasis, dyspnea, hypoxia]. *Skin and Appendages:* genital pruritus, diaphoresis, [conjunctivitis, xerosis]. *Special senses:* taste perversion. *Urinary:* retention, dysuria, oliguria, hematuria, incontinence, [urinary tract infection with trichomonas, yeast in urine]. *Vision:* photophobia. *Vascular (extracardiac):* flushing, [cerebrovascular accident].

Additional adverse events reported from worldwide marketing experience with ZOSYN, where causal relationship to ZOSYN is uncertain: *Gastrointestinal:* hepatitis, cholestatic jaundice. *Hematologic:* hemolytic anemia. *Renal:* rarely, interstitial nephritis. *Skin and Appendages:* erythema multiforme and Stevens-Johnson syndrome, rarely reported.

Adverse Laboratory Events (Seen During Clinical Trials): Of the studies reported, including that of nosocomial lower respiratory tract infections in which a higher dose of ZOSYN was used in combination with an aminoglycoside, changes in laboratory parameters, without regard to drug relationship, include: *Hematologic:* decreases in hemoglobin and hematocrit, thrombocytopenia, increases in platelet count, eosinophilia, leukopenia, neutropenia. The leukopenia/neutropenia appears to be reversible and most frequently associated with prolonged administration, i.e., ≥21 days of therapy. These patients were withdrawn from therapy; some had accompanying systemic symptoms (e.g., fever, rigors, chills). *Coagulation:* positive direct Coombs' test, prolonged prothrombin time, prolonged partial thromboplastin time. *Hepatic:* transient elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin. *Renal:* increases in serum creatinine, blood urea nitrogen. *Urinalysis:* proteinuria, hematuria, pyuria.

Additional laboratory events include abnormalities in electrolytes (i.e., increases and decreases in sodium, potassium, and calcium), hyperglycemia, decreases in total protein or albumin.

The following adverse reaction has also been reported for PIPRACIL® (sterile piperacillin sodium): *Skeletal:* prolonged muscle relaxation (See **PRECAUTIONS—Drug Interactions**.)

OVERDOSAGE

Information on overdosage of ZOSYN in humans is not available.

Excessive serum levels of either piperacillin or tazobactam may be reduced by hemodialysis. No specific antidote is known. As with other penicillins, neuromuscular excitability or convulsions have occurred following large intravenous doses, primarily in patients with impaired renal function.

In the case of motor excitability or convulsions, general supportive measures, including administration of anticonvulsive agents (e.g., diazepam or barbiturates) may be considered.

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This Brief Summary is based on ZOSYN direction circulars CI 4630-2 and CI 4813-1 (Revised March 25, 1999).

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