

Ponstan® 
Erfa Canada Inc.
Mefenamic Acid
Analgesic

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Pharmacology: Mefenamic acid, an anthranilic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID) with demonstrated anti-inflammatory, analgesic and antipyretic activity in laboratory animals. Its mode of action is not completely understood, but may be related to prostaglandin synthetase inhibition. In animal studies the drug was found to inhibit prostaglandin synthesis and to compete for binding at the prostaglandin receptor site.

Pharmacokinetics: Mefenamic acid appears to be rapidly absorbed from the gastrointestinal tract following oral administration to humans. Peak plasma levels were reached 1 to 2 hours after the administration of two 250 mg capsules; the C_{max} of free mefenamic acid was 3.5 µg/mL and the half-life in plasma about 3 to 4 hours.

Following a single 1000 mg oral dose, peak plasma levels of 10 µg/mL occurred in 2 to 4 hours, with a half-life of 2 hours. Following multiple doses, plasma levels are proportional to dose with no evidence of drug accumulation. Repeated administration of mefenamic acid (250 mg capsules q.i.d.) yielded peak plasma levels of 3.7 to 6.7 µg/mL within 1 to 2.5 hours after administration of each dose.

Mefenamic acid has 2 distinct metabolic products, namely a hydroxymethyl and a carboxy derivative, both have been identified in both plasma and urine. The parent drug and the metabolites are conjugated with glucuronic acid and excreted primarily in the urine but to a lesser extent also in the feces.

Following a single dose, 67% of the total dose is excreted in the urine as unchanged drug or as 1 of 2 metabolites. Twenty to twenty-five per cent of the dose is excreted in the feces during the first 3 days.

In controlled, double-blind, clinical trials, mefenamic acid was evaluated for the treatment of primary spasmodic dysmenorrhea. The parameters used in determining efficacy included pain assessment by both patient and investigator; the need for concurrent analgesic medication; and evaluation of change in frequency and severity of symptoms characteristic of spasmodic dysmenorrhea. Patients received either mefenamic acid 500 mg (2 capsules) as an initial dose and 250 mg every 6 hours, or placebo at onset of bleeding or of pain, whichever began first. After 3 menstrual cycles, patients were crossed over to the alternate treatment for an additional 3 cycles. Mefenamic acid was significantly superior to placebo in all parameters, and both treatments (drug and placebo) were equally tolerated.

Indications: For the relief of pain of moderate severity in conditions such as muscular aches

and pains, primary dysmenorrhea, headaches and dental pain.

Contraindications: In patients who have previously exhibited hypersensitivity to it.

Because the potential exists for cross-sensitivity to ASA or other nonsteroidal anti-inflammatory drugs, mefenamic acid should not be given to patients in whom these drugs induce symptoms of bronchospasm, allergic rhinitis, or urticaria.

Mefenamic acid is contraindicated in patients with active ulceration or chronic inflammation of the upper or lower gastrointestinal tract.

Mefenamic acid should be avoided in patients with pre-existing renal disease.

Warnings: If diarrhea occurs, the dosage should be reduced or temporarily suspended (see Adverse Effects and Dosage). Certain patients who develop diarrhea may be unable to tolerate the drug because of recurrence of the symptoms on subsequent exposure.

Risk of Gastrointestinal Ulceration, Bleeding and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous gastrointestinal tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper gastrointestinal ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for 1 year.

Physicians should inform patients about the signs and/or symptoms of serious gastrointestinal toxicity and what steps to take if they occur. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious gastrointestinal 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 other individuals and most spontaneous reports of fatal gastrointestinal events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. 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 gastrointestinal toxicity.

Precautions: If rash occurs, the drug should be promptly discontinued.

A false-positive reaction for urinary bile, using the diazo tablet test, may result after mefenamic acid administration. If biliuria is suspected, other diagnostic procedures, such as the Harrison spot test, should be performed.

In chronic animal toxicity studies mefenamic acid at 7 to 28 times the recommended human dose, caused minor microscopic renal papillary necrosis in rats, edema and blunting of the renal papilla in dogs, and renal papillary edema in monkeys. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria and occasionally nephrotic syndrome. A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and the elderly.

Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. In normal human volunteers, BUN levels were slightly elevated following the prolonged administration of mefenamic acid at greater than therapeutic doses. Since mefenamic acid is eliminated primarily through the kidneys, it should not be administered to patients with significantly impaired renal function.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver function tests may occur. These abnormalities may remain essentially unchanged, or may be transient with continued therapy. Meaningful (3 times the upper limit of normal) elevations of ALT or AST occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of development of more severe hepatic reaction while on therapy with mefenamic acid. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), mefenamic acid should be discontinued.

Mefenamic acid may prolong ASA induced gastrointestinal bleeding. However, mefenamic acid itself appears to be less liable than ASA to cause gastrointestinal bleeding.

Mefenamic acid 500 mg and ASA 650 mg 4 times a day both caused significant further lowering of the prothrombin concentration (mefenamic acid 3.48% and ASA 2.75%) in patients in whom the concentration had been initially lowered by anticoagulant therapy. Caution, therefore, should be exercised in administering mefenamic acid to patients on anticoagulant therapy and should not be given when prothrombin concentration is in the range of 10 to 20% normal. Careful monitoring of blood coagulation factors is recommended.

It is recommended that estimations of hemoglobin and blood counts be carried out at regular intervals.

Mefenamic acid should be used with caution in known asthmatics.

Information to Be Provided to the Patient: Patients should be informed about the signs and/or symptoms of serious gastrointestinal toxicity and what steps to take if they occur. Patients should be advised that if diarrhea, other digestive problems or a skin rash arise, they should stop taking the drug promptly and consult their physician. Patients in whom ASA or other nonsteroidal anti-inflammatory drugs induce symptoms of bronchospasm, allergic rhinitis, or urticaria should be aware of potential cross-sensitivity to mefenamic acid. Women on mefenamic acid therapy should consult their physician if they decide to become pregnant.

Pregnancy: There are 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 only if clearly needed. The use of mefenamic acid in late pregnancy is not recommended because of the effects on the fetal cardiovascular system of drugs of this class.

Lactation: Trace amounts of mefenamic acid may be present in breast milk and transmitted to the nursing infant; thus mefenamic acid should not be taken by the nursing mother because of the effects of this class of drugs on the infant cardiovascular system.

Children: Safety and effectiveness in children below the age of 14 have not been established.
Geriatrics: Impairment of renal function, sometimes leading to acute renal failure, has been reported. Elderly or debilitated patients seem unable to tolerate ulceration or bleeding as well as some other individuals; most spontaneous reports of fatal gastrointestinal events are in this population (see Warnings).

Drug Interactions: Protein-bound Drugs: Because mefenamic acid is highly protein bound, it could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants, hydantoins, salicylates, sulfonamides and

sulfonylureas. Patients receiving mefenamic acid with any of these drugs should be observed for adverse effects.

Anticoagulants and Thrombolytic Agents: Mefenamic acid may prolong prothrombin time. Therefore when the drug is administered to patients receiving oral anticoagulant therapy, frequent monitoring of prothrombin time is necessary. In addition, the ulcerogenic potential of mefenamic acid and the effect of the drug on platelet function may further contribute to the hazard of concomitant therapy with any anticoagulant or thrombolytic agent (e.g., streptokinase).

Lithium: NSAIDs, including mefenamic acid have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when mefenamic acid and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

Adverse Effects: The most frequently reported adverse reactions associated with the use of mefenamic acid involve the gastrointestinal tract. In controlled studies for up to 8 months, the following disturbances were reported in decreasing order of frequency: diarrhea (approximately 5% of patients), nausea with or without vomiting, other gastrointestinal symptoms and abdominal pain. In certain patients, the diarrhea was of sufficient severity to require discontinuation of medication. The occurrence of the diarrhea is usually dose related, generally subsides on reduction of dosage and rapidly disappears on termination of therapy. Other gastrointestinal reactions less frequently reported were anorexia, pyrosis, flatulence, constipation, enterocolitis, colitis, steatorrhea, cholestatic jaundice, hepatitis, pancreatitis, hepatorenal syndrome and mild hepatic toxicity.

Gastrointestinal ulceration with or without hemorrhage has been reported.

Hematopoietic: Cases of autoimmune hemolytic anemia have been associated with continuous administration of NSAIDs, including mefenamic acid, for 12 months or longer. In such cases the Coombs' test results are positive, with evidence of both accelerated RBC production and RBC destruction. The process is reversible upon termination of mefenamic administration.

Decreases in hematocrit have been noted in 2 to 5% of patients and primarily in those who have received prolonged therapy.

Leukopenia, eosinophilia, thrombocytopenic purpura, agranulocytosis, pancytopenia, bone marrow hypoplasia and aplastic anemia have also been reported on occasion with NSAID treatment.

CNS: Dizziness, drowsiness, blurred vision, convulsions, insomnia, nervousness and headache have occurred.

Integumentary: Urticaria, rash, facial edema, angioedema, edema of the larynx, Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis), erythema multiforme and perspiration have been reported.

Renal: As with other nonsteroidal anti-inflammatory agents, renal failure, including papillary necrosis, has been reported. In elderly patients renal failure has occurred after taking mefenamic acid for 2 to 6 weeks. The renal damage may not be completely reversible.

Hematuria, dysuria and hyponatremia have also been reported with mefenamic acid.

Body as a Whole: anaphylaxis.

Special Senses: eye irritation, ear pain, reversible loss of color vision.

Other: glucose intolerance in diabetic patients, hypotension, asthma, palpitation, dyspnea. Mild hepatic toxicity and increased need for insulin in a diabetic patient have been reported.

Overdose: Symptoms and Treatment: Although doses up to 6 000 mg/day have been given, no specific information is available on the management of acute massive overdosage. Should accidental overdosage occur, the stomach should be emptied by inducing emesis or by careful gastric lavage followed by the administration of activated charcoal. Laboratory studies indicate that mefenamic acid should be adsorbed from the gastrointestinal tract by activated charcoal. Vital functions should be monitored and supported. Because mefenamic acid and its metabolites are firmly bound to plasma proteins, hemodialysis and peritoneal dialysis may be of

little value.

Seizures, acute renal failure, and coma have been reported with mefenamic acid overdoses. Overdose has led to fatalities.

Dosage: Administration is by the oral route, preferably with food.

The recommended regimen in acute pain for adults and children over 14 years of age is 500 mg as an initial dose followed by 250 mg every 6 hours as needed, usually not to exceed 1 week.

For the treatment of primary dysmenorrhea, the recommended dosage is 500 mg as an initial dose followed by 250 mg every 6 hours, starting with the onset of bleeding and associated symptoms. Clinical studies indicate that effective treatment can be initiated with the start of menses and should not be necessary for more than 2 to 3 days.

Supplied: Each Coni-snap capsule with an ivory opaque body and an aqua blue opaque cap contains: mefenamic acid 250 mg. Nonmedicinal ingredients: gelatin, lactose and sodium lauryl sulfate. Capsule shell: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, silicon dioxide, sodium lauryl sulfate and titanium dioxide. Energy: 2.5 kJ (0.6 kcal). Sodium: <1 mmol (0.1 mg). Gluten-, paraben-, sulfite- and tartrazine-free. Bottles of 100 and 500. Store at controlled room temperature, 15 to 30°C.

(Shown in Product Identification Section)

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