DICYCLOMINE HYDROCHLORIDE - dicyclomine  tablet

DESCRIPTION
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CLINICAL PHARMACOLOGY
CLINICAL PHARMACOLOGYDicyclomine relieves smooth muscle spasm of the gastrointestinal tract. Animal studies indicate that this action is achieved via an dual mechanism: (1) a specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites with approximately 1/8 themilligram potency of atropine (in vitro, guinea pig ileum); and (2) a direct effect upon smooth muscle (musculotropic) as evidenced by dicyclomine's antagonism of bradykinin- and histamine-induced spasms of the isolated guinea pig ileum. Atropine did not affect responses to these two agonists. In vivo studies in cats and dogs showed dicyclomine to be equally potent against acetylcholine (ACh)- or barium chloride (BaCl2)-induced intestinal spasm while atropine was at least 200 times more potent against effects of ACh than BaCl2. Tests for mydriatic effects in mice showed that dicyclomine was approximately 1/500 as potent as atropine; atisialagougetests in rabbits showed dicyclomine to be 1/300 as potent as atropine. In man, dicyclomine is rapidly absorbed after oral administration, reaching peak values within 60-90 minutes. The principal route of elimination is via the urine (79.5% of the dose). Excretion also occurs in the feces, but to a lesser extent (8.4%). Mean half-life of plasma elimination in one study was determined to be approximately 1.8 hours when plasma concentrations were measured for 9 hours after a single dose. In subsequent studies, plasma concentrations were followed for up to 24 hours after a single dose, showing asendary phase of elimination with a somewhat longer half-life. Mean volume of distribution for a 20 mg oral dose is approximately 3.6 L/kg suggesting extensive distribution in tissues. In controlled clinical trials involving over 100 patients who received drug, 82% of patients treated for functional bowel/irritable bowel syndrome with dicyclomine hydrochloride at initial doses of 160 mg daily (40 mg q.i.d.) demonstrated a favorable clinical response compared with 55% treated with placebo. (P<.05). In these trials, most of the side effects were typically anticholinergic in nature (see table) and were reported by 61% of the patients. Dicyclomine Hydrochloride Side (40 mg q.i.d.) Placebo Effect % % Dry Mouth 33 5 Dizziness 29 2 Blurred Vision 27 2 Nausea 14 6 Light-Headedness 11 3 Drowsiness 9 1 Weakness 7 1 Nervousness 6 2 Nine percent (9%) of patients were discontinued from the drug because of one or more of these side effects (compared with 2% in the placebo group). In 41% of the patients with side effects, side effects disappeared or were tolerated at the 160 mg daily dose without reduction. A dose reduction from 160 mg daily to an average daily dose of 90 mg was required in 46% of the patients who withdrew from the study because of a favorable clinical response; their side effects either disappeared or were tolerated. (See

ADVERSE REACTIONS
ADVERSE REACTIONS, INDICATIONS AND USAGEFor the treatment of functional bowel/irritable bowel syndrome. page 2 of 4

CONTRAINDICATIONS
CONTRAINDICATIONS1. Obstructive uropathy2. Obstructive disease of the gastrointestinal tract3. Severe ulcerative colitis (See

PRECAUTIONS
PRECAUTIONS)4. Reflux esophagitis5. Unstable cardiovascular status in acute hemorrhage6. Glaucoma7. Myasthenia gravis8. Evidence of prior hypersensitivity to dicyclomine hydrochloride or other ingredients of these formulations9. Infants less than 6 months of age (See

WARNINGS AND PRECAUTIONS
Information for Patients: Dicyclomine hydrochloride may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or to perform hazardous work while taking this drug.

WARNINGS
In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). If symptoms occur, the drug should be discontinued and supportive measures instituted. Diaphoresis may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with this drug would be inappropriate and possibly harmful. Dicyclomine hydrochloride may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. Psychosis has been reported in sensitive individuals given anticholinergic drugs. CNS symptoms include confusion, disorientation, short-term memory loss, hallucinations, dysarthria, ataxia, coma, euphoria, decreased anxiety, fatigue, insomnia, agitation and mannerisms, and inappropriate affect. These CNS signs and symptoms
usually resolve within 12 to 24 hours after discontinuation of the drug. DICYCLOMINE IS CONTRAINDICATED IN INFANTS LESS THAN 6 MONTHS OF AGE AND IN NURSING MOTHERS. (See CONTRAINDICATIONS and PRECAUTIONS: Nursing Mothers and Pediatric Use). Safety and efficacy of dicyclomine hydrochloride in children have not been established.

INFORMATION FOR PATIENTS
Information for Patients.10.

NURSING MOTHERS
Nursing Mothers (See WARNINGS and PRECAUTIONS: Information for Patients.)WARNINGSIn the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). If symptoms occur, the drug should be discontinued and supportive measures instituted. Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with this drug would be inappropriate and possibly harmful. Dicyclomine hydrochloride may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. Psychosis has been reported in sensitive individuals given anticholinergic drugs. CNS signs and symptoms include confusion, disorientation, short-term memory loss, hallucinations, dystarthritis, ataxia, coma, euphoria, decreased anxiety, fatigue, insomnia, agitation and mannerisms, and inappropriate affect. These CNS signs and symptoms usually resolve within 12 to 24 hours after discontinuation of the drug. DICYCLOMINE IS CONTRAINDICATED IN INFANTS LESS THAN 6 MONTHS OF AGE AND IN NURSING MOTHERS. (See CONTRAINDICATIONS and PRECAUTIONS: Nursing Mothers and Pediatric Use.) In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). If symptoms occur, the drug should be discontinued and a physician contacted.

PEDIATRIC USE
Pediatric Use. Safety and efficacy of dicyclomine hydrochloride in children have not been established. PRECAUTIONSGeneral: Use with caution in patients with: 1. Autonomic neuropathy2. Hepatic or renal disease3. Ulcerative colitis - large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon (see CONTRAINDICATIONS)4. Hyperthyroidism5. Hypertension6. Coronary heart disease. Congestive heart failure 8. Cardiac tachyarrhythmia 9. Hiatal hernia (see CONTRAINDICATIONS: reflux esophagitis)10. Known or suspected prostatic hypertrophy. Investigate any tachycardia before administration of dicyclomine hydrochloride, since it may increase the heart rate. With OVERDOSAGE overdosage, a curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis). Information for Patients: Dicyclomine hydrochloride may produce drowsiness or blurred vision. The patient should be warned not to engage in activities requiring mental alertness, such as operating a motor vehicle or other machinery or to perform hazardous work while taking this drug. Dicyclomine hydrochloride is contraindicated in infants less than 6 months of age and in nursing mothers. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Nursing Mothers and Pediatric Use.) Investigation any tachycardia before administration of dicyclomine hydrochloride, since it may increase the heart rate. With DRUG INTERACTIONS Drug Interactions: The following agents may increase certain actions or side effects of anticholinergic drugs: amantadine, antiarrhythmic agents of class I (e.g., quinidine), antihistamines, antipsychotic agents (e.g., phenothiazines), benzodiazepines, MAO page 3 of 4 inhibitors, narcotic analgesics (e.g., meperidine), nitrites and nitrates, sympathomimetic agents, tricyclic antidepressants, and other drugs having anticholinergic activity. Anticholinergics antagonize the effects of antiglaucoma agents. Anticholinergic drugs in the presence of increased intraocular pressure may be hazardous when taken concurrently with agents such as corticosteroids. (See also CONTRAINDICATIONS.) Anticholinergic agents may affect gastrointestinal absorption of various drugs, such as slowly dissolving dosage forms of digoxin; increased serum digoxin concentrations may result. Anticholinergic drugs may antagonize the effects of drugs that alter gastrointestinal motility, such as metoclopramide. Because antacids may interfere with the absorption of anticholinergic agents, simultaneous use of these drugs should be avoided. The inhibiting effects of anticholinergic drugs on gastric hydrochloric acid secretion are antagonized by agents used to treat chlorhydria and those used to test gastric secretion. Carcinogenesis, Mutagenesis, Impairment of Fertility: There are no known human data on long-term potential for carcinogenicity or mutagenicity. Long-term studies in animals to determine carcinogenic potential are not known to have been conducted. In studies in rats at doses of up to 100 mg/kg/day, dicyclomine hydrochloride produced no deleterious effects on breeding, conception, or parturition.

PREGNANCY
Teratogenic Effects: Pregnancy Category B Reproduction studies have been performed in rats and rabbits at doses up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of impaired fertility or harm to the fetus due to dicyclomine. Epidemiologic studies in pregnant women with products containing dicyclomine hydrochloride (at doses up to 40 mg/day) have not shown that dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg/
day). Because animal reproduction studies are not always predictive of human response, dicyclomine hydrochloride as indicated for functional bowel/irritable bowel syndrome should be used during pregnancy only if clearly needed.

TERATOGENIC EFFECTS
Teratogenic Effects: Pregnancy Category B.Reproduction studies have been performed in rats and rabbits at doses up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of impaired fertility or harm to the fetus due to dicyclomine. Epidemiologicstudies in pregnant women with products containing dicyclomine hydrochloride (at doses up to 40 mg/day) have not shown that dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg/day). Because animal reproductionstudies are not always predictive of human response, dicyclomine hydrochloride as indicated for functional bowel/irritable bowelsyndrome should be used during pregnancy only if clearly needed.

Nursing Mothers: Since dicyclomine hydrochloride has been reported to be excreted in human milk, DICYCLOMINEHYDROCHLORIDE IS CONTRAINDICATED IN NURSING MOTHERS. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Pediatric Use and ADVERSE REACTIONS.) Pediatric Use: (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Nursing Mothers.) DICYCLOMINEHYDROCHLORIDE IS CONTRAINDICATED IN INFANTS LESS THAN 6 MONTHS OF AGE. Safety and effectiveness in pediatric patients have not been established. ADVERSE REACTIONS Controlled clinical trials have provided frequency information for reported adverse effects of dicyclomine hydrochloride listed in adecrasing order of frequency. (See CLINICAL PHARMACOLOGY.) Not all of the following adverse reactions have been reported with dicyclomine hydrochloride. Adverse reactions are included herethat have been reported for pharmacologically similar drugs with anticholinergic/antispasmodic action. Gastrointestinal: dry mouth, nausea, vomiting, constipation, bloated feeling, abdominal pain, taste loss, anorexia Central Nervous System: dizziness, light-headedness, tingling, headache, drowsiness, weakness, nervousness, numbness, mental confusion and/or excitement (especially in elderly persons), dyskinesia, lethargy, syncope, speech disturbance, insomnia Ophthalmologic: blurred vision, diplopia, mydriasis, cycloplegia, increased ocular tension Dermatologic/Allergic: rash, urticaria, itching, and other dermal manifestations; severe allergic reaction or drug idiosyncrasies including anaphylaxis Genitourinary: urinary hesitancy, urinary retention Cardiovascular: tachycardia, palpitations Respiratory: Dyspnea, apnea, asphyxia (see WARNINGS) Other: decreased sweating, nasal stuffiness or congestion, sneezing, throat congestion, impotence, suppression of lactation (see PRECAUTIONS: Nursing Mothers)

DRUG ABUSE AND DEPENDENCE
Abuse and/or dependence on dicyclomine for anticholinergic effects have been rarely reported.

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DEPENDENCE
DEPENDENCE Abuse and/or dependence on dicyclomine for anticholinergic effects have been rarely reported. OVERDOSAGE: Signs and Symptoms: The signs and symptoms of overdosage are headache; nausea; vomiting; blurred vision; dilated pupils; hot, dry skin; dizziness; dryness of the mouth; difficulty in swallowing; and CNS stimulation. A curare-like action may occur (i.e., neuromuscular blockade leading to muscular weakness and possible paralysis). A 37-year old female reported numbness on the left side, cold fingertips, blurred vision, abdominal and flank pain, decreased appetite, dry mouth, and nervousness following ingestion of 320 mg daily (four 20 mg tablets QID) for four days. These events resolved after discontinuing the dicyclomine. Oral LD50: The acute oral LD50 of the drug is 625 mg/kg in mice. page 4 of 4 Minimum Human Lethal Dose/Maximum Human Dose Recorded: The amount of drug in a single dose that is ordinarily associated with symptoms of overdosage or that is likely to be life threatening, has not been defined. The maximum human oral doserecorded was 600 mg by mouth in a 10-month-old child and approximately 1500 mg in an adult, each of whom survived. In three of the infants who died following administration of dicyclomine hydrochloride (see WARNINGS), the blood concentrationsof drug were 200, 220, and 505 ng/mL, respectively. Dialysis: It is not known if dicyclomine hydrochloride is dialyzable. Treatment: Treatment should consist of gastric lavage, emetics, and activated charcoal. Sedatives (e.g., short-acting barbiturates, benzodiazepines) may be used for management of overt signs of excitement. If indicated, an appropriate parenteral cholinergic agent may be used as an antidote. DOSAGE AND ADMINISTRATION DOSAGE MUST BE ADJUSTED TO INDIVIDUAL PATIENT NEEDS. (See CLINICAL PHARMACOLOGY.) Adults-Oral The only oral dose clearly shown to be effective is 160 mg per day (in 4 equally divided doses). Since this dose is associated with a significant incidence of side effects, it is prudent to begin with 80 mg per day (in 4 equally divided doses). Depending upon the patient's response during the first week of therapy, the dose should be increased to 160 mg per day unless side effects limit dosageescalation. If efficacy is not achieved within 2 weeks or side effects require doses below 80 mg per day, the drug should be discontinued. Documented safety data are not available for doses above 80 mg daily for periods longer than 2 weeks.

HOW SUPPLIED
HOW SUPPLIED Dicyclomine Hydrochloride Tablets USP, 20 mg are supplied as blue, round, unscored tablets; embossed 223WW 27224 and are available in: Bottles of 100 tablets. Bottles of 1000 tablets. Unit Dose Boxes of 100 tablets. To prevent fading, avoid exposure to direct sunlight. Store at 20260-25260°C (68260-77260°F) [See USP Controlled Room Temperature]. Protect from light and
moisture. Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure. Manufactured By: Westward Pharmaceutical Corp. Eatontown, NJ 07724 Revised March 200

PACKAGE LABEL. PRINCIPAL DISPLAY PANEL
DRUG: Dicyclomine Hydrochloride
GENERIC:
DOSAGE: TABLET
ADMINISTRATION: ORAL
NDC: 49349-002-02
STRENGTH: 20 mg
COLOR: blue
SHAPE: ROUND
SCORE: No score
SIZE: 2 mm
IMPRINT: 30
QTY: 30