ANTICHOLINERGICS/ANTISPASMODICS (Systemic)

VA CLASSIFICATION (Primary/Secondary)
Anisotropine¾AU305/GA801
Atropine
Oral¾AU305/; GU201; AD900
Parenteral¾AU305/; CV300; GU201; AD900
Belladonna¾AU305/
Clidinium¾AU305/
Dicyclomine¾AU305/
Glycopyrrolate
Oral¾AU305/; GA208
Parenteral¾AU305/; CV300; GA208; AD900
Homatropine¾AU305/
Hyoscyamine
Oral¾AU305/; GU201
Parenteral¾AU305/; GU201; CV300; AD900
Mepenzolate¾AU305/
Methantheline¾AU305/; GU201
Methscopolamine¾AU305/
Pirenzepine¾AU305/
Propantheline¾AU305
Scopolamine
Oral¾AU305/; CN550; GA609 ; GU201
Parenteral¾AU305/; CV300; CN206; CN550; GA609
Rectal¾AU305
Transdermal¾CN550

Accepted

Ulcer, peptic (treatment adjunct)¾All anticholinergics included in this monograph, except dicyclomine and scopolamine hydrobromide, are FDA approved in conjunction with antacids or histamine H 2-receptor antagonists in the treatment of peptic ulcer, to reduce further gastric acid secretion and delay gastric emptying. However, the use of most anticholinergics as treatment adjunct in peptic ulcer has been replaced by the use of more effective agents. Results with anticholinergics usually are inconsistent and transient and require high doses, which result in significant side effects. 12 Atropine 99 , belladonna, clidinium, hyoscyamine, pirenzepine 100, 101, 102, 103 , and propantheline taken orally may be used rarely. Intravenous use of hyoscyamine may be indicated for prompt relief of pain in the treatment of both the moderately severe and the severe peptic ulcer. 14, 34, 36, 41, 42, 44, 45, 48, 53, 64, 67 Anisotropine, glycopyrrolate, homatropine, mepenzolate, methantheline, and methscopolamine are generally no longer used for this indication. 97

Bowel syndrome, irritable (treatment)¾Atropine 33 , belladonna 26, 104 , [clidinium] , dicyclomine 2, 37, 104 , [glycopyrrolate] , hyoscyamine 94, 104 , [propantheline] 104 , and [scopolamine] 42, 97 are indicated in the treatment of irritable bowel syndrome, mainly in patients in whom other therapy, such as sedation and/or change in diet, has failed. However, results usually are inconsistent and transient and

require high doses, which result in significant side effects. Anisotropine, mepenzolate, methantheline, methscopolamine, and pirenzepine are generally no longer used for this indication. 97

Urologic disorders, symptoms of (treatment)¾Oral hyoscyamine is indicated to control hypermotility in cystitis. 42 However, results of anticholinergic treatment usually are inconsistent and transient and require high doses, which result in significant side effects. 97 Atropine and scopolamine butylbromide are generally no longer used for this indication. 97

Urinary incontinence (treatment)¾[Propantheline] * 74, 75, 97, 105 is used in the treatment of uninhibited hypertonic neurogenic bladder to increase bladder capacity by reducing amplitude and frequency of bladder contractions. 46 Atropine and methantheline are generally no longer used for this indication. 97

Hypersecretory conditions, gastric, in anesthesia (prophylaxis)¾Parenteral glycopyrrolate is indicated as preanesthetic medication to reduce gastric acid secretion. 39, 88

Salivation and respiratory tract secretions, excessive, in anesthesia (prophylaxis)¾Oral and parenteral atropine 33, 34, 35, 89 and the parenteral forms of glycopyrrolate 39, 89 and scopolamine * 51 are indicated as antisialagogue preanesthetic medications to prevent or reduce salivation and respiratory tract secretions. Parenteral hyoscyamine is no longer used for these indications. 97

Arrhythmias, succinylcholine-induced (prophylaxis) or

Arrhythmias, surgical procedure-induced (prophylaxis)¾The parenteral form of atropine 35 is indicated as adjunct to anesthesia to prevent reflex bradycardia, sinus arrest, and hypotension induced by succinylcholine during intubation of the trachea or produced by certain surgical manipulations. 26 Parenteral scopolamine is generally no longer used for these indications.

Arrhythmias, cardiac (treatment) or

Bradycardia, sinus (treatment)¾Parenteral atropine 35 is indicated to reduce severe sinus bradycardia 83 and syncope associated with hyperactive carotid sinus reflex; and to lessen the degree of atrioventricular heart block in Type I atrioventricular (AV) conduction deficits. It is also used to treat ventricular asystole. 83, 84, 85 Parenteral atropine also is indicated as an antidote for sinus bradycardia resulting from the improper administration of a choline ester medication. 12 Parenteral hyoscyamine is generally no longer used for these indications. 97

Arrhythmias, in anesthesia (treatment) or

Arrhythmias, in surgery (treatment)¾The parenteral form of atropine is indicated to restore cardiac rate and arterial pressure when increased vagal activity has reduced pulse rate and cardiac action. Parenteral glycopyrrolate is indicated to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation. 39 Parenteral glycopyrrolate is also indicated intraoperatively to counteract drug-induced or vagal traction reflexes with the associated arrhythmias. 39 Parenteral hyoscyamine and parenteral scopolamine are generally no longer used for these indications. 97

Toxicity, cholinesterase inhibitor (prophylaxis)¾The parenteral forms of atropine 86 and glycopyrrolate 39, 92 are indicated for administration prior to or concurrently with neostigmine or pyridostigmine

during reversal of nondepolarizing neuromuscular blockade to protect against the muscarinic effects of these drugs, such as bradycardia and excessive secretions. 34, 35 Parenteral hyoscyamine is generally no longer used for this indication. 97

Toxicity, cholinesterase inhibitor (treatment)

Toxicity, muscarine (treatment) or

Toxicity, organophosphate pesticide (treatment)¾Oral and parenteral atropine 33, 35 are indicated in the treatment of poisoning from cholinesterase inhibitors such as neostigmine, pilocarpine, physostigmine, and methacholine, and in the treatment of the rapid type of mushroom (muscarine) poisoning. 12, 35 Atropine is also indicated in the treatment of poisoning caused by pesticides that are organophosphate cholinesterase inhibitors, chemical warfare, and "nerve" gases. 3, 5, 33 Parenteral hyoscyamine is generally no longer used for these indications. 97

Anesthesia, general, adjunct¾Parenteral administration of scopolamine * , in combination with morphine or meperidine, is indicated in preanesthesia to reduce excitement and produce amnesia. 12, 51 Scopolamine may also be used for opioid-induced respiratory depression. 73 Parenteral scopolamine * is also indicated in conjunction with analgesics in cardiopulmonary bypass patients who cannot be deeply anesthetized because of the risk of severe hypotension or circulatory collapse. 51

Motion sickness (prophylaxis and treatment)¾Transdermal scopolamine is indicated for prophylaxis of nausea and vomiting associated with motion sickness. 50, 73, 90, 95

Pneumonitis, aspiration (prophylaxis)¾Parenteral glycopyrrolate may provide some protection against aspiration of gastric contents during anesthesia. 6, 39

[Salivation, excessive, postsurgical (prophylaxis)] * or

[Salivation, excessive, medical condition-related (prophylaxis)] *¾Transdermal scopolamine is used for short-term control of drooling in postsurgical patients and in patients with goiter or other medical conditions in whom excessive salivation becomes a social problem. 11, 15, 72

[Salivation, excessive, in dental procedures (prophylaxis)] *¾The oral forms of atropine 97 , glycopyrrolate 98, 106 , methantheline 1, 97, 106 , and propantheline 98, 106 are used to control excessive salivation that interferes with dental procedures. 1, 13 Belladonna is generally no longer used for this indication.

Anticholinergics/antispasmodics listed below are FDA (U.S.) and HPB (Canada) approved for the following indications; however, they generally have been replaced by more effective agents¾· Biliary tract disorders (treatment adjunct)¾Atropine, hyoscyamine, and scopolamine butylbromide. 97

· Radiography, gastrointestinal, adjunct¾Parenteral atropine and parenteral hyoscyamine. 97

· Dysmenorrhea (treatment)¾Belladonna and scopolamine butylbromide. 76

· Enuresis, nocturnal (treatment)¾Belladonna and scopolamine butylbromide. 76

· Rhinitis, allergic, severe (treatment)¾Oral hyoscyamine. 76

Anticholinergics/antispasmodics listed below have been used for the following indications; however, they generally have been replaced by more effective agents¾· [Diarrhea (treatment)] *¾Glycopyrrolate. 76

· [Parkinsonism (treatment)] *¾Oral atropine, belladonna, parenteral hyoscyamine, oral hyoscyamine and scopolamine combination, and oral scopolamine. 12, 26, 42

Precautions to Consider

Cross-sensitivity and/or related problems

For all anticholinergics¾Patients sensitive to one belladonna alkaloid or derivative may be sensitive to the other belladonna alkaloids or derivatives also.

Pregnancy/Reproduction

Pregnancy¾For anistropine methylbromide¾ Problems in humans have not been documented. 31

FDA pregnancy category not currently included in product labeling.

For atropine¾ Atropine crosses the placenta. Well-controlled studies in humans have not been done. Intravenous administration of atropine during pregnancy or near term may produce tachycardia in the fetus.

Studies in mice have not shown that atropine given in doses of 50 mg per kg of body weight (mg/kg) has adverse effects on the fetus.

FDA Pregnancy Category C. 34

For belladonna¾ Belladonna crosses the placenta. Studies with belladonna have not been done in either animals or humans.

FDA Pregnancy Category C.

For clidinium¾ Adequate and well-controlled studies in humans have not been done.

Reproduction studies in rats have not shown that clidinium has adverse effects on the fetus. 1, 36

FDA pregnancy category not currently included in product labeling.

For dicyclomine¾ Dicyclomine has been associated in several isolated cases with human malformations; however, in retrospective studies there has been no evidence of dicyclomine having any untoward effect on the embryo.

FDA pregnancy category not currently included in product labeling.

For glycopyrrolate¾ Controlled studies in humans have not been done.

Studies in rats and rabbits have not shown that glycopyrrolate causes teratogenic effects. 39 However, studies in rats have shown that rates of conception and of survival at weaning decreased in a dose-

related manner with glycopyrrolate. Studies in dogs with high doses of glycopyrrolate suggest that this may be caused by a decrease in seminal secretion. 39

FDA Pregnancy Category B. 39

For hyoscyamine¾ Hyoscyamine crosses the placenta. Studies with hyoscyamine have not been done in either animals or humans. 42 Intravenous administration of hyoscyamine during pregnancy, especially near term, may produce tachycardia in the fetus.

FDA Pregnancy Category C.

For mepenzolate¾ Adequate and well-controlled studies in humans have not been done.

Reproduction studies in rats and rabbits have not shown that mepenzolate has adverse effects on the fetus. 1, 45

FDA pregnancy category not currently included in product labeling.

For propantheline¾ Studies have not been done in either animals or humans.

FDA Pregnancy Category C. 49

For scopolamine¾ Scopolamine crosses the placenta. Studies with scopolamine have not been done in either animals or humans.

FDA Pregnancy Category C.Labor¾For scopolamine: Parenteral administration of scopolamine before the onset of labor may cause CNS depression in the neonate and may contribute to neonatal hemorrhage 108 due to reduction in vitamin K-dependent clotting factors in the neonate.

Breast-feeding

For all anticholinergics¾Anticholinergics may inhibit lactation. 36, 44

For atropine, belladonna, and hyoscyamine¾These drugs are distributed into breast milk. Although amounts have not been quantified, the chronic use of these medications should be avoided during nursing since infants are usually very sensitive to the effects of anticholinergics. 1, 18

For dicyclomine¾Although a causal relationship has not been established, the use of dicyclomine in nursing mothers is not recommended, since respiratory distress has been reported in infants less than 3 months of age who ingested dicyclomine directly (not through breast milk). 1, 18

For quaternary ammonium compounds¾It is unlikely that these drugs are excreted in breast milk since they are incompletely absorbed from the gastrointestinal tract and have poor lipid solubility. 18

Pediatrics

For all anticholinergics¾ Infants and young children are especially susceptible to the toxic effects of anticholinergics.

Close supervision is recommended for infants and children with spastic paralysis or brain damage since an increased response to anticholinergics has been reported in these patients and dosage adjustments are often required.

When anticholinergics are given to children where the environmental temperature is high, there is risk of a rapid increase in body temperature because of these medications" suppression of sweat gland activity.

A paradoxical reaction characterized by hyperexcitability may occur in children taking large doses of anticholinergics.

For dicyclomine¾ Respiratory symptoms, such as difficulty in breathing, shortness of breath, respiratory collapse and apnea; as well as seizures, syncope, asphyxia, pulse rate fluctuations, muscular hypotonia, and coma have been reported in some infants, 3 months old and under, with the use of dicyclomine syrup. These side effects occurred within minutes of ingestion and lasted 20 to 30 minutes. They are believed to have been caused by local irritation and/or aspiration rather than by a direct pharmacologic action.

Geriatrics

Geriatric patients may respond to usual doses of anticholinergics with excitement, agitation, drowsiness, or confusion.

Geriatric patients are especially susceptible to the anticholinergic side effects, such as constipation, dryness of mouth, and urinary retention (especially in males). If these side effects occur and continue or are severe, medication should probably be discontinued.

Caution is also recommended when anticholinergics are given to geriatric patients, because of the danger of precipitating undiagnosed glaucoma.

Memory may become severely impaired in geriatric patients, especially those who already have memory problems, with the continued use of anticholinergics since these drugs block the actions of acetylcholine, which is responsible for many functions of the brain, including memory functions. 16, 17, 18, 19

Dental

Prolonged use of anticholinergics may decrease or inhibit salivary flow, thus contributing to the development of caries, periodontal disease, oral candidiasis, and discomfort. 1

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Only specific interactions between anticholinergics and other oral medications have been identified in this monograph. However, because of decreased gastrointestinal motility and delayed gastric emptying, absorption of other oral medications may be decreased during concurrent use with anticholinergics. 31

For all anticholinergics

Alkalizers, urinary, such as: 32

Antacids, calcium- and/or magnesium-containing

Carbonic anhydrase inhibitors

Citrates

Sodium bicarbonate

(urinary excretion of anticholinergics may be delayed by alkalinization of the urine, thus potentiating the anticholinergics' therapeutic and/or side effects)

>> Antacids or

>> Antidiarrheals, adsorbent

(simultaneous use of these medications may reduce absorption of anticholinergics, resulting in decreased therapeutic effectiveness; doses of these medications should be spaced 2 or 3 hours apart from doses of anticholinergics 25, 26, 43)

>> Anticholinergics or other medications with anticholinergic activity, other (see Appendix II)

(concurrent use with anticholinergics may intensify anticholinergic effects; patients should be advised to report occurrence of gastrointestinal problems promptly since paralytic ileus may occur with concurrent therapy 24, 45)

Antimyasthenics

(concurrent use with anticholinergics may further reduce intestinal motility; therefore, caution is recommended; although atropine may be used to reduce or prevent the muscarinic effects of antimyasthenics, routine concurrent use is not recommended since the muscarinic effects may be the first signs of antimyasthenic overdose, and masking such effects with atropine may prevent early recognition of cholinergic crisis 56, 57)

>> Cyclopropane

(concurrent intravenous administration of anticholinergics with cyclopropane anesthesia may result in ventricular arrhythmias; however, if the anticholinergic used is glycopyrrolate, the risk is reduced if glycopyrrolate is given in increments of 100 mcg [0.1 mg] or less 1, 9, 39)

Haloperidol 34, 37

(antipsychotic effectiveness of haloperidol may be decreased in schizophrenic patients)

>> Ketoconazole

(anticholinergics may increase gastrointestinal pH, possibly resulting in a marked reduction in ketoconazole absorption during concurrent use with anticholinergics; patients should be advised to take these medications at least 2 hours after ketoconazole 20)

Metoclopramide

(concurrent use with anticholinergics may antagonize metoclopramide's effects on gastrointestinal motility 21, 23)

Opioid (narcotic) analgesics

(concurrent use with anticholinergics may result in increased risk of severe constipation, which may lead to paralytic ileus, and/or urinary retention 61, 62)

>> Potassium chloride, especially wax-matrix preparations

(concurrent use with anticholinergics may increase severity of potassium chloride-induced gastrointestinal lesions 13, 27, 28)

For scopolamine (in addition to interactions listed above)

>> CNS depression-producing medications, other (see Appendix II)

(concurrent use may potentiate the effects of either these medications or scopolamine, resulting in additive sedation 30)

Lorazepam, parenteral

(concurrent use of scopolamine and parenteral lorazepam is reported to have no added beneficial effect and their combined effect may increase the incidence of sedation, hallucination, and irritational behavior 58)