PRODUCT MONOGRAPH

AVA-OXYBUTYNIN

(Oxybutynin Chloride)

Tablets, USP

ANTICHOLINERGIC / ANTISPASMODIC AGENT

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THERAPEUTIC CLASSIFICATION

Anticholinergic / Antispasmodic Agent

ACTION AND CLINICAL PHARTMACOLOGY

Oxybutynin chloride is a tertiary amine anticholinergic agent which exerts anti-muscarinic as well as direct antispasmodic action on smooth muscle. In vitro studies have shown that its anticholinergic effects are weaker than those of atropine, but that it possesses greater antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or in autonomic ganglia (no antinicotinic effects).

In addition to its smooth muscle relaxing effects, oxybutynin chloride exerts an analgesic and a local anesthetic effect. In animal studies the central nervous system and cardiovascular actions of oxybutynin chloride were shown to be similar to, but weaker than, those of atropine.

Oxybutynin chloride relaxes bladder smooth muscle. In patients with uninhibited neurogenic and reflex neurogenic bladder, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination. These effects are more consistently improved in patients with uninhibited neurogenic bladder.

Oxybutynin chloride is readily absorbed from the gastrointestinal tract. The onset of action is approximately one hour after an oral dose and its duration 6 to 10 hours.

Comparative Bioavailability

A two-way, single-dose, open-label, randomized crossover bioavailability study in 18 normal male volunteers was conducted to evaluate the relative bioavailability of a 10 mg dose of AVA-OXYBUTYNIN 5 mg tablets and Ditropan® 5 mg tablets manufactured by Norwich-Eaton. The results from measured data are summarized as follows:

	Geometric Mean Arithmetic Mean (CV%)		
Parameter	Ava-Oxybutynin	Ditropan®	Ratio of Means (%)
AUC_T (ng·hr/mL)	16.78	15.96	105
	20.12 (70)	19.04 (69)	
AUC_I (ng·hr/mL)	18.17	17.46	104
	21.54 (66)	20.39 (66)	
C_{max} (ng/mL)	9.97	9.68	103
	12.16 (65)	11.55 (75)	
T_{max}* (hr)	0.58 (41)	0.50 (43)	-
$t_{1/2}$ *(hr)	1.49 (27)	1.46 (24)	-

* The T_{max} and $t_{1/2}$ parameters are expressed as the arithmetic means (CV).

INDICATIONS AND CLINICAL USE

AVA-OXYBUTYNIN (oxybutynin chloride) is indicated for the relief of symptoms associated with voiding in patients with uninhibited neurogenic and reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

AVA-OXYBUTYNIN (oxybutynin chloride) is contraindicated in patients with glaucoma, partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis, myasthenia gravis, obstructive uropathy, and when the patient has an unstable cardiovascular status in acute hemorrhage. AVA-OXYBUTYNIN is containdicated in patients who have demonstrated hypersensitivity to the product.

WARNINGS

AVA-OXYBUTYNIN (oxybutynin chloride), when administered in the presence of high environmental temperature, can cause heat prostration (fever and heat stroke due to decreased sweating).

Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In such cases, treatment with AVA-OXYBUTYNIN would be inappropriate and possibly harmful.

Oxybutynin chloride may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. Alcohol or other sedative drugs may enhance the drowsiness caused by AVA-OXYBUTYNIN.

Pretreatment examinations should include cystometry and other appropriate diagnostic procedures. Cystometry should be repeated at appropriate intervals to evaluate response to therapy. The appropriate antimicrobial therapy should be instituted in the presence of infection.

PRECAUTIONS

AVA-OXYBUTYNIN (oxybutynin chloride) should be used with caution in the elderly and in patients with autonomic neuropathy, hepatic or renal disease. Administration of oxybutynin chloride in large doses to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

The symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension and prostatic hypertrophy may be aggravated following administration of oxybutynin chloride. AVA-OXYBUTYNIN should be administered with caution to patients with hiatal hernia associated with reflux esophagitis, since anticholinergic drugs may aggravate this condition.

Use in Pregnancy

The safety of oxybutynin chloride in pregnancy has not been established. Therefore, oxybutynin chloride should not be used in women of childbearing potential, unless, in the opinion of the physician, the expected benefit to the patient outweighs the possible risk to the fetus.

Use in Children

Because the safety of oxybutynin chloride in children under the age of five has not been established, use of the drug in this age group is not recommended.

Use in Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AVA-OXYBUTYNIN is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions have been reported with oxybutynin chloride administration: dry mouth and throat, difficulty swallowing, decreased sweating, urinary hesitance and retention, blurred vision, dilation of the pupil, cycloplegia, increased ocular tension, palpitations, tachycardia, chest pain, syncope, flushing, nose bleed, drowsiness, weakness, dizziness, headache, insomnia, mood changes, nausea, vomiting, anorexia, metallic taste, constipation, bloated feeling, edema, impotence, suppression of lactation, interference with normal heat regulation, severe allergic reactions or drug idiosyncrasies including urticaria and other dermal manifestations.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The symptoms of overdosage with AVA-OXYBUTYNIN (oxybutynin chloride) may be any of those seen with other anticholinergic agents. Symptoms may include signs of central nervous system excitation (eg., restlessness, tremor, irritability, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia, hypotension or hypertension, respiratory failure, paralysis and coma.

In the event of an overdose or exaggerated response, treatment should be symptomatic and supportive. Induce emesis or perform gastric lavage (emesis is contraindicated in precomatose, convulsive or psychotic state) and maintain respiration. Activated charcoal may be administered as well as magnesium sulphate. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication. Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.

DOSAGE AND ADMINISTRATION

AVA-OXYBUTYNIN (oxybutynin chloride) tablets are for oral administration.

Adults

The usual dose is one 5 mg tablet two to three times a day. The maximum recommended dose is one 5 mg tablet four times a day.

In elderly and debilitated patients it is advisable to initiate treatment at the lowest recommended dosage and to increase the dosage carefully according to tolerance and response.

Children Over 5 Years of Age

The usual dose is one 5 mg tablet two times a day. The maximum recommended dose is one 5 mg tablet or three times a day.

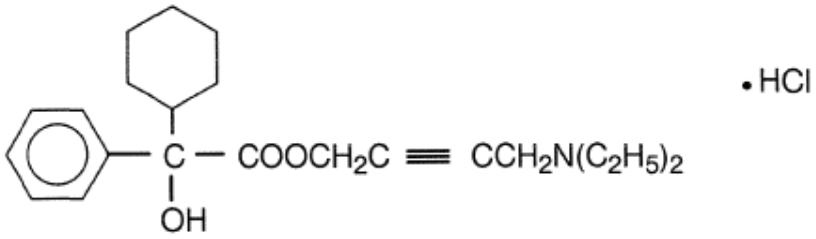
PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Oxybutynin chloride

Chemical Names:
1) Benzeneacetic acid, α-cyclohexyl-α-hydroxy-,4-(diethylamino)-2-butynyl ester hydrochloride, (±)-
2) 4-(Diethylamino)-2-butynyl (±)-α-phenylcyclohexane-glycolate hydrochloride.

Structural Formula:



Molecular Formula: $C_{22}H_{31}NO_3 \cdot HCl$

Molecular Weight: 393.95

Description: White, crystalline, practically odourless powder with a melting point of 124 to 129°C. Oxybutynin chloride is freely soluble in water and in alcohol; very soluble in methanol and in chloroform; soluble in acetone; slightly soluble in ether; very slightly soluble in hexane.

Composition

AVA-OXYBUTYNIN (oxybutynin chloride) tablets contain the following non-medicinal ingredients: lactose, magnesium stearate, microcrystalline cellulose and FD&C blue #1.

Stability and Storage Recommendations

Store at room temperature (15-30°C) in tight, light-resistant containers.

AVAILABILITY OF DOSAGE FORMS

AVA-OXYBUTYNIN (oxybutynin chloride) 5 mg tablets: each blue, biconvex, scored tablet contains 5 mg of oxybutynin chloride. Available in bottles of 100.

PHARMACOLOGY

In a series of in vitro tests, oxybutynin chloride was found to be more effective than propantheline, methantheline and atropine in inhibiting barium chloride-induced contractions in rabbit bladder detrusor muscle. It was, however, less active than the other drugs in inhibiting contractions caused by histamine and carbamylcholine.

Oxybutynin chloride was more effective than atropine in relieving morphine-induced spasm in the anesthetized dog. Atropine had a partial effect, presumably due to the musculotropic component of its action, while methscopolamine, a neurotropic compound, was ineffective.

Against neostigmine-induced spasm, oxybutynin showed about 15% of the potency of atropine. These results suggest that the major antispasmodic activity of oxybutynin chloride is musculotropic rather than neurotropic.

Oxybutynin chloride was less potent than atropine in producing mydriasis in the mouse and in inhibiting the sialogogic response in dogs.

In tests for analgesic activity, oxybutynin chloride was shown to be 35% as potent as codeine in the mouse tail-clip test and approximately equal to acetylsalicylic acid in the acetic acid stretch test. It was approximately twice as potent as lidocaine in producing local anesthesia in the rabbit cornea.

Oxybutynin chloride was less potent than atropine but similar in potency to methscopolamine in producing characteristic anticholinergic CNS effects in dogs. The cardiovascular actions of oxybutynin in the anesthetized dog were also relatively weak.

Using oxybutynin chloride doses at least seven times greater than the maximum recommended therapeutic dosage, the following results were obtained in various drug interaction tests: Dicumarol effects were potentiated; hexobarbital sleep time was not significantly affected; zoxazolamine paralysis time was not significantly affected; there were no effects on aniline or hexobarbital hydroxylation; O-demethylation of codeine was possibly inhibited; the nitro-reduction of p-aminobenzoic acid was stimulated; and oxyphenbutazone metabolism was not affected.

TOXICOLOGY

Acute Toxicity

Species	Route	LD_{50} (95% C.L.)*	Slope (95% C.L.)*
Mouse	p.o.	1550 mg/kg (1372-1751)	1.69 (1.48-1.93)
Mouse	i.p.	260 mg/kg (186-346)	2.20 (1.6-3.1)
Mouse	i.v.	40 mg/kg (36-45)	1.25 (1.1-1.4)
Rat	p.o.	1600 mg/kg (1176-2176)	1.94 (1.39-2.72)
Rat	i.p.	430 mg/kg (371-499)	1.32 (1.2-1.4)
Newborn rat	p.o.	560 mg/kg (528-594)	1.07 (0.82-1.39)
Dog	i.v.	>25 but <50 mg/kg**	
Dog	p.o.	>750 but <1000 mg/kg**	

* 95% confidence limits;
** Approximate minimum lethal dose.

Signs and symptoms of toxicity in mice and rats were exophthalmos, CNS stimulation, ataxia and convulsions. In rats receiving the drug orally, intraocular tension was increased in some animals at each dose level. Females were more susceptible to toxicity and mortality than males. In newborn rats, laboured respiration and decreased activity were the only toxic symptoms noted,

with most deaths occurring on day 2. Mydriasis, hyperventilation, ataxia, emesis, muscular weakness of hind limbs and convulsions were commonly seen in dogs.

Subacute and Chronic Toxicity

In a three-month study, 0, 50, 100 and 150 mg/kg/day of oxybutynin chloride were administered orally to groups of 20 rats. At the highest dose, mortality was approximately 50%, while at lower doses it did not differ significantly from the control rate. Other effects observed at high dosage were ataxia, depression, hypersensitivity to stimulation and pilomotor erection.

In a six-month rat study, 20-200 mg/kg/day p.o. was administered 6 days per week. At the lowest dose no significant toxic effects were observed, while rats receiving 63-200 mg/kg/day showed signs of continuous acute pharmacologic effects, decreased food consumption with suppression of weight gain, and somewhat dose-related pathological changes consisting primarily of irregular and enlarged hepatic cells and of degenerative changes in kidney tubules.

In a two-year oral study in rats, 0, 20, 80 and 160 mg/kg/day were given to 50 animals of each sex per group. No high dose and only a few mid-dose animals survived beyond 90 weeks. A dose-related reduction in weight gain was observed at all dose levels. Slight mydriasis was noted in a few rats at 20 mg/kg/day and mydriasis, tenseness, hyperactivity and excessive salivation in the higher dose groups. Serum alkaline phosphatase values for most high dose rats were slightly higher than those of controls at most intervals of analysis. Microscopic examination of the urine showed an increase in the number of red and white blood cells in mid-dose males and in the number of red cells in high dose males at termination. No other drug-related changes were observed in hematology, ophthalmologic examinations, organ weights, or gross or histopathology. Tumour incidence was similar in the control and experimental groups.

A six-month study in dogs showed no toxic effects following administration of 3 and 6 mg/kg/day of oxybutynin chloride 6 days per week, while higher doses produced anorexia, tremors and nervousness during the first four weeks. These signs of toxicity diminished during the remainder of the study and no other abnormalities were observed.

Groups of 4 male and 4 female beagle dogs received 0, 4, 8 and 16 mg/kg/day p.o. for one year. Dogs in the 16 mg/kg/day group were initiated at 4 mg/kg b.i.d. and the dose was gradually increased over 8 weeks to 8 mg/kg b.i.d. There were no mortalities. Dry oral mucous membranes and mydriasis were noted in all treated dogs. Some animals at 8 and 16 mg/kg/day had a dry nose, and at the highest dose level occasional increased activity, purulent ocular or nasal discharge, emaciation and/or dehydration were also observed. A dose-related decrease in body weight was seen at all dose levels, although food consumption did not differ significantly from control values.

Slightly microcytic normochromic erythrocytes were noted in a few treated dogs after one month only. Slight decreases in erythrocyte count, hemoglobin concentration and hematocrit values were noted in the 16 mg/kg/day group at all intervals of analysis. No other drug-related changes were seen in hematologic, biochemical or urinalysis values, in ophthalmoscopic examinations, or in electrocardiograms, and no gross or microscopic pathologic lesions or significant variations in organ weights were observed in any treated dogs.

Reproductive Studies

Twenty female rats per group were administered 0, 20 and 160 mg/kg/day orally from day 6 to 16 of gestation. Dams were sacrificed on day 20 and fetuses examined. One dam in the 20 mg/kg/day group died during the gestation period. Slight mydriasis was noted at the low dose and slight to marked mydriasis and occasional tenseness at the high dose. No drug-related effects on any fetal parameters evaluated were observed at either dose level.

The teratogenic potential of oxybutynin has also been studied in mice, hamsters and rabbits at doses of up to 180 mg/kg/day. No abnormalities were observed.

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