PRODUCT MONOGRAPH

NTP–OXYBUTYNIN

(oxybutynin chloride)

Tablets

USP

Anticholinergic/Antispasmodic Agent

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PHARMACOLOGICAL CLASSIFICATION

Anticholinergic/Antispasmodic Agent

ACTION AND CLINICAL PHARMACOLOGICAL

NTP–OXYBUTYNIN (oxybutynin chloride) is a tertiary amine anticholinergic agent which exerts antimuscarinic in addition to direct antispasmodic action on smooth muscle. Studies *in vitro* have shown that its anticholinergic effects are weaker than those of atropine, however, it possesses greater antispasmodic activity. No blocking effects occur at either skeletal neuromuscular junctions or in autonomic ganglia (no antinicotinic effects).

Oxybutynin chloride exerts an analgesic and a local anesthetic effect in addition to its smooth muscle relaxing effects. Studies conducted in animals revealed that the central nervous system and cardiovascular actions of oxybutynin were similar to but weaker than those of atropine.

Bladder smooth muscle is relaxed by oxybutynin chloride. Cystometric studies in patients with uninhibited neurogenic and reflex neurogenic bladder 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. Therefore, urgency and the frequency of both incontinent episodes and voluntary urination are decreased by oxybutynin chloride. In patients with uninhibited neurogenic bladder, these effects are more consistently improved.

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.

A single-dose, fasting comparative bioavailability study was performed on two 5 mg oxybutynin chloride products, NTP-OXYBUTYNIN 5 mg tablets and Ditropan® 5 mg tablets. The pharmacokinetic data calculated for plasma oxybutynin in the NTP-OXYBUTYNIN and Ditropan® tablet formulations is tabulated in Table 1.

Table 1

	Geometric Mean Arithmetic Mean (C.V.)		
	NTP-Oxybutynin (2 x 5 mg)	Ditropan®** (2 x 5 mg)	Percentage of Ditropan®
AUC_T (ng•hr/mL)	13.58 17.39 (86)	13.24 18.08 (61)	103
AUC_I (ng•hr/mL)	17.25 21.27 (76)	18.01 21.18 (53)	96
C_{max} (ng/mL)	7.60 10.84 (96)	7.37 10.89 (72)	103
T_{max}* (hr)	0.77 (0.03)	0.85 (0.02)	---
$T_{1/2}$* (hr)	1.53 (0.03)	1.70 (0.05)	---

*For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

**Ditropan ® manufactured by Norwich Eaton Pharmaceutical Inc.(Canada).

INDICATIONS AND CLINICAL USE

NTP–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

NTP–OXYBUTYNIN (oxybutynin chloride) is contraindicated in patients with glaucoma, partial or complete obstruction of 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.

NTP–OXYBUTYNIN is contraindicated in patients who have demonstrated hypersensitivity to the product.

WARNINGS

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

Diarrhea may be an early symptom of incomplete intestinal obstruction, particularly in patients with ileostomy or colostomy. Treatment with NTP–OXYBUTYNIN in such cases would be inappropriate and potentially harmful.

Drowsiness or blurred vision may result from use of NTP–OXYBUTYNIN. The patient should be cautioned regarding activities requiring mental alertness while taking this drug, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. The drowsiness caused by NTP–OXYBUTYNIN may be enhanced by alcohol or other sedative drugs.

Pretreatment examinations should include cystometry, and other appropriate diagnostic procedures. Cystometry should be repeated at appropriate intervals to evaluate response to treatment. In the presence of infection, the appropriate antibiotic therapy should be instituted.

PRECAUTIONS

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

Following administration of NTP–OXYBUTYNIN the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension and prostatic hypertrophy may be aggravated. NTP–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, use of NTP–OXYBUTYNIN in women of childbearing potential is not recommended, unless, in the opinion of the physician, the expected benefit to the patient outweighs the possible risk to the fetus.

Use In Children:

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

Use In Nursing Mothers:

It is not known whether oxybutynin chloride is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when NTP–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 NTP–OXYBUTYNIN (oxybutynin chloride) may be any of those seen with other anticholinergic agents. Symptoms may include signs of central nervous system excitation (e.g., 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. Induction of emesis or gastric lavage should be performed (emesis is contraindicated in precomatose, convulsive or psychotic state) and respiration should be maintained. Activated charcoal may be administered as well as magnesium sulphate. In order to reverse symptoms of anticholinergic intoxication, physostigmine may be considered.

Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.

DOSAGE AND ADMINISTRATION

Adults:

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

PHARMACEUTICAL INFORMATION

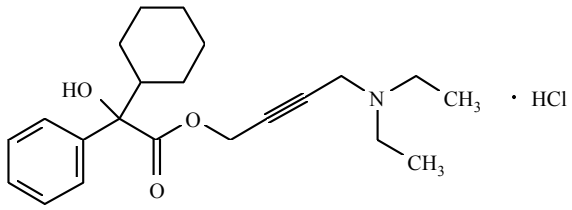
DRUG SUBSTANCE:

Trade Name: NTP–OXYBUTYNIN

Proper Name: Oxybutynin Chloride Tablets

Chemical Name: Benzeneacetic acid, a-cyclohexyl-a-hydroxy-, 4-(diethylamino)-2-butynyl ester hydrochloride, (±)-.

Structural Formula:



Molecular Formula: $C_{22}H_{31}NO_3 \bullet HCl$ Molecular Weight: 393.96

Description: Oxybutynin chloride is a white crystalline practically odorless powder. The melting range is 124°C–129°C. Freely soluble in water and alcohol, very soluble in methanol and chloroform, soluble in acetone, slightly soluble in ether, very slightly soluble in hexane.

STABILITY AND STORAGE RECOMMENDATIONS:

Store between 15°–30°C in tight, light resistant containers.

AVAILABILITY OF DOSAGE FORMS

NTP–OXYBUTYNIN (oxybutynin chloride) 5 mg is available as a blue, scored, round, tablet engraved with "N" and 5 on the scored side and plain on the other. Each tablet contains 5 mg of oxybutynin chloride. Supplied in bottles of 100 and 500 .

PHARMACOLOGY

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

In the anesthetized dog, oxybutynin chloride was more effective than atropine in relieving morphine–induced spasm. Atropine had a partial effect, presumably due to the musculotropic component of its action, while methscopolamine, a neurotropic compound, was not effective. Oxybutynin chloride showed about 15% of the potency of atropine against neostigmine–induced spasm. Results from these studies suggest that the major antispasmodic activity of oxybutynin chloride is musculotropic rather than neurotropic.

Atropine was more potent than oxybutynin chloride in producing mydriasis in the mouse and in inhibiting the sialogogic response in dogs.

Tests for analgesic activity demonstrated that oxybutynin chloride was 35% as potent as codeine in 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.

In dogs, oxybutynin chloride was less potent than atropine but similar in potency to methscopolamine in producing characteristic anticholinergic CNS effects. Studies in the anesthetized dog determined the cardiovascular actions of oxybutynin chloride to also be relatively weak.

In various drug interaction tests using oxybutynin chloride doses at least seven times greater than the maximum recommended therapeutic dosage, the following results were obtained: 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 codeine was possibly inhibited; the nitro–reduction of p–aminobenzoic acid was stimulated; and oxphenbutazone metabolism was not affected.

TOXICOLOGY

Acute Toxicity:

Species	Route	LD_{50} (mg/kg)
Mouse	p.o. i.p. i.v.	1550 260 40
Rat	p.o. i.p.	1600 430
Newborn Rat	p.o.	560

Approximate Minimum Lethal Dose

Species	Route	Approximate Minimum Lethal Dose
Dog	i.v. p.o.	>25 but <50 mg/kg >750 but <1000 mg/kg

Signs and symptoms of toxicity in mice and rats were exophthalmos, CNS stimulation, ataxia and convulsions. Intraocular tension as increased in some rats receiving the drug orally at each dose level. Females were more susceptible to toxicity and mortality than males. Labored respiration and decreased activity were the only toxic symptoms noted in newborn rats, with most deaths occurring on day 2. In dogs, mydriasis, hyperventilation, ataxia, emesis, muscular weakness of hind limbs and convulsions were commonly seen.

Sub–Acute and Chronic Toxicity:

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

In a six month study, 20–200 mg/kg/day p.o. was administered to rats 6 days per week. No significant toxic effects were observed at the lowest dose, 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, 50 animals of each sex per group were administered 0, 20, 80 and 160 mg/kg/day. No high dose and only a few mid–dose animals survived beyond 90 weeks. At all dose levels, a dose–related reduction in weight gain was observed. At 20 mg/kg/day, slight mydriasis was noted in a few rats and mydriasis, tenseness, hyperactivity and excessive salivation in the higher dose groups. In most high dose rats, serum alkaline phosphatase values were slightly higher than those of controls at most intervals of analysis. In mid–dose males, microscopic examination of the urine showed an increase in the number of red and white blood cells 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 histopathology. Tumor incidence was similar in the control and experimental groups.

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

In a one year study, groups of 4 male and 4 female beagle dogs received 0, 4, 8 and 16 mg/kg/day p.o. Animals in the 16 mg/kg/day group were initiated at 4 mg/kg bid and the dose was gradually increased over 8 weeks to 8 mg/kg bid. There were no mortalities. In all treated dogs, dry oral mucous membranes and mydriasis were noted. At the highest dose level occasional increased activity, purulent ocular or nasal discharge , emaciation and/or dehydration were observed and some animals at 8 and 16 mg/kg/day

had a dry nose. At all dose levels a dose-related decrease in body weight was seen, although food consumption did not differ significantly from control values.

After only one month, slightly microcytic normochronic erythrocytes were noted in a few treated dogs. In the 16 mg/kg/day group at all intervals of analysis, slight decreases in erythrocyte count, hemoglobin concentration and hematocrit values were noted. There were no other drug–related changes 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 observed in any treated dogs.

Reproductive Studies

From day 6 to 16 of gestation, twenty female rats per group were administered 0, 20 and 160 mg/kg/day orally. On day 20, dams were sacrificed and fetuses examined. In the 20 mg/kg/day/ group, one dam died during the gestation period. At the low dose slight mydriasis was noted and at the high dose slight to marked mydriasis and occasional tenseness were seen. There were no drug–related effects on any fetal parameters evaluated observed at either dose level.

Studies in mice, hamster and rabbits were conducted to determine the teratogenic potential of oxybutynin chloride at doses of up to 180 mg/kg/day. No abnormalities were observed.

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