PRODUCT MONOGRAPH

Pr OXYBUTYN

Oxybutynin chloride tablets 5 mg, USP

Anticholinergic - Antispasmodic agent

Valeant Canada LP
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ACTION AND CLINICAL PHARMACOLOGY:

Pharmacology:
Oxybutynin chloride is a synthetic tertiary amine which exerts a direct spasmolytic (papaverine-like) action and an antimuscarinic (atropine-like) action on smooth muscle. Oxybutynin does not appear to exhibit antinicotinic effects (i.e., block acetylcholine effects at skeletal myoneural junctions or at autonomic ganglia).

The spasmolytic effect of the drug has been demonstrated on the detrusor muscle of the bladder, the small intestine, and the colon of various animals. Unlike papaverine, however, oxybutynin appears to have little or no effect on the smooth muscle of blood vessels. (5,6)

Cystometric studies in patients with uninhibited neurogenic and reflex neurogenic bladders indicate that oxybutynin chloride increases urinary bladder capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. These effects were more evident in patients with uninhibited neurogenic bladders than in those with reflex neurogenic bladders. (3,4,5,7)

In animal studies, the drug has shown moderate antihistaminic, some local anesthetic, some mild analgesic, and very low mydriatic and antisialagogue activity. (4,6,8)

Pharmacokinetics:
Absorption: Based on animal studies, oxybutynin chloride appears to be rapidly and well absorbed from the gastrointestinal tract following oral administration. In rats, studies using radiolabeled drug indicated that peak radioactivity occurred in plasma approximately 2 hours following oral administration of the drug, and radioactivity was no longer detectable in the plasma 72 hours after administration. Plasma concentrations required for antispasmodic effects of oxybutynin chloride are unknown.

The onset of action of oxybutynin occurs within 30-60 minutes, and peak effects occur within 3-6 hours after administration. The antispasmodic action may last 6-10 hours. (3,6,8)

Distribution: No data are available on the distribution of oxybutynin into human body tissues and fluids. In rats, oxybutynin has been detected in the brain, lungs, kidneys, and liver following oral administration. (3,6,8)

Elimination: Studies in animals using radiolabeled oxybutynin indicate that the drug undergoes some

enterohepatic circulation and is excreted in urine and feces. It has been suggested that oxybutynin chloride is metabolized by the liver and excreted principally in urine. (2,6,8)
A comparative bioavailability study using ICN Canada's product Oxybutyn and Norwich Eaton's product Ditropan produced equivalent data. A summary of the data is shown in the table below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

OXYBUTYN
(5 mg)

From measured data
Geometric Mean
Arythmetic Mean (CV%)

PARAMETER	OXYBUTYN ICN Canada	DITROPAN Norwich Eaton	RATIO OF MEANS
AUC_T	18.92	19.04	99
(ng.hr/mL)	16.75(52%)	17.45(43%)	
AUC_I	20.92	21.19	99
(ng.hr/mL)	18.95(46%)	19.72(39%)	
C_{max}	12.10	11.79	103
(ng/mL)	9.75(68%)	10.26(57%)	
T_{max}	0.66(34.43%)	0.77(69.99%)	
(h)			
$T_{1/2}$	1.6(35.9%)	1.6(19.7%)	
(h)			

The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means.

INDICATIONS AND CLINICAL USE:

Oxybutyn (Oxybutynin chloride is used as an antispasmodic in patients with uninhibited neurogenic or reflex neurogenic bladder for the relief of symptoms associated with voiding, such as urgency, urge incontinence, frequency, nocturia, and incontinence. The diagnosis of neurogenic bladder should be confirmed by cystometry and other appropriate diagnostic procedures before therapy with oxybutynin is initiated. In addition, the patient's response to therapy should be periodically evaluated by cystometry. Appropriate antibacterial therapy should be administered whenever urinary tract infection is present. (3,5,7)

Oxybutynin has been used in children for the treatment of primary nocturnal enuresis. (2,5)

CAUTIONS:

Adverse Effects

Adverse effects of oxybutynin chloride are typical of those produced by antimuscarinic agents and ore occasionally severe enough to require discontinuation of the drug. Adverse Effects of oxybutynin may include dry mouth, decreased sweating, urinary hesitancy and/or retention, hot flushes, fever, tachycardia, palpitation, vasodilation, amblyopia, transient blurred vision, mydriasis, cycloplegia, decreased lacrimation, or increased ocular tension.

Other adverse effects which may occur are drowsiness, weakness, dizziness, asthenia, hallucinations, restlessness, insomnia, nausea, vomiting, decreased GI motility, constipation, a bloated feeling, impotence, or suppression of lactation.

Severe allergic reactions including rash, urticaria, and other dermatologic reactions have occurred with other antimuscarinic agents and presumably might occur in susceptible individuals following oxybutynin administration. Antimuscarinic agents may also produce signs of CNS stimulation when administered in high doses. (2,3,5,7)

PRECAUTIONS AND CONTRAINDICATIONS:

Patients should be warned that oxybutynin chloride may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle). Alcohol or other sedative drugs may enhance drowsiness caused by oxybutynin. Administration of oxybutynin during hot weather can cause heat prostration (i.e., fever and heat stroke secondary to suppression of sweating). Since diarrhea may be a symptom of partial intestinal obstruction, especially in patients with ileostomies or colostomies, the possibility of intestinal obstruction should be excluded before oxybutynin chloride is administered to patients with diarrhea.

Oxybutynin should be used with caution in geriatric patients and in patients with autonomic neuropathy, or hepatic or renal disease. The possibility that oxybutynin may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmia, tachycardia, hypertension, or prostatic hypertrophy should be considered. Oxybutynin should be used with caution in patients with reflux esophagitis, since antimuscarinic agents may aggravate this condition. The possibility that large doses of oxybutynin could precipitate adynamic ileus or toxic megacolon in patients with ulcerative colitis should be considered.

Oxybutynin is contraindicated in patients with increased intraocular pressure associated with angle-closure glaucoma. The drug is also contraindicated in patients with myasthenia gravis, partial or complete obstruction of the GI tract, adynamic ileus, megacolon, severe colitis, or ulcerative colitis when toxic megacolon is present. The drug is also contraindicated in geriatric or debilitated patients with intestinal atony, patients with obstructive uropathy or hemorrhaging patients with unstable cardiovascular status.

Oxybutynin chloride is contraindicated in patients hypersensitive to the drug or any ingredient in the

formulation. (2,3,5,7)

PEDIATRIC PRECAUTIONS:

Appropriate and sufficient studies have not been performed in children with oxybutynin chloride, therefore, the drug should not be administered to children younger than 5 years of age or only when decided by the physician. (2,5)

GERIATRIC PRECAUTIONS:

Geriatric patients may be more sensitive to the anticholinergic effects of oxybutynin. Oxybutynin may also exacerbate underlying disease states in these patients. (1)

PREGNANCY AND FERTILITY:

Reproduction studies in hamsters, mice, rabbits, and rats using oxybutynin have not revealed evidence of harm to the fetus or impaired fertility. Safe use of oxybutynin during pregnancy has not been established, and the drug should be used in pregnant women or women who may become pregnant only when the potential benefits to the patient outweigh the possible risks to the fetus.

Since it is not known whether oxybutynin chloride is distributed into human milk, the drug should be used with caution in nursing women.(1,6)

DENTAL PRECAUTIONS:

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

DRUG INTERACTIONS:
Combination with anticholinergic agents or medications with anticholinergic activity may intensify the anticholinergic effects of oxybutynin. Concurrent use of central nervous system depression-producing medications may increase the sedative effect of either these medications or oxybutynin. (1)

OVERDOSE:

Symptoms and Treatment
Oxybutynin chloride overdosage produces CNS disturbances such as restlessness, tremor, irritability, seizures, delirium, hallucinations, excitement, or psychotic behavior, and cardiovascular symptoms including flushing, tachycardia, hypertension, hypotension, or circulatory failure. Fever, nausea, and vomiting may also occur. Severe overdosage may cause paralysis, respiratory failure, and coma.

Treatment:
Treatment of oxybutynin chloride overdosage generally involves symptomatic and supportive care.

Following acute ingestion of the drug, the stomach should be emptied by immediate gastric lavage (if signs and symptoms of acute toxicity are not too severe) or by inducing emesis. Emesis is contraindicated in patients who are precomatose, having seizures, or in a psychotic state. Activated charcoal may be administered as well as a cathartic. Intravenous administration of 0.5-2.0 mg of physostigmine salicylate may be used to counteract CNS disturbances. The dose of physostigmine may be repeated as needed up to a maximum total dosage of 5 mg. Fever may be treated with ice packs or other cold applications and alcohol sponging. In patients with severe intoxication, slow, carefully titrated IV administration of a 2 % solution of thiopental sodium or rectal infusion of 100-200 mL of a 2 % solution of chloral hydrate may be necessary to combat extreme excitement. Respiration should be maintained; artificial respiration may be required if paralysis of respiratory muscles occurs. (1)

DOSAGE AND ADMINISTRATION:

Administration:
Oxybutyn (Oxybutynin chloride) is administered orally. It may be taken on an empty stomach with water; however, if gastric irritation occurs it may be taken with food or milk.

Like other antimuscarinic agents, Oxybutyn should probably be discontinued periodically to determine whether or not the patient can manage without the drug and to minimize any tendency for the patient to become resistant to the drug.

Dosage:
For the relief of symptoms associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder, the usual adult and adolescent dosage of Oxybutyn is 5 mg 2 or 3 times daily with a maximum of 5 mg 4 times daily. The usual dosage in children older than 5 years of age is 5 mg twice daily with a maximum of 5 mg 3 times, not to exceed 15 mg per day. Dosage for children up to 5 years of age has not been established. The usual geriatric dose is the same as described for adult and adolescent dosage. However, geriatric patients may be more sensitive to the effects of the usual adult dose. (1)

PHARMACEUTICAL INFORMATION:

Proper Name: Oxybutynin Chloride

Chemical Name: (1) Benzeneacetic acid, α-cyclohexyl-α-hydroxy; 4-(diethylamino);2-butynyl ester hydrochloride

(2) 4-(Diethylamino)-2-butynyl-α-phenylcyclo hexaneglycolate hydrochloride

Chemical Formula: $C_{22}H_{31}NO_3$,HCl

Structural Formula:

Molecular weight: 393.95

Chemistry: Oxybutynin chloride occurs as white to off-white crystals and is freely soluble in water and in alcohol. The drug has a pKa of 6.96.

Stability: Oxybutyn tablets should be stored in tight, light-resistent containers at controlled room temperature (15-30^{o} C).

COMPOSITION:

Oxybutyn 5 mg tablets contain:	Oxybutynin chloride, USP
Non-Medicinal Ingredients:	Lactose
	Microcrystalline Cellulose
	Magnesium Stearate
	FD&C Blue #1 Aluminum Lake 12%

AVAILABILITY:

Each blue, round, biconvex Oxybutyn tablet, scored on one side and imprinted with ICN 021 on the other side contains Oxybutynin chloride 5 mg, USP. Bottles of 100 and 500.

SPECIAL INSTRUCTIONS:

Mutagenicity and Carcinogenicity

Oxybutynin chloride was not mutagenic when tested in Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae, and Salmonella typhimurium test systems. There was no evidence of carcinogenicity when the drug was given to rats for 24 months at dosages up to approximately 400 times the usual human dosage. (1)

Pregnancy and Fertility

Reproduction studies in hamsters, mice, rabbits, and rats using oxybutynin have not revealed evidence of harm to the fetus or impaired fertility. The teratogenic potential of oxybutynin chloride has also been studied in mice, hamsters and rabbits at doses of up to 180 mg/kg/day. No abnormalities were observed. (1,5)

Safe use of oxybutynin chloride during pregnancy has not been established. It is not known whether oxybutynin chloride is distributed into human milk. (1,5)

CLINICAL PHARMACOLOGY:

In limited clinical studies, oxybutynin was more effective than placebo in relieving urinary symptoms associated with neurogenic bladder; however, the drug was not superior to a standard antimuscarinic agent such as propantheline bromide.

In one uncontrolled study, oxybutynin was reported to relieve mild to moderate urinary tract discomfort resulting from prostatectomy, radiation therapy, or infection.

Oxybutynin has been used in children for the treatment of primary nocturnal enuresis. In one study in children with a history of nocturnal, but not daytime, enuresis and normal bladders, there was no significant difference in the frequency of nocturnal enuresis when the children were receiving oxybutynin compared to when they were receiving placebo.

Oxybutynin has been used as an antispasmodic in the symptomatic treatment of various GI disorders without conclusive evidence of efficacy. (1,5)

TOXICOLOGY:

Acute Toxicity

Oxybutynin chloride overdosage in different animal species produced symptoms of CNS stimulation, ataxia, convulsions and exophthalmos. Intraocular tension was increased in some animals at each dose level when given orally. Newborn rats suffered from labored respiration and reduced activity and when death occurred it was on day 2 in most of the cases. The signs and symptoms observed in dogs were convulsions, ataxia, hyperventilation, mydriasis, emesis, muscular weakness of the hind limbs and were observed more often in females than in males.

Species	Route	LD_{50}
Mouse	p.o.	1550 mg/kg (1372-1751)
Mouse	i.p.	260 mg/kg (186-346)
Mouse	i.v.	40 mg/kg (36-45)

Rat	p.o.	1600 mg/kg (1176-2176)
Rat	i.p.	430 mg/kg (371-499)
Rat (newborn)	p.o.	560 mg/kg (528-594)

The approximate minimum lethal dose in dogs has been found to be

i.v. >25 but <50 mg/kg

p.o. >750 but <1000 mg/kg

The acute toxicity observed in humans produces CNS disturbances such as restlessness, tremor, irritability, seizures, delirium, hallucinations, excitement, or psychotic behavior, and cardiovascular symptoms including flushing, tachycardia, hypertension, hypotension, or circulatory failure. Fever, nausea, and vomiting may also occur. Severe overdosage may cause paralysis, respiratory failure and coma. These symptoms have been observed in dosages higher than the recommended once of 5 mg in single dose and 20 mg total dose daily.

Subacute and Chronic Toxicity

Three month (rat): oxybutynin chloride was given orally to rats in groups of 20 animals, in dosages of 0, 50, 100, and 150 mg/kg/day. The mortality rate in the highest dosage group was approximately 50 %. In the lower dosage groups no significant difference was reported between treatment and control groups. Symptoms reported were ataxia, depression, hypersensitivity to stimulation and pilomotor erection.

Six month (rat): oxybutynin chloride was given orally to rats in dosages of 20-200 mg/kg/day for 6 days per week. At the 20 mg/kg/day dose, no significant toxic effects were observed. Rats receiving the higher doses of 60-200 mg/kg/day experienced continuous acute pharmacologic effects, decreased food consumption with suppression of weight gain and pathological changes which seemed to be dose-related. Those changes consisted of irregular and enlarged hepatic cells and degenerative changes in kidney tubules.

Twenty-two months (rat): oxybutynin chloride was given per os to rats of both sex, 50 animals per group, in dosages of 0, 20, 80, and 160 mg/kg/day. None of the animals receiving the high doses survived beyond 90 days. From the mid-dose animals only a few survived the same time period. The loss of weight gain observed at all given doses seemed to be dose-related. Animals receiving the lowest dose of 20 mg/kg/day experienced a slight mydriasis and animals receiving the higher doses experienced mydriasis, tenseness, hyperactivity and excessive salivation. The serum alkaline phosphatase was found to be higher in rats receiving high doses of oxybutynin chloride than those serving as controls. An increase of the number of red and white blood cells in the urine was observed in male animals receiving mid-doses. Males receiving the high doses had an increased number of red

cells in the urine at termination of dosing. No other drug-related changes were observed in hematology, organ weight, gross pathology or histopathology, or ophthalmologic examinations. No significant difference was observed between the groups for tumor incidence.

Six months (dog): no toxic effects were observed when oxybutynin chloride was administered to dogs in dosages of 3 and 6 mg/kg/day for 6 days per week. Doses exceeding those produced anorexia, tremor and nervousness during the first treatment weeks. However, these signs of toxicity diminished during the rest of the study period and no other abnormalities were observed. Twelve months (dog): equal numbers per group of beagle dogs of both sex received 0, 4, 8 and 16 mg/kg/day of oxybutynin chloride orally. Dogs in the highest dosage group were started with 4 mg/kg b.i.d. and gradually increased to 8 mg/kg b.i.d. over 8 weeks of treatment. No mortalities occurred. All animals treated with oxybutynin chloride experienced dry mucous membranes and mydriasis. In the 8 and 16 m/k/day treatment groups, some animals were observed to suffer from dry nose and animals in the 16 mg/kg/day group presented occasionally with increased activity, purulent ocular or nasal discharge, emaciation and/or dehydration. Decrease of body weight seemed to be dose-related and 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 months of treatment only. Slight decreases in erythrocyte count, hemoglobin concentration and hematocrit values were observed in the animals receiving 16 mg/kg/day at all intervals of analysis. No other drug-related changes were seen in haematologic, 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.

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