Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Oxybutynin Chloride Tablets also contain: FD&C Blue #1 aluminum lake, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

Oxybutynin Chloride Tablets are for oral administration.

Clinical Pharmacology

Oxybutynin chloride exerts a direct antispastic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-tenth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (anticholinergic effects).

Oxybutynin chloride relases bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the desire to void. Oxybutynin chloride thus reduces urgency and the frequency of both incontinent episodes and voluntary urination.

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in in vitro studies.

Pharmacokinetics

Absorption

Following oral administration of oxybutynin chloride, oxybutynin is rapidly absorbed achieving Cmax within an hour, following which plasma concentration decreases with an effective half-life of approximately 2 to 3 hours. The absolute bioavailability of oxybutynin is reported to be about 6% (range 1.6 to 10%) for the tablets. Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of oxybutynin.

The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 1. Mean R-oxybutynin plasma concentrations following three doses of oxybutynin chloride 5 mg administered every 8 hours (n=23)

<table>
<thead>
<tr>
<th>Parameter (limits)</th>
<th>Oxybutynin</th>
<th>S-oxybutynin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>3.5 (2.2)</td>
<td>7.8 (4.1)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.89 (0.34)</td>
<td>0.65 (0.32)</td>
</tr>
<tr>
<td>AUC0-1 (ng•h/mL)</td>
<td>25.0 (7.5)</td>
<td>20.8 (7.5)</td>
</tr>
<tr>
<td>AUC0-inf (ng•h/mL)</td>
<td>24.3 (12.3)</td>
<td>37.3 (13.8)</td>
</tr>
</tbody>
</table>

Figure 1. Mean R-oxybutynin plasma concentrations following three doses of oxybutynin chloride 5 mg administered every 8 hours for 1 day in 23 healthy adult volunteers.

Oxybutynin chloride steady-state pharmacokinetics were also studied in 11 pediatric patients with detrusor overactivity associated with a neurological condition (e.g., spina bifida). These pediatric patients were on oxybutynin chloride tablets with total daily dose ranging from 7.5 mg to 15 mg (0.22 to 0.53 mg/kg). Overall, 23 patients (86.9%) were taking a total daily oxybutynin chloride dose between 10 mg and 15 mg. Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg twice daily oxybutynin chloride, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg twice daily.

Table 2. Mean AUC and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters In Children Aged 5 to 15 Following Administration of 7.5 mg to 15 mg Total Daily Dose of Oxybutynin Chloride Tablets (N=11)

<table>
<thead>
<tr>
<th>Parameter (limits)</th>
<th>Oxybutynin</th>
<th>S-oxybutynin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.53 (0.45)</td>
<td>0.39 (0.32)</td>
</tr>
<tr>
<td>AUC0-t (ng•h/mL)</td>
<td>15.4 (11.9)</td>
<td>12.4 (11.0)</td>
</tr>
<tr>
<td>AUC0-inf (ng•h/mL)</td>
<td>51.4 (37.3)</td>
<td>41.5 (30.4)</td>
</tr>
</tbody>
</table>

Figure 2. Mean steady-state (AUC0-inf) R-oxybutynin plasma concentrations following administration of total daily oxybutynin chloride tablet dose of 7.5 mg to 15 mg (0.22 to 0.53 mg/kg) in children 5 to 15 years of age. – Plot represents all available data normalized to the equivalent of oxybutynin chloride 5 mg BID or TID at steady state.

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

Warnings

Angioedema of the face, lips, tongue and/or larynx has been reported with oxybutynin. In some cases, angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, oxybutynin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Precautions

Central Nervous System Effects

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects (see ADVERSE REACTIONS). A variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Oxybutynin chloride should be used with caution in patients with pre-existing dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.

General

Oxybutynin chloride should be used with caution in the frail elderly, in patients with hepatic or renal impairment, and in patients with myasthenia gravis.

Oxybutynin chloride may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, nephritis, tachycardia, hypertension, myasthenia gravis, and prostatic hypertrophy.

Urinary Retention

Oxybutynin chloride should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders

Oxybutynin chloride should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

Administration of oxybutynin chloride 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.

Oxybutynin chloride, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients who have compromised ileocecal function and/or who have ileal obstruction.

Oxybutynin chloride should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

Information For Patients

Patients should be informed that oxybutynin may produce angioedema that could result in life-threatening airway obstruction. Patients should be advised to promptly discontinue oxybutynin therapy and seek immediate medical attention if they experience edema of the tongue, edema of the laryngopharynx, or difficulty breathing.

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin chloride are administered in the presence of high environmental temperature.
Because anticholinergic agents such as oxybutynin may produce dryness (soreness), or blurred vision, patients should be advised to exercise caution.

Patients should be informed that alcohol may enhance the dryness caused by anticholinergic agents such as oxybutynin.

Drug Interactions

The concurrent use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

Mean oxybutynin chloride plasma concentrations were approximately 3 to 4 fold higher when oxybutynin chloride was administered with ketocarbazone, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as anticoagulants (e.g., warfarin and ticlopidine) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., Cmax, AUC, and t1/2). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on body surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in bacterial/mammalian assays, S. typhimurium, and Salmonella typhimurium test systems.

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride administered to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

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 oxybutynin chloride is administered to a nursing woman.

Pediatric Use

The safety and efficacy of oxybutynin chloride administration have been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of oxybutynin chloride tablets were studied in 30 children in a 24-week, open-label trial. Patients were aged 5 to 15 years, all had symptoms of decreased urinary output in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and were all current users of oxybutynin chloride. Study results demonstrated that the administration of oxybutynin chloride was associated with improvement in clinical and urodynamic parameters.

At total daily doses ranging from 5 mg to 15 mg, treatment with oxybutynin chloride tablets was associated with increased incontinence in mean urine volume or catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume at morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%. Urodynamic results in these patients were consistent with the clinical results. Treatment with oxybutynin chloride tablets was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 cm H2O to 33 cm H2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H2O) from 38% to 20%.

As there is insufficient clinical data for pediatric populations under age 5, oxybutynin chloride is not recommended for this age group.

Geriatric Use

Clinical studies of oxybutynin chloride did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Clinical geriatric experience has not identified differences in responses between healthy elderly and younger patients; however, a lower initial starting dose of not less than 2.5 mg two or three times a day has been recommended for the frail elderly due to a prolongation of the elimination half-life from 2 to 3 hours to 5 hours in general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety and efficacy of oxybutynin chloride was evaluated in a total of 199 patients in three clinical trials. These participants were treated with oxybutynin chloride 5 to 20 mg/day for up to 6 weeks. Table 3 shows the incidence of adverse events judged by investigators to be at least possibly related to treatment and reported by at least 5% of patients.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
<th>Oxybutynin Chloride (5 to 20 mg/day) (n=199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infections</td>
<td>Urinary tract infection</td>
<td>6.5%</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Depression</td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>6.5%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dizziness</td>
<td>16.8%</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>14.2%</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>7.5%</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Blurred vision</td>
<td>9.6%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Dry mouth</td>
<td>71.1%</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>15.1%</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>9.6%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>10.0%</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Urinary Retention</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

The most common adverse events reported by patients receiving oxybutynin chloride 5 to 20 mg/day were the expected side effects of anticholinergic agents.

The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 1 to 5% of patients using oxybutynin chloride (5 to 20 mg/day) in all studies. Infections and infestations: nasopharyngitis, upper respiratory tract infection, bronchitis, cystitis, fungal infection.

REFERENCES


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