PharmaNote®

VOLUME 20, ISSUE 5 FEBRUARY 2005

APIDRA®: A RAPID-ACTING INSULIN FOR THE TREAMENT OF DIABETES

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Current estimates report that more than 18 million Americans have diabetes (approximately 6.3% of the population).[1] Of these, 13 million are diagnosed, while 5.2 million are unaware of their disease.[1] Among adults diagnosed with diabetes in 2002, about 12% require insulin and oral medications, 19% administer insulin alone, 53% take oral medications, and 15% are untreated.[1] Diabetic patients with uncontrolled hyperglycemia are at greater risk for diabetes-related complications and premature death. In 2000, diabetes was the 6th leading cause of death according to a conservative estimate.[1] Furthermore, diabetes is the leading cause of ESRD, adult blindness, non-traumatic lower-extremity amputation, and impotence. Heart disease and stroke are 2 to 4 times more likely in a patient with diabetes. In 2002, diabetes-related complications (amputation, death from cardiovascular disease or stroke, and nervous system disease) occurred in 60-70% of diabetic patients.[1] Diabetes costs the United States $132 billion per year in 2002, with direct medical costs accounting for $92 billion while indirect costs (disability, work loss, premature mortality) consume an additional $40 billion.[1]

Insulin replacement is the bedrock for management of type 1 DM and is often necessary to control diabetes and prevent complications in type 2 patients with more advanced disease. Reduced blood glucose is directly related to improved outcomes. It is estimated that for every 1% decrease in the hemoglobin A1c (HbA1c) the risk of microvascular complications (eye, kidney and nerve disease) is reduced by 40%.[1] Early administration of insulin is associated with β-cell preservation. Furthermore, insulin receptor substrate (IRS)-2 has been implicated in β-cell growth and survival.[2] Regular insulin inhibits β-cell apoptosis by 15%, while insulin glulisine (Apidra®), a new rapid-acting insulin and IRS-2 substrate, provides a 55-60% inhibition of apoptosis.[2] The clinical significance of this biochemical effect has yet to be determined by randomized clinical trials. Insuline glulisine (IG) was approved by the FDA in April 2004. It is manufactured and distributed by Aventis Pharmaceuticals under the trade name Apidra®. IG is indicated for the treatment of adult patients with diabetes mellitus. This article will explore evidence-based trials to delineate the safe and effective use of IG.

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Table 1. Pharmacokinetics of insulin glulisine compared to insulin aspart

	Following subcutaneous injection	
Kinetic Parameters	**Glulisine**	**Aspart**
Bioavailablity	~70%	~70%
Cmax†	82 mU/L	82 mU/L
Tmax	55 minutes	40-50 minutes
Vd*	~13 Liters	N/A
Route of elimination‡	Dual	Dual
Half-life	42 minutes	81 minutes
Onset of action	10-15 minutes	5-15 minutes
Duration of action	3.5-5 hours	3.5-5 hours

Data compiled from reference 3. *Vd after IV administration. †Cmax is dose-dependent; data reflects Cmax following 0.15 U/kg subcutaneous injection ‡A small portion is inactivated by peripheral tissues, but the majority is metabolized by the liver and kidneys. Insulin is filtered and reabsorbed by the kidneys. Abbreviations: Cmax=maximum concentration reached after administration; Tmax=time from administration to Cmax; Vd=volume of distribution; U=units; kg=kilograms; mU=micro units; mL=milliliter.

Pharmacology and Pharmacokinetics

The pharmacology of IG is similar to other insulins except it is more selective for IRS-2 in pancreatic β-cells compared to aspart (Novolog®), lispro (Humulog®), and regular insulins.[2] In vitro, this selectivity is responsible for enhanced β-cell protection against cytokine- and fatty acid-mediated apoptosis.[2] However, the clinical significance of this selectivity in vivo can only be determined by reliable clinical trials. The pharmacokinetics of IG are comparable to other rapid-acting insulins and are summarized in Table 1.

Clinical Trials

The safety and efficacy of IG has been evaluated in type 1 and 2 diabetic patients. The primary outcome in these studies was glucose control measured by HbA1c. These studies compared IG versus lispro (Humalog®), aspart (NovoLog®) and regular insulin. Insulin glargine(Lantus®) or NPH where concomitantly administered as basal insulin in each case. (Table 2)

Type I Diabetes

There are three phase III trials conducted in type I diabetic patients. One of these studies was designed to determine the safety and efficacy of IG compared to lispro (IL). Another study was designed to determine the safety and efficacy of IG administration before and after a meal compared to regular insulin. The final study was designed to determine the compatibility of IG administered via a pump compared to insulin aspart.

In a 26 week, randomized, open-label, active-control study Dreyer and colleagues evaluated the safety and efficacy of IG compared to IL.[3,4] (Table 2) This study was designed to show noninferiority of IG compared to IL with respect to glycemic control. The study included 672 type 1 diabetic patients. The baseline demographics between treatment groups were comparable except for history of diabetes, and duration of insulin treatment, which were approximately 2 years longer in the IG group. A 4-week run-in phase with insulin glargine and lispro provided uniform dosing for optimal 2-hour postprandial and fasting blood glucose. IG and IL were administered 0-15 minutes before each meal. Glargine was administered as the basal insulin at bedtime. Glycemic control measured by reductions in HbA1c (-0.14% from 7.6% for both groups) and rates of hypoglycemia were comparable for both treatment groups. However, during the study, patients in the IG group required significantly less upward titration of basal insulin (compared to baseline, the increase was 0.12 IU for IG vs. 1.82 IU for IL; p=0.0001). There was also a statistically significant difference in the total insulin dose (compared to baseline, -0.86 IU for IG vs. +1.01 IU for IL; p=0.0123). Thus, the IG group experienced a similar decrease in HbA1c with less total insulin compared to the IL group. More cardiac and musculoskeletal events were seen in the IG group com-

Table 2. Summary of clinical trials [3,4]

Clinical Trial	Pivotal Study* 3001	Study 3006*	Study 3004*	Pivotal Study* 3002
		Type I Diabetes		Type II Diabetes
Design	Randomized, parallel, open-label, active-control	Randomized, active-control	Randomized, open-label, active-control	Randomized, open-label, active-control
Sample Size	672	59	860	876
Patient population	97% Caucasian 58% male Mean age=38.5 yr	100% Caucasian Mean age=45.8 yr	94% Caucasian Mean age=40.3 yr	85% Caucasian Mean age=58.3 yr 50% on oral medications
Exclusion	< 18 y.o. Insulin therapy for <1yr	<18 y.o. Insulin therapy for < 1 yr <6 months of CSII use <3 months of the same pump	<18 y.o. Insulin therapy for <1 yr	<Insulin for < 6 months HbA1c <6%, >11.0% Active retinopathy Impaired hepatic and/or renal function, cardiovascular, neurologic, endocrine, active cancer, or other major systemic diseases
Insulin comparator	Lispro	Aspart	Regular	Regular
Insulin combination	Lantus	N/A	Lantus	NPH
Methods	IG or IL SC 0-15min AC; Glargine QHS	Both administered via CSII pump	IG 0-15 min AC or immediately PC; regular 30-45 min AC; Glargine QHS	IG 0-15min AC; Regular 30-45 min AC; NPH bid
Duration	26 weeks	12 weeks	12 weeks	26 weeks
Hypoglycemia	No difference between groups (mild, mod or severe)	Comparable between groups (requiring intervention)	Comparable between groups (requiring intervention)	No difference between groups (requiring intervention)
Change in HbA1c (%)	Both groups decreased from baseline by 0.14%	Similar endpoint HbA1c 6.98% vs. 7.18% for IG vs. aspart respectively	Similar; IG pc vs. IG ac 0.15 (only significance difference)	Similar, slightly favoring IG: -0.46 vs -0.30 for IG and regular respectively

Abbreviations: n=sample size; yr=year(s); <=less than; y/o= year(s) old; >=greater than; CSII=continuous subcutaneous insulin injection; IG=insulin glulisine; IL=insulin lispro; sub-Q=subcutaneous; min=minute(s); ac=before meals; q= every; hs=at bedtime; bid=twice daily; pc=after meals; b/w=between; mod=moderate; Δ HbA1c= change in hemoglobin A1c. *Study designs were multinational and multicenter as reported by the manufacturer

pared to the IL group. However, investigators determined that these adverse events were not related to IG. One explanation is that patients in the IG group tended to be at higher cardiovascular risk and had a longer duration of diabetes and insulin therapy compared to the IG group.

A 12 week, randomized, open-label, active-control study by Garg and colleagues evaluated the safety and efficacy of IG given 15 minutes before a meal or immediately after a meal compared to regular insulin given 30-45 minutes before a meal.[3,4] (Table 2) Glargine was given to all three groups once at bedtime as basal insulin. This study was designed to show non-inferiority of post-meal IG when compared to pre-meal IG and pre-meal regular insulin. The study included 860 type I diabetic patients. The baseline demographics were comparable. A 4- week run-in phase with glargine and regular insulin provided uniform dosing for optimal 2-hr postprandial and fasting blood glucose. Glycemic control, measured as reductions in HbA1c (-0.11% with post-meal IG vs. -0.26% with pre-meal IG vs. -0.13% with regular insulin), and rates of hypoglycemia were comparable for the 3 treatment groups. The only statistically significant difference for decreased HbA1c was between post-

Table 3. Important considerations for insulin glulisine [3,4]

Kinetics will vary with individuals, site of injection, blood supply, temperature and physical activity
May not provide adequate glycemic control when used as monotherapy
Hypoglycemia similar to other insulins
Renal impairment may require reduced dosing
Should not be diluted or mixed with other insulins
Other considerations parallel those of other insulins

and pre-meal IG, favoring pre-meal administration (p=0.0062). Adverse drug reactions were similar between the groups with the exception of weight gain, which was greater with pre-meal dosing of IG and regular insulin.

A 12 week, randomized, active-control study by Hanaire-Broutin and colleagues was designed to evaluate the compatibility and safety of IG administration via continuous subcutaneous insulin infusion (CSII) compared to insulin aspart administered via CSII.[3,4] Both insulins were bolused immediately before meals with a continuous basal rate. The study included 59 Caucasian type I diabetic patients. The baseline demographics were comparable. Patients underwent a 4-week run-in phase with insulin aspart. The 2 pumps used were the Disetronic pump H-Tron plus V100 (66.1%) and the MiniMed programmable pump (30.5%). Glycemic control measured by HbA1c (increased 0.21% with IG vs 0.10% with aspart) and rates of hypoglycemia or hyperglycemia were comparable for both treatment groups. Adverse reactions, such as number of catheter occlusions per month (0.08 with IG vs 0.15 with aspart), infusion site reactions (10.3% with IG vs 13.3% with aspart), and treatment emergent adverse events(10.3% with IG vs 13.3% with aspart) were also similar between the groups.

Type II Diabetes

In a 26 week, randomized, open-label, active-control study, Dailey and colleagues evaluated the safety and efficacy of IG given 15 minutes before a meal compared to regular insulin administered 30-45 minutes before a meal in 876 patients.[5] NPH was given twice daily as basal insulin in both groups. Most patients mixed the short-acting insulin with NPH prior to injection (74% IG vs. 83% regular). Patients were continued on oral medications. The study was designed to demonstrate non-inferiority of IG compared to regular insulin. The baseline demographics were comparable, except age and duration of diabetes (IG group was older and had diabetes for approximately 1.3 years longer). A 4-week run-in period with NPH and regular insulin was included in the protocol. Reductions in HbA1c were greater for the IG group (-0.46% IG vs. -0.30% regular insulin; $p<0.05$) proving non-inferiority of IG. This statistically significant difference between both groups was maintained through week 26 in an extension phase of the trial.[3,4] Adverse reactions, including severe hypoglycemia, were comparable for both treatment groups.[5] In the long-term extension study, there was no statistically significant difference in adverse reactions between the groups.[3,4]

Dosing/Administration

Dosing and administration of IG are similar to other insulins, most closely resembling rapid-acting insulin.[3,4] IG dosing should be individualized. Routes of administration supported by clinical trials include subcutaneous injections and CSII. Injection sites include the abdomen, deltoid, and thigh. As with other insulins, patients should rotate around a site of injection. IG should be administered 15 minutes before to 20 minutes after a meal via subcutaneous injection. The onset of action (rate of absorption) may be affected by injection site, exercise, and other variables. IG should not be mixed with other insulins or diluents. Important consideration are listed in Table 3.

Cost/How Supplied

Apidra® is not yet available for sale to the public and therefore pricing is not yet established. It will be reportedly launched to the market early in 2005 in a pre-filled pen device (Personal communication with Aventis, October15, 2004). Apidra® U-100 is a clear, aqueous and colorless solution supplied in a 10 mL vial.

Toxicity and Safety

The safety and toxicity profiles are similar to other rapid-acting insulins. (Table 4) The most common adverse reaction is hypoglycemia (Table 4). Adverse reactions occurring in 5% or more of patients include: upper respiratory tract infection, peripheral edema, arthralgia, nasopharyngitis, diarrhea, influenza, headache, back pain, UTI, bronchitis and sinusitis.

Table 4. Adverse Events Documented During Clinical Trials [3,4]

Adverse Event	IG[a] (n=672)	IL[a] (n=672)	IG[b] (n=876)	Regular[b] (n=876)	IG[c] (n=860)	Regular[c] (n=860)	IG[d] (n=59)	Aspart[d] (n=860)
Severe hypoglycemia	7.0%	3.5%	3.9%	2.7%	8.4%*	10.1%	-	-
1st time hypoglycemia	3.0%	3.1%	-	-	-	-	-	-
Weight changes	Similar to baseline	Similar to baseline	+1.8 kg	+2.0 kg	+/-3 kg**	+3 kg	Similar to baseline	Similar to baseline
Catheter occlusions/mo	-	-	-	-	-	-	0.08	0.15
Injection site reactions	-	-	3.2%	2.3%	-	-	10.3% (3/29)	13.3% (4/30)

a Study 3001 as reported by manufacturer; b Study 3002 as reported by manufacturer; c Study 3004 as reported by manufacturer; d Study 3006 as reported by manufacturer; *For both pre- and post-meal IG; **Pre-meal IG increased by 3 kg vs. post-meal IG decreased 3 kg .

Summary

Insulin glulisine (IG) is a novel, rapid-acting insulin that has selectivity for the IRS-2 receptor. The importance of this receptor selectivity is currently being elucidated. In vitro, IRS-2 selectivity appears to be beta-cell protective and might delay the progression of diabetes or permit utilization of lower total insulin doses. However, the clinical significance of this selectivity in vivo has not been proven in a long-term trial. IG is indicated for both type I and II diabetes and appears to be comparable to other rapid acting insulins, such as insulin lispro. Until additional research on the long-term use of IG establishes a clear advantage over other insulins, it's role in the management of diabetes will be comparable to that of the already widely used rapid-acting insulins.

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SANCTURA®: A NEW ALTERNATIVE FOR OVERACTIVE BLADDER

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Approximately 15-30% of elderly persons living at home, one third of those in the acute-care setting, and at least half of those in nursing homes suffer from urge incontinence. The condition increases with increasing age and affects twice as many women as it does men.[1] Urge incontinence is a condition where urinary storage is inadequate because of over-activity of the detrusor muscle. The most common symptoms include urinary incontinence, urgency, and frequency. The term frequency is defined as emptying the bladder more than 8 times daily. Symptoms can be disturbing since nocturia and enuresis are also common. It is important that patients receive adequate treatment because untreated or under-treated, it can lead to social isolation, low quality of life, low self-esteem, and can affect general health.[1]

The etiology of urinary incontinence is often unknown but often referred to as idiopathic detrusor instability. Nonpharmacological treatments such as limiting intake of caffeine and alcohol and decreasing evening fluid consumption can help minimize the symptoms of urge incontinence.[1] Pel-

Table 1- Urodynamic Parameters[8]

Medication	Difference	Increase in maximum bladder capacity (ml)	Increase in volume at first unstable contraction (ml)	Increase in volume at first sensation to void (ml)
Trospium	Start to Week 26	92.0 N=203	63.5 N=63	73.6 N=201
	Start to Week 52	115.0 N=189	46.1 N=51	78.6 N=186
Oxybutynin	Start to Week 26	117.0 N=65	61.2 N=20	76.93 N=64
	Start to Week 52	119.4 N=62	36.7 N=18	70.2 N=62

vic floor muscle rehabilitation, acupuncture, and scheduling regimens such as timed voiding, habit retraining, and bladder training may also help with urge incontinence, but are cumbersome in clinical practice.

Treatment options for patients include anticholinergic medications such as oxybutynin (Ditropan®) and hyoscyamine sulfate (Levsin®). Anticholinergic agents work by antagonizing muscarinic cholinergic receptors, blocking efferent parasympathetic nerve impulses, which induce detrusor contraction. These drugs are associated with a high incidence of adverse effects because of the widespread activity of the parasympathetic nervous system. These drugs also increase bladder volume and should not be used in patients with urinary retention. Currently, tolterodine (Detrol®), a competitive muscarinic receptor antagonist, and oxybutynin (Ditropan®), a tertiary amine exerting antimuscarinic and antispasmodic activity on smooth muscle, are considered first-line treatments for urge incontinence.[2] Other agents available for the treatment of urinary incontinence are tricyclic antidepressants (TCAs) such as desipramine and nortriptyline, alpha$_1$-adrenergic agonists such as prazosin, and antispasmodic agents such as flavoxate and estrogen. TCAs have antimuscarinic activity that is helpful with urinary incontinence especially nocturnal enuresis, but they have extensive side effects. Antispasmodic agents such as flavoxate are less effective than oxybutynin.[4] Evidence regarding the use of estrogen is inconclusive but estrogens may be helpful in the adjunctive treatment of postmenopausal women with symptoms of urgency, frequency, and nocturia. Unfortunately, the role of hormone replacement therapy has diminished in light of findings from the Women's Health Initiative studies.[9] Trospium chloride (Sanctura®) manufactured by Odyssey Pharmaceuticals was approved by the FDA in May 2004 for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. This article will examine the safety, efficacy, and tolerability of trospium.

Pharmacology and Pharmacokinetics

Trospium is an antispasmodic and non-specific antimuscarinic agent. It antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs, thereby reducing smooth muscle tone in the bladder. Trospium decreases the frequency of voluntary and involuntary detrusor contractions and increases maximum cystometric bladder capacity and volume at first detrusor contraction.[5] As a result, trospium decreases urinary urgency, frequency, and incontinence. When used at therapeutic doses, trospium has negligible affinity for nicotinic receptors.[3] Furthermore, since trospium is a quaternary amine it is less likely to penetrate the blood brain barrier, which may result in a milder side effect profile including less drowsiness, nervousness, and dizziness compared to oxybutynin, a tertiary amine.[3]

Trospium's peak plasma concentrations (C_{max}) are reached at 5 to 6 hours following oral administration. Less than 10% of the dose is absorbed.[5] Absorption is reduced by the simultaneous intake of food, especially with a high fat content. For that reason, it is recommended that trospium be taken at least one hour prior to meals or on an empty stomach. Forty percent of the absorbed dose is excreted as metabolites while 60% is excreted unchanged in the urine via active tubular secretion. Cytochrome P450 (CYP450) is not believed to contribute sig-

Table 2. Mean change from baseline* for urinary frequency, urge incontinence episodes, and void volume.[5]

Efficacy Endpoint	Placebo N=256	Trospium N=253	P-value
Urinary Frequency/24 hrs [a, †]			
Mean baseline	12.9	12.7	
Mean change from baseline (SE)	-1.3 (0.2)	-2.4 (0.2)	<0.001
Urge Incontinence episodes/week [b,†]			
Mean baseline	30.1	27.3	
Mean change from baseline (SE)	-13.9 (1.2)	-15.4 (1.1)	0.012
Urinary void volume/toilet void (ml) [a,]			
Mean baseline	156.6	155.1	
Mean change from baseline (SE)	7.7 (3.1)	32.1 (3.1)	<0.001

SE denotes standard error. *Week 12 or last observation carried forward in ITT population. †Denotes co-primary endpoint. [a]Treatment differences assessed by analysis of variance for ITT:LOCF data set. [b] Treatment differences assessed by ranked analysis of variance for ITT:LOCF data set.
ITT = intention to treat, LOCF = last observation carried forward .

nificantly to the elimination of trospium, but trospium does inhibit the CYP2D6 isoenzyme.[3] The majority of trospium is distributed into plasma, where its plasma half-life is approximately 20 hours. Trospium has been shown to cross the placenta.

Clinical Trials

A controlled, double-blind, multicenter clinical trial was conducted to determine the tolerability and efficacy of trospium in doses of 20 mg twice daily for long term therapy (52 weeks) in patients with urge syndrome.[8] The trial was comprised of 358 patients with urge syndrome who were randomized to either trospium 20 mg twice daily or oxybutinin 5 mg twice daily for 52 weeks of continuous treatment. Analysis of micturition diaries demonstrated a reduction of the micturition frequency (-3.5/d versus -4.2/d for trospium and oxybutynin, respectively), incontinence frequency (-1/day in both groups), and a reduction of the number of urgencies (-3.5/d versus -3.6/d for trospium and oxybutynin, respectively). Mean maximum cystometric bladder capacity increased during treatment with trospium by 92 mL after 26 weeks and 115 mL after 52 weeks (P=0.001). (Table 1) Adverse events occurred in 64.8% of the patients treated with trospium chloride and 76.6% of those patients treated with oxybutynin. Trospium demonstrated comparable efficacy and a better benefit to risk ratio compared to oxybutynin due to improved tolerability. The incidence of side effects during 52 weeks of therapy was no greater than during short-term therapy. Adverse events, especially xerostemia, were more frequent and began earlier in the oxybutynin group compared with the trospium group.

A randomized, double-blind, placebo-controlled, parallel group study of 523 patients was conducted to evaluate trospium for the treatment of patients with overactive-bladder. Of the 523 patients, 262 patients received trospium 20 mg twice daily and 261 patients received placebo. The patients were mainly Caucasian (85%) and female (74%), with a mean age of 61 years (range 21 to 90 years.) Inclusion criteria for the trial included symptoms of urge or mixed incontinence confirmed by medical history and urinary diary, at least 7 episodes of urge incontinence episodes per week, and greater than 70 micturitions per week. The symptom burden at baseline is listed in Table 2. After 12 weeks, the mean change from baseline for urinary frequency per 24 hours was -2.4 with trospium and -1.3 with placebo. The urge incontinence episodes decreased by 15.4/wk with trospium and 13.9/wk with placebo. Urinary void volume increased by 32.1 mL with trospium and 7.7 mL with placebo.

Indications and Dosing

Trospium is indicated for the treatment of overactive bladder with symptoms of urge inconti-

Table 3. Most frequent adverse reactions with trospium and other overactive bladder medications.

Adverse Reaction	Trospium	Tolterodine	Oxybutynin
Dry Mouth	20.1%	39.5% (LA, 23%)	61-71%
Constipation	9.6%	7% (LA, 6%)	13%
Flatulence	n/a	n/a	n/a
Headache	4.2%	7% (LA, 6%)	n/a
Abdominal Pain	n/a	5% (LA., 4%)	n/a
Fatigue	n/a	n/a	2-7%
Urinary Retention	1.2%	2%	11%
Dry Eyes	1.2%	3%	n/a
Dizziness	n/a	n/a	6-16%
Postural Hypotension	n/a	n/a	n/a

LA denotes long-acting dosage form (Detrol LA®)

nence, urgency, and urinary frequency. The recommended dose for trospium is 20 mg twice daily on an empty stomach at least 1 hour prior to meals. The need for continued treatment should be assessed at regular intervals of 3 to 6 months.[4] For the population older than 75 years of age, a dose of 20 mg once daily based upon tolerability should be given. Also, a dose of 20 mg once a day at bedtime should be administered to those patients with severe renal impairment (CrCl <30 ml/min).

Precaution and Warnings/Contraindications

Age does not significantly affect the pharmacokinetics of trospium but it does correlate with increased anticholinergic side effects; patients older than 75 years of age are more likely to experience anticholinergic symptoms (e.g., xerostomia, constipation, cognitive impairment). Trospium is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. Precautions should be observed in patients with renal insufficiency and hepatic impairment. In patients with severe renal insufficiency (CrCl <30 ml/min), dose modification is recommended. A dose of 20 mg once a day at bedtime should be administered to this population. In patients with mild or moderate hepatic impairment, Cmax increases by 12% and 63%, respectively; however, the mean AUC is unchanged.[3] The effect of severe hepatic impairment on the pharmacokinetics of trospium is unknown; therefore, caution is advised in this population.

Adverse Reactions

The two most common adverse events experienced by patients receiving trospium 40 mg/d are dry mouth and constipation. The severity of xerostemia seems to be less severe than that encountered by patients on oxybutynin.[6] Also, since trospium does not readily cross the blood brain barrier or conjuctiva, anti-muscarinic-related adverse events such as xerophthalmia, blurred vision, and other CNS-related events might occur less frequently.[3] Table 3 lists the frequency of common adverse effects compared to other agents used for overactive-bladder.

As with all anticholinergics, major effects of overdosage include delirium, hallucinations, tachycardia, hypertension, hypotension, altered mental status, mydriasis, peripheral vasodilation, coma, seizures, and diminished bowel signs.[4] Effects may be delayed and cyclical. Symptomatic and supportive treatments should be provided in such instances. Rarely, life-threatening dysrhythmias (including bradycardia), cardiogenic shock, or car-

Table 4. Cost of Common Overactive Bladder Treatments

Drug	Regimen	Cost
Trospium	20 mg twice daily	$91.49
Tolterodine	2 mg twice daily	$117.79
Tolterodine LA	4 mg daily	$101.89
Oxybutynin	5 mg twice daily	$18.99
Oxybutynin XL	5 mg daily	$100.99
Flavoxate	100 mg three times daily	$54.79

Cost calculated based on the average retail cost of one-month supply from 3 local pharmacies, Gainesville, FL.

diorespiratory arrest have been reported with anticholinergic drugs.[4] Therefore, ECG monitoring is recommended in the event of overdosage since tachycardia and ventricular arrythmias could occur. It is not known whether or not trospium is excreted into breast milk; caution is advised when trospium is administered to a woman who is breast-feeding due to potential newborn exposure and decreased milk volume.

Drug Interactions

Currently, there are no *in vivo* drug-drug interaction studies available to assess the pharmacokinetic effects of concomitant medications taken with trospium. *In vitro* studies suggest that no clinically relevant interactions are expected. However, drugs that are actively secreted may interact with trospium by competing for renal tubular secretion, resulting in an increase in the serum concentration of trospium and/or the coadministered drug. Also, co-administration of trospium with medications that exhibit anticholinergic effects can cause additive anticholinergic effects. Furthermore, trospium, like other antimuscarinic drugs, can raise gastric pH reducing the oral bioavailability of medications that require an acidic environment for absorption (eg. ketoconazole).[7] Trospium is an inhibitor of CYP2D6; however, drug interactions via cytochrome P-450 pathways have not proven to be significant in *in vitro* models. This is because at the usual oral regimen of trospium, serum concentrations do not reach sufficient concentrations to inhibit CYP2D6.

Cost

Comparative cost data for medications used to treat overactive bladder are presented in Table 4.

Summary

Trospium chloride is a new antimuscarinic agent that has been used in Europe for over 20 years. It has recently been approved by the FDA for the treatment of overactive bladder with symptoms of urge incontinence, urgency, and urinary frequency. Trospium may be better tolerated than currently available anticholinergic agents. Trospium adds to the limited arsenal of medications available to treat overactive bladder and may offer symptomatic relief to patients unable to tolerate older agents.

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New Drug Approvals

- Eszopiclone (Lunesta™, Sepracor Inc.), is the first non-benzodiazepine sedative-hypnotic indicated for the chronic treatment of insomnia in patients with difficulty falling asleep or staying asleep. The dose is 2 mg by mouth immediately before retiring. The dose can be titrated to 3 mg if clinically indicated. Signs of withdrawal have been reported with abrupt discontinuation in clinical studies of 6 months and 6 weeks duration. Eszopiclone is a CYP3A4 substrate; inhibitors of this enzyme may decrease systemic clearance of eszopiclone leading to prolonged effects.

- Darifenacin (Enablex® extended-release tablets, Novartis Pharmaceuticals) is a competitive, selective M_3 muscarinic antagonist approved for the treatment of overactive bladder and associated symptoms. The recommended starting dose is 7.5 mg daily. Based on initial response, the dose may be increased to 15 mg daily as early as 2 weeks after initiating therapy. For patients with moderate hepatic impairment or when coadministered with a potent CYP3A4 inhibitor, the maximum dose is 7.5 mg.

- Solifenacin (Vesicare®, GlaxoSmithKline), a competitive, selective M_3 muscarinic antagonist, improves bladder control and is comparable to tolterodine in safety and other efficacy parameters. The initial dose is 5 mg once daily for the treatment of overactive bladder, but may be increased to 10 mg daily. In patients treated with CYP3A4 inhibitors, or with significant renal or hepatic impairment the maximal recommended dose is 5 mg once daily.

New Drug Approvals (continued)

- Pregabalin (Lyrica™ capsules, Pfizer), a follow-up drug to Pfizer's gabapentin (Neurontin®) has been approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Approved dosages are not yet available, but the effective dosage range in clinical trials appears to be 300–600 mg/day. Pregabalin is a controlled substance, but DEA classification is pending. Common adverse reactions reported include dizziness, somnolence, peripheral edema, blurred vision, weight gain, difficulty with concentration/attention, and dry mouth.

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacy Practice
University of Florida