Lintiz

2mg, 4mg Tablets

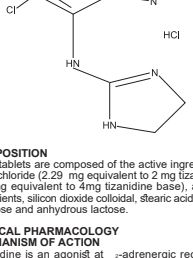
(Tizanidine)

(Product Specs.: U.S.P.)

لِنٹِز ٹیبلٹ

DESCRIPTION

Lintiz (tizanidine hydrochloride) is a centrally acting α_2-adrenergic agonist. Tizanidine HCl (tizanidine) is a white to off-white, fine crystalline powder, which is odorless or with a faint characteristic odor. Tizanidine is slightly soluble in water and methanol; solubility in water decreases as the pH increases. Its chemical name is 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiodiazole hydrochloride. Tizanidine's molecular formula is $C_9H_8ClN_5S$·HCl, its molecular weight is 290.2 and its structural formula is:



COMPOSITION

Lintiz tablets are composed of the active ingredient, tizanidine hydrochloride (2.29 mg equivalent to 2 mg tizanidine base and 4.58mg equivalent to 4mg tizanidine base), and the inactive ingredients, silicon dioxide colloidal, stearic acid, microcrystalline cellulose and anhydrous lactose.

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Tizanidine is an agonist at α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, tizanidine has no direct effect on skeletal muscle fibers or the neuro muscular junction, and no major effect on monosynaptic spinal reflexes. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

PRESCRIBING INFORMATION

The 40 imidazoline chemical structure of tizanidine is related to that of the anti-hypertensive drug clonidine and other α_2-adrenergic agonists. Pharmacological studies in animals show similarities between the two compounds, but tizanidine was found to have one-tenth to one-fiftieth (1/50) of the potency of clonidine in lowering blood pressure.

PHARMACOKINETICS

Absorption and Distribution

Following oral administration, tizanidine is essentially completely absorbed. The absolute oral bioavailability of tizanidine is approximately 40% (CV = 24%), due to extensive first-pass hepatic metabolism. Tizanidine is extensively distributed throughout the body with a mean steady state volume of distribution of 2.4 L/kg (CV= 21%) following intravenous administration in healthy adult volunteers. Tizanidine is approximately 30% bound to plasma proteins. **Pharmacokinetics, Metabolism and Excretion** Tizanidine has linear pharmacokinetics over a dose of 1 to 20 mg. Tizanidine has a half-life of approximately 2.5 hours (CV=33%). Approximately 95% of an administered dose is metabolized. The primary cytochrome P450 isoenzyme involved in tizanidine metabolism is CYP1A2. Tizanidine metabolites are not known to be active; their half-lives range from 20 to 40 hours.

Following single and multiple oral dosing of 14C-tizanidine, an average of 60% and 20% of total radioactivity was recovered in the urine and feces, respectively.

SPECIAL POPULATIONS

Age Effects: No specific pharmacokinetic study was conducted to investigate age effects. Cross study comparison of pharmacokinetic data following single dose administration of 6mg tizanidine showed that younger subjects cleared the drug four times faster than the elderly subjects. Tizanidine has not been evaluated in children.

Hepatic Impairment: The influence of hepatic impairment on the pharmacokinetics of tizanidine has not been evaluated. Because tizanidine is extensively metabolized in the liver, hepatic impairment would be expected to have significant effects on pharmacokinetics of tizanidine. Tizanidine should ordinarily be avoided or used with extreme caution in this patient population.

Renal Impairment: Tizanidine clearance is reduced by more than 50% in elderly patients with renal insufficiency (creatinine clearance < 25 mL/min) compared to healthy elderly subjects; this would be expected to lead to a longer duration of clinical effect. Tizanidine should be used with caution in renally impaired patients.

DRUG INTERACTIONS

Fluvoxamine: The effect of fluvoxamine on the pharmacokinetics of tizanidine was studied in 10 healthy subjects. The Cmax, AUC, and half-life of tizanidine increased by 12-fold, 33-fold and 3-fold, respectively. These changes resulted in significant decreases in blood pressure, increased drowsiness, and psychomotor impairment.

Ciprofloxacin:

The effect of ciprofloxacin on the pharmacokinetics of tizanidine was studied in 10 healthy subjects. The Cmax and AUC of tizanidine increased by 7-fold and 10-fold, respectively. These changes resulted in significant decreases in blood pressure, increased drowsiness, and psychomotor impairment.

CYP1A2 Inhibitors:

The interaction between tizanidine and either fluvoxamine or ciprofloxacin is most likely due to inhibition of CYP1A2 by fluvoxamine or ciprofloxacin. Although there have been no clinical studies evaluating the effects of other CYP1A2 inhibitors on tizanidine, other CYP1A2 inhibitors, such as zileuton, other fluoroquinolones, antiarrythmics (amiodarone, mexiletine, propafenone and verapamil), cimetidine, famotidine oral contraceptives, acyclovir and ticlopidine, may also lead to substantial increases in tizanidine blood concentrations.

Oral Contraceptives:

No specific pharmacokinetic study was conducted to investigate interaction between oral contraceptives and tizanidine. Retrospective analysis of population pharmacokinetic data following single and multiple dose administration of 4 mg tizanidine, however, showed that women concurrently taking oral contraceptives had 50% lower clearance of tizanidine compared to women not on oral contraceptives.

CLINICAL STUDIES

Tizanidine's capacity to reduce increased muscle tone associated with spasticity was demonstrated in two adequate and well controlled studies in patients with multiple sclerosis or spinal cord injury.

In one study, patients with multiple sclerosis were randomized to receive single oral doses of drug or placebo. Patients and assessors were blind to treatment assignment and efforts were made to reduce the likelihood that assessors would become aware indirectly of treatment assignment (e.g., they did not provide direct care to patients and were prohibited from asking questions about side effects). In all, 140 patients received either placebo, 8 mg or 16 mg of tizanidine.

Response was assessed by physical examination; muscle tone was rated on a 5 point scale (Ashworth score), with a score of 0 used to describe normal muscle tone. A score of 1 indicated a slight spastic catch while a score of 2 indicated more marked muscle resistance. A score of 3 was used to describe considerable increase in tone, making passive movement difficult. A muscle immobilized by spasticity was given a score of 4. Spasm counts were also collected.

Assessments were made at 1, 2, 3 and 6 hours after treatment. A statistically significant reduction of the Ashworth score for Zanaflex compared to placebo was detected at 1, 2 and 3 hours after treatment. The greatest reduction in muscle tone was 1 to 2 hours after treatment. By 6 hours after treatment, muscle tone in the 8 and 16 mg tizanidine groups was indistinguishable from

muscle tone in placebo treated patients. Within a given patient, improvement in muscle tone was correlated with plasma concentration. Plasma concentrations were variable from patient to patient at a given dose. Although 16 mg produced a larger effect, adverse events including hypotension were more common and more severe than in the 8 mg group. There were no differences in the number of spasms occurring in each group.

In a multiple dose study, 118 patients with spasticity secondary to spinal cord injury were randomized to either placebo or tizanidine. Steps similar to those taken in the first study were employed to ensure the integrity of blinding.

Patients were titrated over 3 weeks up to a maximum tolerated dose or 36 mg daily given in three unequal doses (e.g., 10 mg given in the morning and afternoon and 16 mg given at night). Patients were then maintained on their maximally tolerated dose for 4 additional weeks (i.e., maintenance phase). Throughout the maintenance phase, muscle tone was assessed on the Ashworth scale within a period of 2.5 hours following either the morning or afternoon dose. The number of daytime spasms was recorded daily by patients.

At endpoint (the protocol-specified time of outcome assessment), there was a statistically significant reduction in muscle tone and frequency of spasms in the tizanidine treated group compared to placebo. The reduction in muscle tone was not associated with a reduction in muscle strength (a desirable outcome) but also did not lead to any consistent advantage of tizanidine treated patients on measures of activities of daily living.

INDICATIONS AND USAGE
Tizanidine is a short-acting drug for the management of spasticity. Because of the short duration of effect, treatment with tizanidine should be reserved for those daily activities and times when relief of spasticity is most important.

CONTRAINDICATION
Concomitant use of tizanidine with fluvoxamine or with ciprofloxacin, potent inhibitors of CYP1A2, is contraindicated. Significant alterations of pharmacokinetic parameters of tizanidine including increased AUC, t1/2, Cmax, increased oral bioavailability and decreased plasma clearance have been observed with concomitant administration of either fluvoxamine or ciprofloxacin. This pharmacokinetic interaction can result in potentially serious adverse events. Lintiz is contraindicated in patients with known hypersensitivity to Lintiz or its ingredients.

WARNINGS HYPOTENSION
Tizanidine is an α_2-adrenergic agonist (like clonidine) and can produce hypotension. The hypotensive effect is dose related and has been measured following single doses of ≥ 2 mg. The chance of significant hypotension may possibly be minimized by titration of the dose and by focusing attention on signs and symptoms of hypotension prior to dose advancement. In addition, patients moving from a supine to fixed upright position may be at increased risk for hypotension and orthostatic effects.

SEDATION
In the multiple dose, controlled clinical studies, 48% of patients receiving any dose of tizanidine reported sedation as an adverse event. In 10% of these cases, the sedation was rated as severe compared to < 1% in the placebo treated patients. Sedation may interfere with everyday activity. The effect appears to be dose related. In a single dose study, 92% of the patients receiving 16 mg, when asked, reported that they were drowsy during the 6 hour study. This compares to 76% of the patients on 8 mg and 35% of the patients on placebo. Patients began noting this effect 30 minutes following dosing. The effect peaked 1.5 hours following dosing. Of the patients who received a single dose of 16 mg, 51% continued to report drowsiness 6 hours following dosing compared to 13% in the patients receiving placebo or 8 mg of tizanidine. In the multiple dose studies, the prevalence of patients with sedation peaked following the first week of titration and then remained stable for the duration of the maintenance phase of the study.

USE IN PATIENTS WITH HEPATIC IMPAIRMENT
The influence of hepatic impairment on the pharmacokinetics of tizanidine has not been evaluated. Because tizanidine is extensively metabolized in the liver, hepatic impairment would be expected to have significant effects on the pharmacokinetics of tizanidine. Tizanidine should ordinarily be avoided or used with extreme caution in patients with hepatic impairment.

USE IN RENALLY IMPAIRED PATIENTS
Tizanidine should be used with caution in patients with renal insufficiency (creatinine clearance < 25 mL/min), as clearance is reduced by more than 50%. In these patients, during titration, the individual doses should be reduced. If higher doses are required, individual doses rather than dosing frequency should be increased. These patients should be monitored closely for the onset or increase in severity of the common adverse events (dry mouth, somnolence, asthenia and dizziness) as indicators of potential overdose.

DISCONTINUING THERAPY
If therapy needs to be discontinued, particularly in patients who have been receiving high doses for long periods, the dose should be decreased slowly to minimize the risk of withdrawal and rebound hypertension, tachycardia, and hypertonia.

PREGNANCY
Pregnancy Category C
LABOR AND DELIVERY
The effect of tizanidine on labor and delivery in humans is unknown.
NURSING MOTHERS
It is not known whether tizanidine is excreted in human milk, although as a lipid soluble drug, it might be expected to pass into breast milk.
GERIATRIC USE
Tizanidine should be used with caution in elderly patients because clearance is decreased four-fold.
PEDIATRIC USE
There are no adequate and well-controlled studies to document the safety and efficacy of tizanidine in children.

COMMON ADVERSE EVENTS LEADING TO DISCONTINUATION
Most frequently leading to withdrawal of tizanidine treated patients in the controlled clinical studies were asthenia (weakness, fatigue and/or tiredness) (3%), somnolence (3%), dry mouth (3%), increased spasm or tone (2%), and dizziness (2%).

MOST FREQUENT ADVERSE CLINICAL EVENTS SEEN IN ASSOCIATION WITH THE USE OF TIZANIDINE
The most frequent adverse effects were dry mouth, somnolence/sedation, asthenia (weakness, fatigue and/or tiredness) and dizziness. Three-quarters of the patients rated the events as mild to moderate and one-quarter of the patients rated the events as being severe. These events appeared to be dose related.

DOSAGE AND ADMINISTRATION
A single dose of 8 mg of tizanidine reduces muscle tone in patients with spasticity for a period of several hours. The effect peaks at approximately 1 to 2 hours and dissipates between 3 to 6 hours. Effects are dose-related. Although single doses of less than 8 mg have not been demonstrated to be effective in controlled clinical studies, the dose-related nature of tizanidine's common adverse events make it prudent to begin treatment with single oral doses of 4 mg. Increase the dose gradually (2 to 4 mg steps) to optimum effect (satisfactory reduction of muscle tone at a tolerated dose). The dose can be repeated at 6 to 8 hour intervals, as needed, to a maximum of three doses in 24 hours. The total daily dose should not exceed 36 mg.

PRESENTATION
Lintiz 2mg tablets: Pack of 1x10's tablets.
Lintiz 4mg tablets: Pack of 1x10's tablets.

STORAGE :
Protect from light & moisture. Store at room temperature.
Keep out of the reach of children.

WARNING: To be sold on prescription of a registered medical practitioner only.

ہدایات :
روشنی اور نمی سے محفوظ کمرے کے درجہ حرارت میں رکھیں۔
بچوں کی پہنچ سے دُور رکھیں۔
ڈاکٹری ہدایت کے مطابق استعمال کریں۔
انتباہ : صرف رجسٹرڈ میڈیکل پریکٹیشنر کے نسخے پر فروخت کے لئے۔

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