Attachment 1b

Safety Related Notification

Clean Version of the Product Information for Quilonum SR® (lithium carbonate) Tablets 450 mg [AUST R 53377]

DESCRIPTION

Quilonum SR contains lithium carbonate, a white, light alkaline powder with molecular formula Li_2CO_3 and molecular weight 73.89. Quilonum SR tablets also contain inactive ingredients including povidone, starch maize, lactose, gelatin, carmellose calcium, talc purified, calcium behenate, magnesium stearate, titanium dioxide, macrogol 6000, and Eudragit E100.

PHARMACOLOGY

Preclinical studies have shown that lithium alters sodium transport in nerve and muscle cells and effects a shift toward intraneuronal metabolism of catecholamines, but the specific biochemical mechanism of lithium action in mania is unknown.

Pharmacokinetics

Whilst Quilonum SR tablets are designed to reduce fluctuations in plasma lithium concentrations, the formulation is not controlled-release in the usual sense; rather, the delayed uptake results primarily from the physicochemical characteristics of the lithium carbonate.

Quilonum SR is almost completely absorbed from the gastrointestinal tract, with peak serum concentrations occurring 2.5 to 5.5 hours after ingestion.

Lithium does not bind to plasma proteins, is not metabolised, and is distributed non-uniformly throughout body water. The volume of distribution of lithium is approximately equivalent to total body water (0.6 L/kg). Lithium does not cross the blood-brain barrier rapidly. The half-life of lithium is approximately one day, and equilibrium is reached after five to seven days of regular intake.

No hepatic metabolism of lithium occurs, and glomerular filtration eliminates the entire dose. The proximal renal tubule resorbs 60 to 70% of the filtered lithium load, whereas no absorption occurs in the distal tubule. Renal clearance of lithium is *decreased with renal insufficiency and hyponatraemia. Pregnancy and an alkaline urine increase lithium clearance.

INDICATIONS

Lithium is indicated in the treatment of acute episodes of mania and hypomania and for the prophylaxis of recurrent manic-depressive illness.

CONTRAINDICATIONS

Lithium should not be given to patients with significant renal or cardiovascular disease, including conduction abnormalities, or untreated hypothyroidism. Lithium should not be given to patients with low body sodium including dehydrated patients, those with Addison's Disease or reduced dietary salt intake, since the risk of lithium toxicity is higher in these patients.

Quinolum SR should not be given to patients with a previous history of hypersensitivity to lithium or any of the excipients contained in the tablets (see Description).

PRECAUTIONS

Lithium toxicity is closely related to serum lithium concentrations and can occur at doses close to therapeutic concentrations. Early clinical signs of toxicity include diarrhoea, vomiting, tremor, mild ataxia, drowsiness and muscular weakness.

Diuretics should only be used with caution during lithium treatment (see interactions). Lithium levels should be monitored at shorter intervals and appropriate dosage adjustment should be made.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when the lithium is discontinued.

Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Some structural changes have also been reported in manic-depressives never exposed to lithium. The relationship between renal function, morphologic changes and lithium therapy has not been established. When kidney function is assessed, routine urinalysis and other tests may be used to evaluate tubular function (e.g. urine SG or osmolality following water deprivation, or 24 hour urine volume) and glomerular function (e.g. serum creatinine or creatinine clearance).

An encephalopathic syndrome, (characterised by weakness, lethargy, fever tremulousness, confusion, extrapyramidal symptoms leucocytosis, elevated serum enzymes), has occurred in a few patients treated with lithium and neuroleptics. In some instances, the syndrome was followed by irreversible brain damage. Because a possible causal relationship between these events and treatment with lithium and neuroleptics, patients receiving combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if symptoms appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome.

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside.

Vomiting, diarrhoea, intercurrent infection, fluid deprivation, excess sweating and some drugs (see Interactions with other drugs), may reduce the renal clearance of lithium and thereby precipitate intoxication. Lithium excretion may also be reduced in elderly patients. The elderly often respond to reduced dosage and may exhibit signs of toxicity at serum concentrations ordinarily tolerated by younger patients.

It is important to maintain a normal diet and fluid intake particularly an adequate and constant salt and water intake. Patients should be informed of, and told to report signs of intoxication, polyuria and polydipsia, or episodes of nausea and vomiting. The family should be instructed in the early signs of toxicity.

Acute renal failure has been reported rarely with lithium toxicity.

Lithium should be temporarily discontinued before commencing electroconvulsive therapy (ECT) to reduce the risk of delirium, which may occur when the two treatments are co-administered.

Treatment should be discontinued during intercurrent illness.

Driving or operating machinery

At the beginning of treatment the occasional onset of fatigue can impair reflexes. Lithium may cause disturbances of the CNS (e.g. somnolence, dizziness or hallucinations). Patients should be warned of the possible hazards when driving or operating machinery.

Check the following before use

Renal, cardiac and thyroid function should be assessed prior to initiating therapy, and periodically thereafter.

Use in Pregnancy (Category D)

Lithium crosses the placental barrier. In animal studies, lithium has been reported to interfere with fertility, gestation, and foetal development. In humans, lithium may cause fetal harm when administered to a pregnant woman. Data from the lithium birth register, which collects data on the known cases of first trimester exposure to lithium suggests an increase in cardiac and other abnormalities, especially Ebstein's anomaly. As of 1980, 225 infants were included in the register. Of these, 25 infants were born with congenital abnormalities, including 18 with serious cardiovascular malformations, 6 of which were cases of Ebstein's anomaly.

Lithium taken near term may produce symptoms of lithium toxicity in the newborn which include disturbance of thyroid function. Most effects are self-limiting with resolution within 1-2 weeks.

Lithium should not be used in pregnancy, especially during the first trimester, unless in the judgement of the physician it is considered necessary. Patients should be informed of potential hazards to the fetus.

In certain cases where a severe risk to the patient could have existed if treatment were stopped, lithium has been continued during pregnancy. If given, serum levels should be measured frequently because of the changes in renal function associated with pregnancy and parturition.

Use in Lactation

Lithium is excreted in human milk. Breastfeeding should be discontinued during lithium therapy.

Use in Children

Since information regarding the safety and efficacy in children under 12 years of age is not available, lithium therapy is not recommended in this age group.

Use in Elderly

Lithium should be used with care in the elderly. Elderly patients often require lower lithium dosages to achieve therapeutic serum concentrations. They may also exhibit adverse reactions at serum concentrations ordinarily tolerated by younger patients.

INTERACTIONS with other drugs

Clinicians should be aware that lithium may interact with a variety of drugs. Caution should therefore be exercised when lithium is co-administered with any other medication. In particular, the following important clinical interactions have been reported:

Interactions which:

increase serum lithium concentrations

The following have been reported to increase steady state serum lithium concentrations, possibly resulting in lithium toxicity:

- Metronidazole
- Non-steroidal anti-inflammatory drugs

  -Lithium levels should be monitored when patients initiate or discontinue NSAID use. In some cases, lithium toxicity has resulted from interactions between an NSAID and lithium. Indomethacin and piroxicam have been reported to increase significantly steady-state plasma lithium concentrations. There is also evidence that other non-steroidal anti-inflammatory agents, including the selective cyclooxygenase-2 (COX-2) inhibitors, have the same effect.
- ACE inhibitors
- Diuretics (see also below):

  -thiazides, which show a paradoxical antidiuretic effect resulting in possible water retention and lithium intoxication.

  -potassium-sparing

  -loop

decrease serum lithium concentrations:

A decrease in the serum lithium concentration may be seen on the concomitant administration of lithium with:

- Urea
- Xanthines
- Alkalinizing agents such as sodium bicarbonate
- Diuretics (see also above):
  - -osmotic
  - -carbonic anhydrase inhibitors including acetazolamide

Other drugs affecting electrolyte balance (eg. appetite suppressants, steroids) may alter lithium excretion.

Serum lithium concentrations should therefore be monitored more frequently if concomitant therapy with any of the above drugs is initiated.

Interactions causing neurotoxicity:

The following have been reported as causing neurotoxicity when used concomitantly with lithium:

- *Neuroleptics*, particularly haloperidol, which may result in an encephalopathic syndrome (see precautions). Concurrent dosage should be lower than usual.
- *Antiepileptics*
- *Methyldopa*
- *Selective serotonin reuptake inhibitors (SSRI's):* Possible interactions have been reported with fluoxetine, therefore, concomitant use of other SSRIs (paroxetine, sertraline) should be undertaken with caution as this combination may precipitate a serotonergic syndrome.
- *Calcium channel blockers.* These may increase the neurotoxic effects of lithium, and serum lithium concentrations may need to be at the lower end of the therapeutic range.
- *Tri-cyclic antidepressants.*

Additional interactions:

Lithium may prolong the effects of neuromuscular blocking agents.

ADVERSE REACTIONS

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations as well as to individual sensitivity to lithium and generally occur more frequently and with greater severity at higher concentrations. Fine hand tremor, polyuria, thirst and nausea may occur during initial therapy, and may persist throughout acute treatment. Nausea is usually transient. All of these symptoms usually subside with continued therapy or with reduction in dosage.

Other adverse events commonly reported during lithium therapy include, weight gain, fatigue and mild cognitive impairment.

Diarrhoea, vomiting, drowsiness, muscular weakness and incoordination are early signs of lithium toxicity, however, they can occur at lithium concentrations less than 2.0 mmol/L. At higher concentrations ataxia, tinnitus, blurred vision, giddiness and increasing polyuria are seen. Treatment should be discontinued immediately on the first sign of toxicity.

The following reactions appear to be related to serum lithium concentrations. Adverse reactions can occur in patients with serum concentrations within the therapeutic range (i.e. below 1.5mmol/L or lower in the elderly).

Body as a whole: oedema.

Cardiovascular: cardiac arrhythmia, hypotension, ECG changes including nonspecific T wave changes, oedema, Raynaud's phenomena, peripheral circulatory collapse, bradycardia, sinus node dysfunction.

Dermatologic: alopecia, acne, folliculitis, pruritus, psoriasis exacerbation, rash.

Endocrine: euthyroid goitre, hypothyroidism, rare cases of hyperthyroidism, hyperglycaemia, hypercalcaemia, hyperparathyroidism, weight gain.

Gastrointestinal: anorexia, nausea, vomiting, diarrhoea, gastritis, excessive salivation, abdominal pain.

Haematological: leucocytosis.

Hypersensitivity: angioedema.

Neuromuscular/CNS: tremor, fasciculations, twitching clonic movements of extremities, ataxia, choreoathetoid movements, hyperactive deep tendon reflexes, extrapyramidal symptoms, syncope, seizures, slurred speech, dizziness, vertigo, nystagmus, somnolence, stupor, coma, hallucinations, taste distortion, taste impairment, scotomata, pseudotumour cerebri, autonomic effects including blurred vision, dry mouth, dysgeusia and impotence/sexual dysfunction. Myasthenia gravis has been observed rarely.

Renal: symptoms of nephrogenic diabetes insipidus.

DOSAGE AND ADMINISTRATION

Quilonum SR tablets should be given every 12 hours. Tablets should not be broken in half, crushed or chewed, nor taken with a hot drink. No attempt should be made to dissolve them. Dosage must be individualised according to serum concentrations and clinical response. It is advisable that serum lithium concentrations are estimated 4 to 5 days after starting treatment. Blood samples for serum lithium concentrations should be drawn 12 hours after the last dose, immediately prior to next dose.

Lithium should be taken with food, as this appears to reduce the likelihood of gastrointestinal adverse effects, such as diarrhoea. However, the precise effect of food on the absorption of Quilonum SR is not known.

When switching a patient from immediate release form to controlled release, give the same total daily dose when possible. Most patients on maintenance therapy are stabilised on 900 mg daily. These patients should be monitored at 1-2 week intervals, and dosage adjusted if necessary, until stable and satisfactory serum concentrations and clinical state are achieved.

Acute mania: Optimal patient response can usually be established with 1800 mg per day in divided doses. Such doses will normally produce the desired serum lithium concentrations between 0.8 and 1.4 mmol/L. Dosage must be individualised according to serum levels and clinical response. Regular monitoring of the patients clinical state and serum lithium concentrations is necessary. Serum concentrations should be determined once or twice per week during the acute phase, and until the serum level and clinical condition of the patient have been stabilised.

Long term therapy/prophylaxis: Dosage should be adjusted to maintain a serum lithium concentration 0.6 to 1.0 mmol/L. Dosage will vary from one individual to another, but usually 900mg to 1200mg per day in divided doses will maintain this concentration. Serum lithium concentration should be assessed frequently during the acute phase, and in uncomplicated cases/during maintenance, every 2 months.

OVERDOSAGE

The toxic levels for lithium are close to therapeutic concentrations. Symptoms of moderate to severe lithium toxicity include anorexia, persistent nausea and vomiting, blurred vision, muscle fasciculations, clonic limb movement, hyperactive deep tendon reflexes, choreoathetoid movements, delirium, syncope, stupor, EEG changes, coma and circulatory failure. In severe intoxication generalized seizure, renal failure and death may ensue.

No specific antidote to lithium poisoning is known. Lithium toxicity is a medical emergency, since it can result in permanent neuronal damage and death. Treatment consists of ceasing lithium and the induction of vomiting and/or gastric lavage together with supportive and symptomatic measures. Particular attention should be paid to maintenance of fluid and electrolyte balance and of adequate renal function. Where convulsions are present, diazepam may be used. Peritoneal dialysis or haemodialysis may help eliminate the lithium ion. The latter method is preferable, particularly in chronic toxicity where serum lithium exceeds 4 mmol/L. Forced diuresis/saline diuresis has resulted in serious problems with electrolyte balance and is inferior to dialysis.

PRESENTATIONS

Slow Release Tablets containing 450mg lithium carbonate per tablet, in blister packs of 100. Quilonum SR tablets are white, film-coated tablets, with breaklines on both sides.

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