Graylands Hospital

DRUG BULLETIN

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Lithium-Induced Hypothyroidism When to Treat?

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It is well known that treatment with lithium increases the incidence of thyroid dysfunction. Hypofunction is the most common abnormality and can present as an abnormal test result, goitre without hypothyroidism or symptomatic hypothyroidism. Serum levels of lithium are not thought to correlate with incidence and severity of hypothyroidism. In rare cases, lithium has been associated with *hyper*thyroidism.

Subclinical Hypothyroidism

Subclinical hypothyroidism, a milder form of thyroid dysfunction, has been reported to occur in up to 23% of patients on lithium therapy, compared to rates of approximately 10% in the background population [(1)].

Subclinical hypothyroidism is characterised by a mildly elevated serum thyroid stimulating hormone (TSH) but normal free thyroxine (T_4). Symptoms may or may not be present.

Is lithium-induced hypothyroidism transient?

Some patients may have initial modest rises in serum TSH, the majority of which will be transient, devoid of clinical symptoms and will resolve spontaneously. Prospective studies have shown that many patients who have an abnormal set of thyroid function tests (TFTs) after starting lithium, revert to euthyroid status within 1-2 years [(1)]. However, some patients will develop more persistent subclinical hypothyroidism and others will progress to overt hypothyroidism (elevated TSH and subnormal T_4), at which point thyroid supplementation is a necessity.

Is the development of hypothyroidism while taking lithium a reason to stop the drug?

No. If a good response is achieved and the patient is willing to continue with lithium, the hypothyroidism may be treated with thyroxine in dosages that will maintain normal TSH serum levels. *See table overleaf.*

Symptoms of Hypothyroidism

Fatigue
Dry skin
Weakness
Cold intolerance
Lethargy
Decreased memory/concentration
Constipation
Depressed mood
Weight gain
Changes in menstruation

At what stage should thyroid supplementation be commenced?

If the patient develops affective symptoms, has signs and symptoms of hypothyroidism and/or the TFTs do not normalise, thyroid supplementation is appropriate. Lithium cessation will result in reversal of the abnormalities, usually within 1-2 months.

If a patient on thyroxine is stopping lithium, the thyroxine should be gradually tapered off over a month and the TFTs measured monthly until they return to normal.

Subclinical Hypothyroidism: Serum TSH and suggested action to take

SERUM TSH (mU/L)	INTERVENTION
5 - 10 & patient ***asymptomatic***	✪ Thyroid supplementation not immediately necessary ✪ Repeat TSH level preferably after a month (at least 2 weeks but less than 2 months) ✪ If TSH remains elevated, monitor closely (every 3 months) for symptom exacerbation or progression to overt hypothyroidism
5 - 10 & ***patient reports symptoms related to hypothyroidism***	✪ Initiate thyroxine therapy (see below) ✪ Baseline neurocognitive assessment may be useful to serve as baseline in future for those with cognitive dysfunction
> 10	✪ Initiate thyroxine therapy regardless of whether patient symptomatic or not ✪ These patients are at high risk for progression to overt hypothyroidism

Initiating thyroxine treatment:

- ✪ Check baseline cardiac status.
- ✪ Healthy patients: usual starting dose is 25-50mcg, increasing by 25mcg every 6 weeks until TSH normal. Doses of 50-100mcg are usually sufficient.
- ✪ Elderly or patients with compromised cardiac function: start at 12.5-25mcg and gradually increase the dose with frequent monitoring for side effects.
  (NB. Only 50mcg tablets available in Australia – may be hard to administer 12.5mcg).

References

1. Kleiner J, Altshuler L, Hendrick V, Hershman J. Lithium-Induced Subclinical Hypothyroidism: Review of the Literature and Guidelines for Treatment. J Clin Psychiatry 1999;60:249-255.

Jefferson JW. Lithium. In: Dukes MNG & Aronson JK, editors. Meyler's Side Effects of Drugs, 14th ed. Amsterdam: Elsevier Science, 2000: 88-89.

Bitton R & Schneider B. Endocrine, metabolic, and nutritional effects of psychotropic drugs. In: Kane JM & Lieberman JA, editors. Adverse Effects of Psychotropic Drugs. New York: The Guildford Press, 1992: 345-346.

Perry PJ, Alexander B, Liskow BI. Antimanics. In: Reinburg C, Davenport J, Harley P, Richters R, editors. Psychotropic Drug Handbook, 7th ed. Washington, DC: American Psychiatric Press, 1997: 244-245.

Difficulty Achieving Therapeutic Sodium Valproate Levels

It is generally acknowledged that a valproate plasma level between 50 & 100mg/L correlates with efficacy in mania and bipolar affective disorder [(1)]. Occasionally, this level can be difficult to achieve. Levels may appear to plateau, despite increasing dose, leading to the temptation to increase the dose even further, with potential subsequent toxicity. This "plateau effect" can be explained by the fact that sodium valproate shows non-linear kinetics in the therapeutic range (i.e. plasma drug concentration may not increase in proportion to dose increase) which makes interpretation of results sometimes difficult.

Relevance of Free or Unbound Drug

Valproate is highly bound to plasma proteins. The assays performed by a laboratory use plasma or blood and thus measure *total* (bound and unbound) drug concentration, whereas it is the *unbound* drug (or "free fraction") that produces the desired pharmacological effect.

The extent of protein binding is concentration dependent. *Free* drug levels are thought to be negligible until a *total* level of 40-50mg/L is reached. At 50mg/L, the free fraction is stated to be approximately 5-10%, increasing to 15-20% at 100mg/L [(2)]. Above this, free levels can increase disproportionately. A small study in healthy subjects estimated that increasing the *total* level from 100mg/L to 125mg/L, resulted in a nearly three-fold increase in the active *free* fraction (from less than 10% to 25%) [(3)].

Many other factors can affect the free fraction, including patient's serum protein levels, free fatty acid levels (competition for binding sites) and other drugs that may displace valproate from its binding sites eg. aspirin.

Clinical Consequences of Saturable Protein binding

Non-linear kinetics

At higher doses in particular, saturation of protein binding sites may occur, resulting in non-linear increases in amount of *free* active drug, and hence a larger *free fraction*. The main consequence of this is greater drug clearance and hence a non-linear relationship between dose and steady-state *total* drug levels i.e. plateau effect; levels do not rise as expected.

It is important to note that at higher doses, the change in *free* drug level may actually be much larger than indicated by the change in *total* drug level. Therefore, *free* rather than *total* plasma levels may be a more appropriate measure in this setting as *free* levels may in fact be in the therapeutic range (thought to be approximately 3-7mg/L) [(4)].

Unfortunately, determination of *free* valproate levels is a costly assay and not many laboratories in Western Australia, if any, perform this investigation.

Potential for increased adverse effects

The threshold level thought to be associated with a greater than predicted frequency of adverse events is around that at which saturation of protein binding sites occurs and *free* valproate levels increase in a non-linear fashion.

This suggests an optimal maximum *total* level of 100mg/L and that the benefits of increasing the level above this will probably be negated by an

increased incidence of adverse effects.

Summary

In the absence of an assay to determine *free* drug levels, the possibility of this scenario must be considered when the achievement of therapeutic valproate levels is proving problematic.

A patient may present clinically well, despite an unexpectedly low level or one that is beginning to plateau off. Presuming non-compliance has been ruled out, further increases in dosage should be undertaken cautiously. The unbound *free* drug level may actually be within the therapeutic range and an increase in dose may cause intolerable side effects for the patient or worse still, toxicity.

References

1. Bowden CL, Janicak PG, Orsulak P, Swann AC, Davis JM et al. Relation of serum valproate concentration to response in mania. Am J Psychiatry 1996;153:765-770.

2. Parfitt K. Antiepileptics. In: Martindale, 32nd ed. United Kingdom: Pharmaceutical Press, 1999:363.

3. Henriksen O, Johannessen SI. Clinical and pharmacokinetic observations on sodium valproate: a 5-year follow-up study on 100 children with epilepsy. Acta Neurol Scand 1982;65:504-523.

4. Kilpatrick CJ, Fullinfaw RO, Bury RW, Moulds RFW. Plasma concentrations of unbound valproate and the management of epilepsy. Aust NZ J Med 1987;17:574-579.

Birkett DJ. Non-linear pharmacokinetics. In: Pharmacokinetics Made Easy, 1st ed. Australia: McGraw-Hill, 1998:74-83.

Depot Injections and Nut Allergy

Depot antipsychotic medications are widely used, especially in patients with a history of non-compliance. Hypersensitivity/allergic reactions are possible with all depot preparations, which may be as a result of the drug itself or its vehicle.

Although coconut hypersensitivity is relatively rare, immunological cross-reactivity has been shown between coconut allergens and soy or walnut proteins. Allergies to peanut and tree nut (eg. walnut, brazil nut) are becoming more prevalent. Similarly, reports of hypersensitivity to sesame seed and oil have increased in recent years.

Many clinicians may be unaware of the presence of nut oil within depot preparations. Knowledge of the constituents of these preparations can influence treatment decisions. Patients should first be given a small test-dose to check for allergies that may be previously undiagnosed, as undesirable effects are prolonged due to the long-acting nature of the preparation.

Drug	Oil used as vehicle in depot
Flupenthixol Zuclopenthixol (both decanoate and acetate)	Coconut oil
Haloperidol Pipothiazine Fluphenazine	Sesame oil

NB. The solvent for Risperdal Consta® long-acting injection is an aqueous solution.

Reference

Reeves S, Howard R. Depot injections and nut allergy. Br J Psychiatry 2002;180:188.

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Comments are welcome at the e-mail address: **Druginformation.Graylands@health.wa.gov.au**