Caveats in treating thyroid disease: practical implications

G I Varughese¹ A A Tahrani¹ J Davis²
R N Clayton¹ F W F Hanna¹

J R Soc Med 2006;**99**:582–583

KEY MESSAGE

The timing of treatment in patients with thyroid disease is extremely important. This Grand Round reminds clinicians to be aware of unusual causes for persistent abnormalities in thyroid function tests (TFTs) despite optimal treatment.

CASE HISTORY

This case concerns a 47-year-old woman who was initially diagnosed as having primary hypothyroidism nearly four years prior to this incident; on treatment with levothyroxine sodium (LT₄) 150 µg daily. Despite reasonable doses of LT₄, and being fully compliant with her therapy, at no stage was her TSH less than 20 mU/L (Table 1). Malabsorption was ruled out and there were no clinical features to suggest this. When the patient was reviewed in the endocrine clinic, she was advised to take the tablets on an empty stomach (rather than with the white tea and breakfast that she had regularly been having immediately following her LT₄ tablets). On subsequent follow-up four months later, the TFTs had improved on the same dose of LT₄ and she had lost nearly 2 kg in weight despite the 'Christmas Effect', as she described it, and she felt well in herself. Subsequent TFTs continue to remain in the reference range with the altered timing of intake of LT₄.

COMMENT

Prior to giving her the advice to make alterations to the timing of tablets, her TFTs showed consistently low free thyroxine (T₄) and correspondingly high thyroid stimulating hormone (TSH) concentrations, respectively (Table 1). According to the drug information leaflet of LT₄, the recommendation is to take the tablets preferably *before* breakfast. Ideally, the tablets should be taken on an empty stomach, as the sodium salt enhances the absorption

Table 1 Thyroid function over the years

Year	TSH (0.3–5.0 mU/L)	T ₄ (10–22 pmol/L)
April 2006	2.2	18
December 2005	2.87	15
August 2005	20.18	10
April 2003	24.25	13
October 2002	20.77	11
May 2002	31.04	14
February 2002	50.05	11

of levothyroxine, which is greater in the fasting than in the fed state.^{1,2} Gastrointestinal absorption of LT₄ is on average 80%,³ mainly from the small intestine.⁴ Interestingly, non-specific absorption of LT₄ by dietary fibres has been shown to decrease the bioavailability of LT₄, necessitating a higher dose in patients with a high intake of dietary fibre (e.g. wholewheat bread, bran, granola).⁵ Of note, administration of LT₄ concurrently with soya dietary protein has also resulted in decreased absorption of LT₄ and the need for higher oral doses of LT₄ to attain therapeutic serum thyroid hormone levels.⁶ Formulations containing soy milk were recognized as affecting thyroid function in infants nearly half a century ago^{7,8} and emphasis has been reiterated on this topic more recently.⁹

The timing of treatment in patients with thyroid disease is extremely important and should be explored in detail when TFTs fail to improve despite therapy. The patient described above was not on any other medication that would have interfered with the bioavailability or pharmacokinetics of LT₄. Since factors affecting the management of thyroid dysfunction—such as those detailed in Table 2—are infrequently encountered in clinical practice, patient non-compliance may be suspected; we suggest that an alternative cause should be considered in such patients.

Competing interests None declared.

Guarantor F W F Hanna.

REFERENCES

- DeGroot LJ, Jameson JL. Hypothyroidism and Myxedema Coma. In: *Endocrinology: Volume 2*, 4th edn. Philadelphia: WB Saunders Company, 2001; Chapter 105: pp 1500–1
- Greenspan FS, Gardner DG. The Thyroid Gland. In: *Basic and Clinical Endocrinology*. Maidenhead, UK: McGraw-Hill Companies, 2004; Chapter 7: pp 215
- Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, metabolism, and bioavailability

Departments of Endocrinology¹ & Medicines Information² (Pharmacy), University Hospital of North Staffordshire, Stoke-on-Trent ST4 6QG, UK

Correspondence to: Dr George I Varughese

E-mail: georgeiv@doctors.org.uk

Table 2 Various drugs and conditions causing hypothyroidism in patients on thyroxine

Cause of hypothyroidism	Reference
<i>Impaired absorption of thyroxine</i>	
Dietary Fibre (wholewheat bread, granola, bran)	Liel Y <i>et al. J Clin Endocrinol Metab</i> 1996; 81 :857–9
Bile acid sequestering agents	Witztum JL <i>et al. J Clin Endocrinol Metab</i> 1978; 46 :838–40 Harmon SM <i>et al. Ann Intern Med</i> 1991; 115 :658–9
Sucralfate	Havranoka J <i>et al. Ann Intern Med</i> 1992; 117 :445–6
Aluminium Hydroxide	Sperber AD <i>et al. Arch Intern Med</i> 1992; 152 :183–4
Ferrous sulphate	Campbell NR <i>et al. Ann Intern Med</i> 1992; 117 :1010–3.
Calcium Carbonate	Singh N <i>et al. JAMA</i> 2000; 283 :2822–5
Lithium	Kleiner J <i>et al. J Clin Psychiatry</i> 1999; 60 :249–55
Selenium deficiency	Moncayo R <i>et al. Clin Nutr</i> 2005; 24 :530–1
Omeprazole	Centanni M <i>et al. NEJM</i> 2006; 354 :1787–95
Bone Marrow Transplantation	Carlson K <i>et al. Bone Marrow Transplant</i> 1992; 10 :123–7
Herbal remedies	Geatti O <i>et al. Thyroidology</i> 1993; 5 : 97–102
Soy	Bell DS & Ovalle F. <i>Endocr Pract</i> 2001; 7 :193–4 Van Wyk JJ <i>et al. Pediatrics</i> 1959; 24 :752–60 Hydovitz JD. <i>NEJM</i> 1960; 262 :351–3 Conrad SC <i>et al. Arch Dis Child</i> 2004; 89 :37–40
Malabsorption & short-bowel syndrome	Topliss DJ <i>et al. Can Med Assoc J</i> 1980; 123 :765–6
<i>Increased clearance of thyroxine</i>	
Phenobarbital	Isley WL. <i>Ann Intern Med</i> 1987; 107 :517–8
Phenytoin	Isley WL. <i>Ann Intern Med</i> 1987; 107 :517–8
Carbamazepine	Isley WL. <i>Ann Intern Med</i> 1987; 107 :517–8
Rifampicin	Isley WL. <i>Ann Intern Med</i> 1987; 107 :517–8
<i>Increased need for thyroxine</i>	
Pregnancy	Mandel SJ <i>et al. NEJM</i> 1990; 323 :91–6
Weight gain	Glinier D <i>et al. J Clin Endocrinol Metab</i> 1990; 71 :276–87
<i>Other mechanisms</i>	
Amiodarone	Figge J <i>et al. Ann Intern Med</i> 1990; 113 :553–5
Raloxifene	Siraj ES <i>et al. Arch Intern Med</i> 2003; 163 :1367–70
Sertraline	McCowen KC <i>et al. NEJM</i> 1997; 337 :1010–1
Chloroquine	Munera Y <i>et al. BMJ</i> 1997; 314 :1593
Noncompliance with treatment	Ain KB <i>et al. JAMA</i> 1991; 266 :2118–20

of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. *N Engl J Med* 1987;**316**:764–70

- 4 Topliss DJ, Wright JA, Volpe R. Increased requirement for thyroid hormone after a jejunoileal bypass operation. *Can Med Assoc J* 1980;**123**:765–6
- 5 Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. *J Clin Endocrinol Metab* 1996;**81**:857–9

- 6 Bell DS, Ovalle F. Use of soy protein supplement and resultant need for increased dose of levothyroxine. *Endocr Pract* 2001;**7**:193–4

- 7 Van Wyk JJ, Arnold MB, Wynn J, Pepper F. The effects of a soybean product on thyroid function in humans. *Pediatrics* 1959;**24**:752–60
- 8 Hydovitz JD. Occurrence of goiter in an infant on a soy diet. *N Engl J Med* 1960;**262**:351–3
- 9 Conrad SC, Chiu H, Silverman BL. Soy formula complicates management of congenital hypothyroidism. *Arch Dis Child* 2004;**89**:37–40