CASE REPORT

Once weekly thyroxine treatment as a strategy to treat non-compliance

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Hypothyroidism is a common disorder, which is mainly treated in primary rather than secondary care. Once daily thyroxine replacement restores euthyroidism in most patients; some patients, however, remain hypothyroid despite adequate thyroxine replacement. Non-compliance is the most common cause of lack of response to thyroxine treatment. We describe two cases of primary hypothyroidism in which daily thyroxine treatment did not restore biochemical euthyroidism but once weekly thyroxine treatment was successful. In addition we review the evidence and discuss the differential diagnosis of lack of response to thyroxine treatment. Once weekly thyroxine treatment can be a safe, well-tolerated, and effective therapy for patients with non-compliance.

Hypothyroidism is common in the general population with an incidence of 4.1/1000 per year in women and 0.6/1000 per year in men.¹ These patients are commonly treated in primary rather than secondary care.² Once daily thyroxine replacement restores euthyroidism in most patients; some patients, however, remain hypothyroid despite adequate thyroxine replacement.

In this article we describe two cases of primary hypothyroidism in which daily thyroxine treatment did not restore biochemical euthyroidism but once weekly thyroxine treatment was successful. In addition we discuss the differential diagnosis of lack of response to thyroxine treatment.

CASE HISTORIES

Patient 1

A 47-year-old woman was diagnosed with primary hypothyroidism in 2001 by her general practitioner (GP). At diagnosis, the thyroid stimulating hormone (TSH) concentration was 22.90 mu/l (0.4–4.0 mu/l). Despite titrating the dose of thyroxine to 375 µg once daily, the patient remained hypothyroid with a free T4 (FT4) of 10.9 pmol/l (10–25 pmol/l) and a TSH of 32.5 mu/l. The TSH concentrations were never well controlled since the diagnosis, with values ranging from 20.2–36.1 mu/l. As a result the patient was referred to our endocrine clinic.

The patient denied poor compliance and was not taking any medications that could interfere with thyroxine absorption. Clinical examination was unremarkable apart from a weight of 42 kg. Initial investigations, including full blood count, and renal and liver function tests, were within normal limits. Coeliac disease was ruled out by a normal gastroduodenoscopy and undetectable anti-gliadin and anti-tissue transglutaminase (anti-TTG) antibodies. Thyroxine dose was increased to 400 µg a day. TSH, however, remained elevated.

As there was no obvious cause for lack of response, it was felt that the most likely diagnosis was non-compliance. The patient was started on supervised once weekly thyroxine 1 mg. Four weeks later, the FT4 improved to 28.5 pmol/l and the TSH fell to 0.05 mu/l. As a result, the weekly dose of thyroxine was

reduced to 750 µg, which resulted in the TSH concentration returning to normal (1.25 mu/l).

Patient 2

A 48-year-old woman was diagnosed with primary hypothyroidism during routine work-up for angina. At diagnosis, TSH was >75 mu/l and FT4 was 5.6 pmol/l. She was started on thyroxine 75 µg daily. The TSH concentration remained persistently elevated despite dose adjustments.

The patient denied any non-compliance. There was no evidence of malabsorption and she was not taking any other medications. The thyroxine dose was cautiously increased to 200 µg daily but the TSH remained elevated at 15.5 mu/l.

It was felt that non-compliance was the most likely diagnosis. The patient was started on supervised once weekly thyroxine 750 µg. The TSH concentration came down to 1.93 mu/l after 4 weeks of treatment.

DISCUSSION

Non-compliance with prescribed medical interventions is an old and well recognised problem in patients with chronic disorders.³ The frequency of dosing, duration of treatment and number of medications are all implicated in the development of non-compliance, in addition to other factors such as the doctor–patient relationship and the patient's psychiatric history.³ The daily lifelong administration of thyroxine can lead to patient non-compliance.

The mean treatment dose of oral thyroxine is 1.6 µg/kg/day. The results achieved with this dose are adequate and reproducible.⁴ When larger doses of thyroxine are needed, the treating physician needs to investigate the underlying cause. There are many different causes for non-response to thyroxine treatment ranging from drug-related interference with thyroxine absorption to small bowel disease that could also affect thyroxine absorption (table 1). However, the most common cause of lack of response to thyroxine replacement is poor compliance,⁵ although the major disadvantages of hypothyroidism for the patient (such as fatigue, constipation, weight gain) would seem reason enough for treatment compliance. The

Table 1 Causes of lack of response to thyroxine replacement in hypothyroid patients

Impaired absorption	Increased clearance	Increased demand	Most common
Dietary fibre (bread) Bile acid sequestering agents Sucralfate Omeprazole Soy Herbal remedies Small bowel disorders	Phenobarbital Phenytoin Carbamazepine Rifampicin	Pregnancy Weight gain	Non-compliance

diagnosis of non-compliance is by exclusion, and all other causes must be sought and excluded before making such a diagnosis. Particular attention should be paid to concurrent medications as many commonly used medications can either impair thyroxine absorption or increase its clearance (table 1). The combination of history, examination and primary laboratory investigations is able to exclude most causes.

The use of once weekly thyroxine is scientifically plausible. Thyroxine has an elimination half-life of about 7 days, and its biological effect may last longer.⁶ In addition, the peripheral conversion of serum T4 to T3 (which is the main active thyroid hormone) becomes more efficient at low serum T4 concentrations.⁷ Studies have shown that a single dose of T4 up to 3 mg is well tolerated.⁸ Taylor *et al* compared once daily versus twice weekly thyroxine treatment in seven female patients. The trough and peak serum concentrations of FT4, T3 and TSH were similar.⁹ Grebe *et al* compared daily T4 treatment with once weekly dosing in 12 hypothyroid patients in a randomised crossover trial. All patients tolerated the weekly regimen well and the tissue markers of thyroid hormone effect were not different between both groups, with no evidence of toxicity.⁸ The main problem with these studies is the small number of patients included.

Finally, poor compliance may be due to psychiatric disorders of a depressive nature, which are not uncommon in severe hypothyroidism, although only few patients exhibit true psychopathology.¹⁰ Confronting the patient about issues regarding poor compliance could upset the patient without much improvement in treatment. Therefore, a subtle approach is essential. Though hypothyroidism is common and managed well in primary care, a small number of patients who have persistently raised TSH in spite of adequate replacement doses of thyroxine need specialist assessment. The known physical causes should be excluded before non-compliance is considered most likely, and a trial of weekly supervised thyroxine at the local GP surgery (or pharmacy) may confirm the clinical suspicion. Adequate precautions need to be taken in patients with ischaemic heart disease. Close liaison between primary and secondary care is essential at the initiation of treatment, but once stabilised, supervision of the patient can be undertaken in the primary care setting in the majority of cases.

In conclusion, poor compliance with oral thyroxine is one of the most common causes of non-response to thyroxine treatment. Other causes must be excluded before making the diagnosis of non-compliance. Supervised once weekly oral thyroxine may be a safe, successful and well tolerated treatment regimen, and should be considered as an option in treating these patients in the community. Further studies including larger number of patients are warranted in order to clarify the efficacy and safety of this method further.

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REFERENCES

- 1 Boelaert K, Franklyn JA. Thyroid hormone in health and disease. *J Endocrinol* 2005;**187**:1–15.
- 2 Evans TC. Thyroid disease. *Prim Care* 2003;**30**:625–40.
- 3 Vermeire E, Hearnshaw H, Van Royen P, *et al*. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther* 2001;**26**:331–42.
- 4 Ain KB, Refetoff S, Fein HG, *et al*. Pseudomalabsorption of levothyroxine. *JAMA* 1991;**266**:2118–20.
- 5 Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. *Ann Intern Med* 1993;**119**:492–502.
- 6 Stock JM, Surks MI, Oppenheimer JH. Replacement dosage of L-thyroxine in hypothyroidism. A re-evaluation. *N Engl J Med* 1974;**290**:529–33.
- 7 Keck FS, Loos U. Peripheral autoregulation of thyromimetic activity in man. *Horm Metab Res* 1988;**20**:110–4.
- 8 Grebe SK, Cooke RR, Ford HC, *et al*. Treatment of hypothyroidism with once weekly thyroxine. *J Clin Endocrinol Metab* 1997;**82**:870–5.
- 9 Taylor J, Williams BO, Frater J, *et al*. Twice-weekly dosing for thyroxine replacement in elderly patients with primary hypothyroidism. *J Int Med Res* 1994;**22**:273–7.
- 10 Ogawa D, Otsuka F, Mimura U, *et al*. Pseudomalabsorption of levothyroxine: a case report. *Endocr J* 2000;**47**:45–50.