

Levothyroxine intramuscular administration-Case report and Review of literature

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Abstract

Background: Limited data exist regarding safety and efficacy of levothyroxine given intramuscularly.

Methods: To report a patient with thyroid cancer invading the trachea, with subsequent tracheostomy, gastrostomy tube feeding, and subtotal thyroidectomy complicated by severe hypoparathyroidism. All previous cases in the literature who received intramuscular levothyroxine were also described.

Results: In our patient, levothyroxine administration in gastrostomy tube failed to suppress thyrotropin stimulating factor (TSH) levels, most likely due to concomitant administration of calcium and food constituents. Patient's thyroid function stabilized few days after switching from enteral to intramuscular levothyroxine in a maintenance dose of 200 mcg daily. Review of literature reveals 7 patients who were treated with intramuscular levothyroxine, mostly once a week. Main causes of treatment with intramuscular thyroxine were non-compliance and gastrointestinal (GI) malabsorption. Adverse effects reported were transient tachycardia in one patient and self-limited left side weakness in another patient.

Conclusions: Available data suggest that intramuscular administration of levothyroxine is effective, generally safe, and could be a viable alternative to oral levothyroxine in non-compliant patients or those with GI malabsorption.

Introduction

Levothyroxine is mainly given through the oral route or GI tube feeding. A levothyroxine solution (100 mcg/ml) is also available for intravenous administration [1]. The latter formulation is approved by the Federal Drug Administration (FDA) since 1969 for use in cases of myxedema coma [1]. Meanwhile, little is known about the use of intramuscular levothyroxine, which is currently not approved by the FDA. In the latest guidelines on treatment of hypothyroidism prepared by the American Thyroid Association, it was mentioned: "Parenteral levothyroxine therapy does not appear to have been rigorously studied..., no trials of such therapy were identified" [2]. In fact, in the previous guidelines, no recommendations were specifically provided for intramuscular levothyroxine [2]. Review of literature revealed only 7 patients who received levothyroxine intramuscularly. The author reports here an 8th case, and summarizes available data related to this uncommon form of levothyroxine administration.

Case report

The patient is 40 year-old morbidly obese (weight 131 kg) woman with poorly differentiated thyroid cancer invasive of the trachea that underwent subtotal thyroidectomy followed by tracheostomy and gastrostomy tube insertion for feeding. Surgery was complicated by severe hypoparathyroidism requiring large doses of calcium. The latter consisted of carbonate/vitamin D 600 mg/400 IU tablet, 2 tablets q6 h, calcium acetate 667 mg capsule, 4 capsules (2,668 mg) q6 h through the gastrostomy tube. Initially, intravenous levothyroxine was started in a dose 150 mcg/d for few days then switched to levothyroxine tablet which was crushed and introduced in the gastrostomy tube in a dose of 225 mcg/day. Yet, levothyroxine administered in gastrostomy tube did not normalize thyroid function despite escalation of doses up to

300 mcg/day. Thus, TSH levels were 12.2 uIU/ml (N = 0.35-4.94 uIU/ml), and free thyroxine (T4) levels were 1.11 ng/dl (N = 0.70-1.48 ng/dl). Subsequently, enteral levothyroxine was switched to intramuscular levothyroxine in a starting dose of 250 mcg/d, then few days later decreased to a maintenance dose of 200 mcg/d (1.5 mcg/kg/d). Over the next 15 days after switching to intramuscular levothyroxine, TSH levels were 0.167 uIU/ml, almost at goal for patients with invasive thyroid cancer (TSH < 0.1 uIU/ml) [3], and free T4 levels were high normal at 1.46 ng/dl.

Problems of levothyroxine administered through gastrostomy tube

Decreased absorption of levothyroxine by calcium

In 1998, Schneyer reported development of hypothyroidism in 3 women with thyroid cancer on levothyroxine suppressive therapy after taking levothyroxine and calcium carbonate concomitantly [4]. In one patient, TSH was corrected 3 weeks after stopping calcium carbonate. In the 2 remaining patients, normal thyroid function was restored when they took levothyroxine in the morning and calcium carbonate after lunch and dinner [4]. In healthy volunteers, Singh, *et al.* showed that calcium carbonate significantly decreased the absorption of levothyroxine over the 24 hours following the simultaneous intake of both drugs [5]. In

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20 patients with stable primary hypothyroidism, the same researchers have shown that 20% of such patients developed mild hypothyroidism (highest TSH was 7.8 uIU/ml) when taking levothyroxine with calcium carbonate [6]. Furthermore, this levothyroxine-calcium interaction extends to other calcium preparations. Thus, Zamfirescu and Carlson demonstrated that calcium acetate, calcium citrate, and calcium carbonate reduced the absorption of levothyroxine by 20-25% over a 6 h-hour period [7]. Cow milk also interferes with levothyroxine absorption, presumably due to its calcium content [8]. The mechanism of reduction of levothyroxine bioavailability by calcium is believed to be adsorption of levothyroxine to calcium in an acidic pH [6]. In our patient, we believe failure to achieve normal thyroid function was in part attributed to reduction of levothyroxine absorption in the gut by the high doses of calcium carbonate and acetate given every 6 hours. Some authors recommend holding calcium supplements for 4 hours after levothyroxine. We did not follow this regimen for the following reasons. First, this recommendation is based on expert opinion and not supported by data [1]. Second, as mentioned above, Singh et showed reduced levothyroxine absorption over 24 h after simultaneous intake of calcium [5]. In addition, in the studies of Zamfirescu and Carlson, different calcium formulations interfered with levothyroxine for a least 6 hours [7]. Third, we were concerned that interruption of calcium carbonate and acetate may result in development of hypocalcemic symptoms.

Decreased absorption of levothyroxine by feeding constituents

Absorption of levothyroxine takes place in the jejunum and ileum [1,9]. Acidic gastric pH, as occurs in fasting condition, may be important for subsequent intestinal absorption [1,6,9]. Thus, food is expected to decrease absorption of levothyroxine [1]. In healthy subjects, Wenzel and Kirschsieper have shown that levothyroxine absorption with food was 64% compared with 80% in the fasting state [10]. Therefore, it is recommended to take levothyroxine at least 30 minutes in the morning before breakfast [1,11]. With respect to patients dependent on tube feeding like ours, Dickerson, *et al.* showed that more than half of patients (9 of 13 patients) receiving concurrent levothyroxine and continuous tube feeding developed subclinical or overt hypothyroidism within 2-3 weeks [12]. Holding tube feeding 1 hour before and after levothyroxine did not correct hypothyroidism in 2 of 3 patients [12]. It should be emphasized that, in the latter study, patients receiving nutrients that may interfere with levothyroxine absorption such as calcium, were excluded [12].

Other problems associated with levothyroxine administration in tube feeding

Mannesis, *et al.* examined the amount of levothyroxine that might be adsorbed by the gastrostomy tube [13]. Using radiolabeled

levothyroxine, they found that there was minimal adsorption of levothyroxine during transit through feeding tubes [13]. The authors concluded that this effect was probably clinically insignificant [13]. Another problem that may potentially reduce the dose of levothyroxine is that a percentage of the drug, estimated to be approximately 10%, may be lost during crushing, mixing and diluting levothyroxine tablet prior to its introduction in gastrostomy tube [13].

Intramuscular administration of levothyroxine

Review of the literature revealed only 7 patients who received levothyroxine through the intramuscular route [14-19] (Table 1). Major reasons for using intramuscular injection were lack of compliance with oral drug intake or isolated malabsorption of levothyroxine. As shown in Table 1, 5 of the 7 patients received levothyroxine once a week. We preferred to give intramuscular levothyroxine once a day in an attempt to avoid any possible fluctuations in plasma levothyroxine concentrations. This is particularly important in a patient with metastatic thyroid cancer in whom steady levels of thyroid hormones are essential for proper suppression of TSH. Unfortunately, pharmacokinetics and pharmacodynamics of intramuscular levothyroxine have not been studied. Therefore, the optimum frequency of its administration is unclear. Likewise, the optimum starting dose is unknown. In our patient with thyroid cancer who required TSH suppression, the optimum dose of intramuscular levothyroxine was approximately 1.5 mcg/kg/day. In patients with hypothyroidism who do not require TSH suppression, the optimum dose may be smaller e.g. 1.3 mcg/kg/d. In the elderly and patients with coronary artery disease, it is safer to start smaller doses of 25 mcg/d, similar to the approach followed with oral levothyroxine [2].

Safety of intramuscular administration of levothyroxine

Overall, available studies suggest that intramuscular levothyroxine is safe. However, Peynirci, *et al.* reported transient left side loss of body strength that regressed within one week in a 32 year-old woman 24 h after intramuscular injection of levothyroxine in a dose of 1200 mcg [19]. In another report, Alba *et al.* described a 17 year-woman who developed palpitations one hour after receiving 200 mcg of levothyroxine intramuscularly (0.57 mcg/kg/day) [14]. Palpitations resolved after taking intravenous fluids in emergency department, and patient resumed intramuscular levothyroxine 200 mcg weekly thereafter without adverse effects [14].

Alternative ways of levothyroxine administration

As mentioned above, a levothyroxine solution is approved for intravenous administration [1]. We used this intravenous formulation in a dose of 200 mcg/d for several days following thyroidectomy before

Table 1. Characteristics of patients who received intramuscular (IM) levothyroxine

Reference	Patient's profile	Levothyroxine dosing regimen	Cause for using IM levothyroxine
Alba, <i>et al.</i> [14]	6 year-old female	25 mcg once a week gradually increased to 300 mcg once a week	Malabsorption of levothyroxine through gastrostomy tube
Alba, <i>et al.</i> [14]	12 year-old female	100 mcg once a week increased gradually to 500 mcg once a week	Non-compliance
Alba, <i>et al.</i> [14]	16 year-old female	200 mcg once weekly increased gradually to 500 mcg once a week	Non-compliance
Eledrisi, <i>et al.</i> [15]	41 year-old woman	200 mcg/d	Non-compliance
Anderson, <i>et al.</i> [16]	18 year-old female	500 mcg once weekly increased gradually to 1000 mcg once a week	Idiopathic levothyroxine malabsorption
Gamboa, <i>et al.</i> [17]	55 year-old male	200 mcg twice a week increased over 2 months to 400 mcg on Mondays and 200 mcg on Thursdays	Malabsorption due to intestinal subocclusion
Taylor, <i>et al.</i> [18]	82 year-old female	200 mcg once weekly increased to 500 mcg once weekly after 64 days, then switched back to oral levothyroxine after 86 days of IM levothyroxine	Myxedema coma due to non-compliance
Peynirci, <i>et al.</i> [19]	32 year-old female	500 mcg twice a week	Isolated (idiopathic) malabsorption
Current report	40 year-old female	200 mcg/d (1.5 mcg/kg/d)	Malabsorption of levothyroxine through gastrostomy tube

insertion of gastrostomy tube. However, for long-term therapy, the intravenous route is impractical because it is quite invasive, and the intravenous access is prone for infections. Hence, we used the same solution of levothyroxine approved for the intravenous route to be given intramuscularly without any adverse effects. Levothyroxine was also given subcutaneously with success in a morbidly obese woman (weight 150 kg, body mass index 53 kg/m²) suffering from malabsorption in a dose of 400 mcg every 4 days [20]. Main limitation of subcutaneous levothyroxine is the large volume (500 mcg corresponds to 10 ml), potentially causing pain at the injection site [20].

Pirola, *et al.* compared the traditional tablet form of levothyroxine with a new liquid formulation (1.6 mcg/kg/d) introduced in nasogastric tube in 20 patients after undergoing laryngectomy and thyroidectomy [21]. After 21 days, patients randomized to the liquid form of levothyroxine had similar thyroid functions to those randomized to the tablet form [21]. The latter results occur despite holding tube feeding in the tablet group for 30 min before and after levothyroxine [21]. These results suggest that the liquid formulation of levothyroxine may have less interaction with food constituents compared with the tablet form. Nevertheless, further studies of longer duration are needed to confirm this finding.

Conclusions and current needs

In hypothyroid patients refractory to treatment with oral or enteral levothyroxine, intramuscular levothyroxine appears to be a generally safe, practical and reliable alternative way of this drug administration. Unfortunately, data regarding intramuscular levothyroxine is scant. Investigations are urgently needed to study pharmacodynamics and pharmacokinetics of levothyroxine given through the intramuscular route. Likewise, well-designed clinical trials are required to compare intramuscular levothyroxine with other levothyroxine formulations in terms of safety, efficacy and patients' acceptance.

Conflict of interest

The author has no conflict of interest to declare.

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