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van Zaane, B.

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Chapter 5

The effects of an extremely high dose of levothyroxine on coagulation and fibrinolysis

Danka JF Stuijver, Bregje van Zaane, Alessandro Squizzato, Joost CM Meijers, Hans-Martin Otten

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**Abstract**

Several haemostatic abnormalities have been reported in thyroid hormone excess. However, the overall effect on coagulation and fibrinolysis is still unclear. We were presented the unique opportunity to further explore the effects of excessive levels of thyroid hormone in the case of a young woman who attempted suicide by auto-intoxication with levothyroxine. Levels of thyroid hormones and parameters of coagulation and fibrinolysis were assessed in the days following the auto-intoxication. We found a marked increase in levels of coagulation factors VIII, IX and X, von Willebrand factor and plasminogen activator inhibitor-1, resulting in enhanced thrombin generation after intoxication with 25 mg of levothyroxine. These findings suggest that thyroid hormone excess shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state, and is therefore likely to reflect an increased risk of venous thrombosis.

**Introduction**

Although the link between the haemostatic system and thyroid dysfunction has been known for many years, controversy remains whether thyroid hormone excess leads to an increased risk of venous thrombosis. In patients with hyperthyroidism, a hypercoagulable and hypofibrinolytic state has been suggested. This was further supported by the observation of increased levels of factor VIII (FVIII) and von Willebrand factor (VWF) after administration of oral thyroid hormones in healthy volunteers. However, the overall effect of thyroid hormone on coagulation activation and inhibition of fibrinolysis remains unclear.

A unique situation was presented to us in the case of a young woman who attempted suicide using an extremely high dose of levothyroxine. We assessed levels of thyroid hormones and parameters of coagulation and fibrinolysis in the days following the auto-intoxication and in the succeeding months until restoration of euthyroidism.

**Case report**

A 23-year-old woman, who was on levothyroxine treatment for iatrogenic hypothyroidism after subtotal thyroidectomy for Morbus Graves, was brought to the emergency room on October 17, 2008, three hours after ingestion of 25 mg levothyroxine (250 tablets of 100 µg). Apart from levothyroxine, the patient did not use concomitant medication. After gastric lavage, she was treated with active charcoal and magnesium sulphate. Propanolol was given to prevent cardiac arrhythmias. No clinical adverse effects of the levothyroxine occurred during hospital admittance; the patient was discharged after 6 days.

During her full hospital stay, daily blood sampling was performed for assessment of thyroid hormones, i.e. serum free thyroxine (FT4), total tri-iodothyronine (T3), and thyroid simulating hormone (TSH), as well as coagulation and fibrinolytic parameters, with permission of the patient. Citrated blood was processed two times by centrifugation at 2500 g for 15 minutes at 15 degrees, and stored at -80˚C until further use.

The course of thyroid hormones, and parameters of coagulation and fibrinolysis is shown in Figure 1. Serum free thyroxine levels are a direct reflection of the ingested levothyroxine, whereas total tri-iodothyronine is the active thyroid hormone. T3 levels slowly increased until a maximum at day 2, 24 hours after ingestion, was reached. Subclinical hypothyroidism was noted at day 40, and levothyroxine 0.15 mg once daily was started. Euthyroidism was restored at day 244.

Levels of factor VIII (FVIII), factor X (FX), von Willebrand factor activity (VWF:RCo) and antigen (VWF:Ag) slowly increased during the first days after intoxication until a maximum was reached at day 5 (FVIII 172%, FX 81%, VWF:RCo 148%, VWF:Ag 131%), whereas levels of plasminogen activator inhibitor-1 (PAI-1) peaked shortly after intake (140 ng/ml). Levels of factor X (FIX) were highest at day 19 (103%). As a result of these alterations, enhanced thrombin generation (ETP, area under the curve) was observed during the first days after intoxication, with a maximum at day 3. No clear alterations were observed for coagulation factors II and VII, prothrombin time, activated partial thromboplastin time (aPTT), protein C activity and protein S antigen (total and free), and prothrombin fragment (data not shown).
Levothyroxine auto-intoxication

Levels of T3 positively correlated with levels of ETP (Spearman’s $R = 0.83$) and PAI-1 ($R = 0.89$). A negative correlation was found for TSH and FVIII ($R = -0.92$), FIX ($R = -0.73$), FX ($R = -0.80$), VWF:RiCo ($R = -0.85$), and VWF:Ag ($R = -0.98$) (all p-values <0.01).

**Discussion**

In this case report, we found that levothyroxine activates the coagulation system and inhibits fibrinolysis. In line with the present literature, levels of coagulation factors tended to normalise once euthyroidism was restored. Moreover, levels of FVIII, FIX and VWF even further decreased during subclinical hypothyroidism as previously described\[5;6\].

Although in the present case most coagulation factors remained within the upper range of the local reference range, the combination of an increase of several coagulation factors, ETP and PAI-1 indicates a shift towards a procoagulant and hypofibrinolytic state in this patient. In the absence of well-designed epidemiological studies on the association between thyroid hormone excess and venous thrombosis, the measurement of endogenous thrombin generation (ETG), i.e. the thrombin forming capacity of the plasma, is one way of further elucidating the risk of venous thrombosis\[7\]. In the present case, we observed a clear relation between T3 and ETP suggesting the risk of thrombosis to gradually rise with increasing levels of thyroid hormone. Although the increase of FVIII, FIX and FX was likely to induce enhanced thrombin generation, we cannot explain the earlier normalisation of ETP levels compared to the coagulation factors. Future studies are needed to clarify the relation between ETP and thyroid hormone excess.

The underlying mechanisms by which thyroid hormones may affect coagulation remain ill-defined. However, the observed delay in alterations of these coagulation factors is best explained by enhanced synthesis at hepatic or endothelial level, whereas the rapid increase in PAI-1 may be due to enhanced secretion\[8;9\].

Our results may be influenced by the fact that the patient received concomitant medication at the emergency room, which can obscure the effects of levothyroxine. However, additional administration of propranolol was found not to influence factor VIII levels in healthy volunteers, whereas magnesium sulphate has been reported to have potential antithrombotic effects\[4;10\]. It is therefore unlikely that this would have affected our findings.

In conclusion, these data suggest that thyroid hormone excess shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state, and is therefore likely to reflect an increased risk of venous thrombosis. Further prospective studies should focus on the influence of hyperthyroidism on the risk of venous thrombosis, and subsequently on the mechanisms behind this presumed relationship.

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**Figure 1.** Biochemical and haemostatic parameters after ingestion of a high dose of levothyroxine. T3 indicates total tri-iodothyronine; FT4, serum free thyroxine; TSH, thyroid stimulating hormone; FVIII, factor VIII; VWF:RiCo, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen; FIX, factor IX; FX, factor X; PAI-1, plasminogen activator inhibitor-1; and ETP, endogenous thrombin potential. Local reference ranges: T3 1.2-2.8 nmol/L; FT4: 10-23 pmol/L; TSH 0.31-4.5 mIU/L; FVIII 63-173%; VWF:RiCo 58-172%; VWF:Ag 50-150%; FIX 80-145%; FX 66-125%; PAI-1 <180 ng/ml; ETP 1155-2606 nM.min.
References


