Endocrine and cytokine changes during elective surgery

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Abstract

Elective surgery was used as a model of severe non-thyroidal illness (SNTI) to study the inter-relation between changes in serum thyroid hormones, thyroid stimulating hormone (TSH), cortisol, and interleukin 6 concentrations. The study was designed to determine whether the expected interleukin 6 increases after surgery are the cause of decreased serum tri-iodothyronine (T_3) concentration normally observed following severe trauma. Blood was sampled for 24 hours before, during, and for 48 hours after abdominal surgery under general anaesthesia in 11 patients. Total T_3 decreased 30 minutes after induction and continued to decrease at 24 hours. After a transient increase at 30 minutes, free T_3 also decreased, and free thyroxine (T_4) concentrations, other than a similar transient increase, did not change. TSH concentrations were increased at four hours and the nocturnal surge was suppressed. The increase in the serum interleukin 6 concentration was not observed until four hours. Cortisol concentrations were increased at 30 minutes and peaked at four hours. Therefore, the early changes in thyroid hormones and TSH accompanying surgery do not seem to be caused by changes in interleukin 6 concentrations.

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Severe non-thyroidal illnesses (SNTIs) are associated with a variety of metabolic changes including those arising within the endocrine system. The effects on the pituitary–thyroid axis include a decrease in serum tri-iodothyronine (T_3) concentrations, variable serum thyroxine (T_4) and thyroid stimulating hormone (TSH) concentrations in either the reference range or just under its lower limit. Thus serum TSH concentrations always seems to be inappropriately low compared with the T_3 and T_4 concentrations.[1] Activation of the cytokine system also occurs in SNTIs, commonly manifested by increased serum cytokine concentrations, particularly of interleukin 6.[2]

Recent observations in humans[3] and in animals[4] have lead to suggestions that cytokine administration can reproduce SNTI-induced changes in thyroid physiology and control mechanisms. The observations in humans require confirmation while the results in animals have been somewhat variable. Therefore, the hypothesis that the activation of the cytokine system is at least partially responsible for the thyroid changes in SNTIs needs to be tested. Elective surgery was chosen as a model of SNTI for this purpose as earlier independent studies have shown that serum T_3[5] concentrations decrease and serum interleukin 6 concentrations increase, an occurrence accompanied by smaller increases in interleukin 1 in this model.[6] Later studies revealed that TSH is also suppressed, particularly its normal nocturnal surge.[7] The aim of this study was to establish, by temporal relations, whether cytokine release is implicated in the changes in thyroid hormone concentrations during surgical stress, particularly decreased serum T_3 concentrations.

Methods

Studies were performed in 11 consecutive patients admitted for elective surgery. The operations performed were as follows: open cholecystectomy (two cases); laparoscopic cholecystectomy (three cases); hemicolectomy (two cases); sigmoid colectomy, repair of abdominal incisional hernia, closure of colostomy, laparotomy and repair of rectal prolapse (one case of each). After premedicating with temazepam, general anaesthesia was used, namely with N_2O, O_2, plus enflurane or fentanyl. Omnopon and maxolon were administered following surgery.

A baseline venepuncture was performed immediately before induction of anaesthesia (zero hours) and individual venepunctures were performed thereafter at -24, -20, and -16 hours. Further venepunctures were performed at 30 minutes and at four, eight, 24, 32, and 48 hours following induction. Multiple samples were taken to test and correct for diurnal variations in some parameters.

Total T_3, free T_3, free T_4, and TSH concentrations were measured using an "Amerlite" (Kodal Clinical Diagnostics, Amersham, UK) automated enzyme immunoassay (luminescence signal), the lower limit of detection (LLD) for TSH being 0·03 mU/l. Serum interleukin 6 concentrations were measured using an ELISA ("Biotrak"; Kodak) with a LLD of 1 pg/ml and coefficients of variation of 3·5% (intra-assay) and 7·0% (interassay). Cortisol concentrations were measured using a ("Amerlex"; Kodak) radioimmunoassay.

Results are expressed as means and standard errors. The Student's t test was used to calculate significance, with a critical value of $p < 0.05$.

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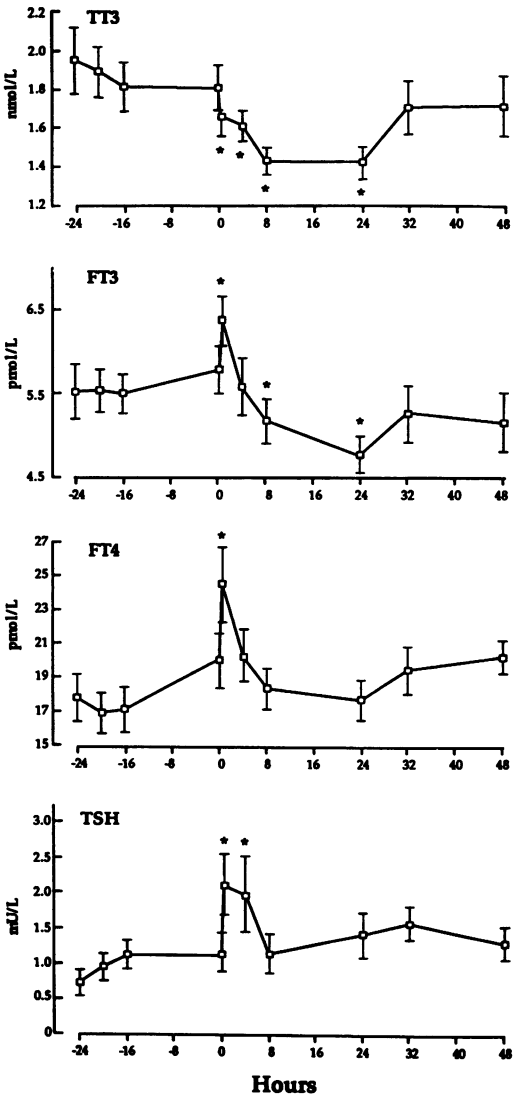

*Figure 1 Changes in serum total T_3 (TT3), free T_3 (FT3), free T_4 (FT4), and thyroid stimulating hormone (TSH) concentrations in patients undergoing elective surgery under general anaesthesia. Zero hours indicates the induction of anaesthesia. Data are expressed as mean ± SE; *p < 0·05 (Student's paired t test).*

Results

Total T_3 concentrations had decreased substantially 30 minutes after induction (1·65±0·10 compared with 1·80±0·12 nmol/l), with the decrease continuing to 24 hours (78% of baseline), and returning to baseline values by 48 hours (fig 1).

Free T_3 concentrations also decreased overall (4·77±0·22 at 24 hours compared with 5·79±0·29 baseline; fig 1). However, a superimposed sharp increase occurred at 30 minutes to a value of 6·37±0·29, after which a rapid decrease to 5·58±0·35 (not greatly different from baseline) occurred by four hours.

Free T_4 concentrations showed a similar transient increase (24·5±2·2 at 30 minutes compared with 20·0±1·6 pmol/l) returning to baseline values (20·3±1·5 pmol/l) at four hours (fig 1). Thereafter, free T_4 values were similar to baseline values.

Thyroid stimulating hormone concentrations, like free T_3 and T_4, were increased at 30 minutes (2·12±0·43 compared with 1·12±0·21 mU/l; fig 1) and the increase was sustained to four hours (1·99±0·52). The normal nocturnal surge was suppressed at eight hours (occurring at about 2000 hours) as the value of 1·15±0·28 was not substantially different from baseline. At 32 hours after induction, the nocturnal surge seemed to return, the value of 1·59±0·24 being higher than the eight hour value.

The ratios of free T_3 to free T_4 are presented in figure 2, giving some indication of the reduced rate of de-iodination of T_4 to T_3 which occurs in SNTI.[8] The ratio dropped rapidly from 0·30±0·01 to 0·25±0·01 at 30 minutes, returning to baseline by eight hours.

For interleukin 6, values recorded for all patients between and including −24 and 30 minutes (with the exception of the value of 58 pg/ml for case 1 at −20 hours) were below the limit of detection of 1·0 pg/ml (fig 2). Interleukin 6 concentrations increased by four hours in response to the surgical procedures but a lag period of response occurred; the 30 minute value being at baseline. The peak increase occurred at eight hours, with a value of 56±32 pg/ml. Values for 24 to 48 hours remained above baseline values (fig 2). Cortisol concentrations were increased at 30 minutes (754±91 compared with the zero hour value of 355±47). Cortisol values peaked at four hours and returned to baseline by 32 hours (fig 2).

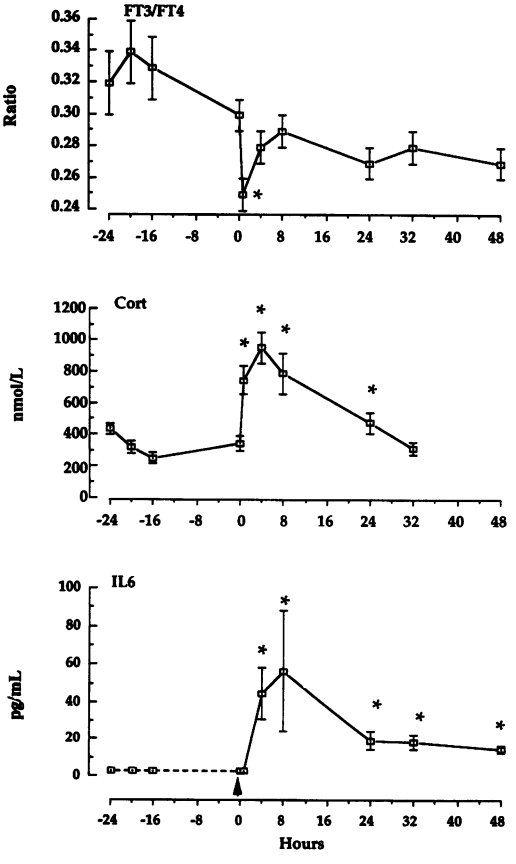

*Figure 2 Changes in the ratio of serum free T_3 to free T_4 (FT3/FT4), cortisol (Cort) and interleukin 6 (IL6) in patients undergoing elective surgery under general anaesthesia. The arrow indicates induction (zero hours) as distinct from the 30 minute sampling. The dotted line indicates that all but one of the values for interleukin 6 are below the detection limit and standard errors could not be calculated. Otherwise data are expressed as means ± SE; *p < 0·05 (Student's paired t test other than for the eight hour interleukin 6 point (56 ± 32 pg/ml) for which Wilcoxson's signed rank test was used).*

Discussion

Elective surgery seems to be a suitable model of SNTI, particularly of the acute variety, because serum T_3 values decreased while serum interleukin 6 concentrations increased in the patients studied, confirming earlier independent studies.[5,6] Furthermore, suppression of the nocturnal TSH surge occurred on the day of surgery in contrast to the more prolonged loss noted previously.[7]

Our study was designed to examine the temporal relation between decreases in serum T_3 and increases in interleukin 6 concentrations and to examine whether changes in interleukin 6 concentrations lead to changes in T_3 concentrations. However, it is first necessary to discuss the somewhat unexpected finding of early transient increases in free T_3 and T_4 concentrations which were accompanied by an early, but somewhat prolonged, increase in TSH values (to four hours). As it is more prolonged, the TSH stimulus is unlikely to be the cause of increases in free T_3 and T_4 concentrations. The increase in free T_4 concentrations may have been caused by halothane anaesthesia, which has been associated with an efflux of hepatic T_4 and a sharp increase in serum protein bound iodine concentrations.[9] The transient increase in serum free T_3 values at 30 minutes, when total T_3 values are falling, is inexplicable especially as thyroxine binding globulin (TBG) concentrations did not change substantially during the study (data not shown); however, this does not preclude the possibility of functional changes in TBG.

The early increase in TSH concentrations is similar to that observed in a recent study[10] where TSH concentrations, as measured by immunoradiometric assay (IRMA), were increased three hours after pre-medication in patients undergoing elective cholecystectomy under general anaesthesia, which included fentanyl administration. The precise timing of this increase with respect to induction and incision is not clear, but in our study TSH concentrations increased as early as 30 minutes after induction. Both pharmacological and stress factors may contribute to the increase in TSH concentrations.

Increases in interleukin 6 values followed decreases in total T_3 concentrations and in the free T_3/free T_4 ratio by up to three and a half hours, but further observations are required to ascertain how soon interleukin 6 concentrations increase after 30 minutes. In patients undergoing elective surgery on the aorta, the increase in interleukin 6 concentrations was first noted at 90 minutes and peaked much later.[6] It seems that interleukin 6 cannot be the cause of the decrease in serum T_3 values occurring during surgery and is an unlikely cause of such decreases in SNTI. However, other cytokines may be involved in SNTI. For example, tumour necrosis factor α (TNFα) may arguably be causally related to decreases in T_3 concentrations in SNTI as, when administered to human volunteers, decreased serum T_3 values were observed,[3] which may be caused by a TNF induced systemic disturbance. Furthermore, TNFα is not measurably increased following surgery[6] and the increases seen in SNTI are restricted mainly to endotoxic shock and inflammatory arthritides.[2]

Substantial increases in serum cortisol values were observed 30 minutes after induction and may be of sufficient magnitude to account for the presumed inhibition of T_4 de-iodination. It is also interesting that the increase in cortisol values precedes that of interleukin 6. The combined increases in cortisol and interleukin 6 values could contribute to the suppression of the nocturnal TSH surge eight hours after induction.

In conclusion, our observations do not support the hypothesis that increased serum interleukin 6 concentrations associated with SNTI cause the decrease in serum T_3 values which arise from reduced peripheral T_4 de-iodination. However, further observations examining these relations more closely in the first three hours following surgery would be helpful.

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