Changes in Thyroid Function Tests During Short-Term Salsalate Use

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Although long-term administration of salsalate depresses blood levels of both total thyroxine (T_4) and total triiodothyronine (T_3) and at least transiently decreases serum thyrotropin (TSH), changes in thyroid function tests have not been fully characterized during its short-term use. It is also unclear if the observed changes are solely the result of decreased hormone binding to carrier proteins or if reduced hepatic 5′-monodeiodinase activity is important. Blood was sampled at baseline (day 0) and after 24 hours (day 1) and 72 hours (day 3) in eight subjects taking a therapeutic dose of salsalate 1,500 mg twice daily. Total T_4 decreased from 90.1 ± 7.7 nmol/L (mean ± SD) on day 0 to 82.9 ± 8.6 nmol/L on day 1 ($P = .1$ *v* baseline) and 68.6 ± 8.7 nmol/L on day 3 ($P = .0001$). Total T_3 decreased from 1.76 ± 0.20 nmol/L to 1.61 ± 0.16 nmol/L on day 1 ($P < .05$) and 1.31 ± 0.27 nmol/L on day 3 ($P = .002$). The T_4/T_3 ratio was 51.7 ± 7.7 at baseline and remained unchanged after 3 days. Levels of reverse T_3 (rT_3) were reduced from 0.24 ± 0.05 nmol/L to 0.18 ± 0.02 nmol/L on day 3 ($P < .05$). While the free T_4 index (FTI) declined in parallel with total T_4, the free T_4 level by direct equilibrium dialysis (FTD) was unchanged after 3 days. Serum TSH decreased from 1.47 ± 0.47 mU/L to 0.91 ± 0.27 mU/L after 1 day ($P < .05$) and remained suppressed after 3 days (0.95 ± 0.49 mU/L, $P < .05$). In conclusion, (1) therapeutic doses of salsalate significantly decrease serum concentrations of total T_4, total T_3, and rT_3 to about 75% of baseline levels after 3 days without altering the T_4/T_3 ratio; (2) although the FTD does not change, serum TSH concentrations remain suppressed; and (3) the proportionate decrease in total thyroid hormone levels suggests that inhibition of hormone binding to serum proteins is more important in producing these changes than reduced hepatic 5′-monodeiodinase activity.

ABNORMAL THYROID FUNCTION test results are common during long-term administration of salsalate, a nonsteroidal antiinflammatory medication that is the dimer of salicylic acid.[1-3] Serum concentrations of total thyroxine (T_4) and total triiodothyronine (T_3) are significantly depressed, and both the free T_4 index (FTI) and free T_4 by unbound analog assay are in the hypothyroid range.[2,3] Thyrotropin (TSH) levels are transiently decreased, but return to baseline if treatment is continued for more than 3 weeks.[2] It is not clear how rapidly these changes occur, since previous studies have examined patients treated for extended periods, typically weeks or months.

Salicylates alter thyroid function primarily by displacing T_4 and T_3 from low-affinity binding sites on serum proteins.[4,5] They also inhibit the hepatic 5′-monodeiodination of both T_4 and reverse T_3 (rT_3), but it is uncertain as to whether this change in peripheral hormone metabolism contributes significantly to the decrease in serum T_3.[6] Since blood levels of rT_3 have not been measured during administration of salicylates to humans, the effects on serum concentrations of this hormone are unknown.

The present study was performed to examine changes in total and free thyroid hormone concentrations, including rT_3, during the first several days of salsalate administration. The relative contributions of reduced binding to serum proteins and decreased hepatic 5′-monodeiodinase activity to the observed changes were then assessed.

SUBJECTS AND METHODS

Eight normal subjects (six men and two women aged 38 to 53 years) were tested after provision of informed consent. All were clinically euthyroid, and none were taking any other medication.

After baseline blood samples were drawn (day 0), the subjects were placed on salsalate 1,500 mg orally twice daily and testing was repeated after 24 hours (day 1) and 72 hours (day 3). Samples acquired during treatment were taken 12 hours after the previous dose to minimize contributions from the unhydrolyzed parent compound. No specimen was obtained more than 4 hours after the last meal, to preclude the effects of caloric deprivation on rT_3 levels, and all samples were stored at −20°C until analysis.

Routine thyroid function tests and serum salicylate determinations were performed on day 0 (eight subjects), day 1 (six subjects), and day 3 (eight subjects), with measurement by commercial assays. Total T_4 and the thyroid hormone binding ratio (THBR) were determined by fluorescent polarization immunoassay, and both total T_3 and TSH were determined by microparticle immunoassay (AxSym System; Abbott Laboratories, Abbott Park, IL). The FTI was calculated as the product of total T_4 and the THBR. The free T_4 level by direct equilibrium dialysis (FTD) was assayed in five subjects and rT_3 in four (both by SmithKline Beecham Clinical Laboratories, Van Nuys, CA) on days 0 and 3. Salicylate levels were measured by a colorimetric method (DuPont Clinical Systems ACA V, DuPont, Wilmington, DE) on days 1 and 3 of the study.

The data are expressed as the mean ± SD and were analyzed by Student's *t* test for paired values (Table 1).

RESULTS

Baseline thyroid function tests were normal, with the exception of an elevated rT_3 in one subject. The serum total T_4 concentration was 90.1 ± 7.7 nmol/L, total T_3 1.76 ± 0.20 nmol/L, rT_3 0.24 ± 0.05 nmol/L, THBR 1.08 ± 0.06, FTI 97.1 ± 8.3, FTD 19.8 ± 4.1 pmol/L, and TSH 1.47 ± 0.47 mU/L. During salsalate treatment, salicylate concentrations were 0.07 to 1.59 mmol/L and were within the therapeutic range (0.14 to 2.10 mmol/L), except for a low day 1 value in one subject.

The initial thyroid hormone values were promptly altered by salsalate administration (Table 1). Total T_4 decreased moderately on day 1 (82.9 ± 8.6 nmol/L, $P = .1$ *v* baseline) and was significantly decreased on day 3 (68.6 ± 8.7 nmol/L, $P = .0001$). Total T_3 decreased faster and was already significantly de-

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Table 1. Thyroid Function Test Results (mean ± SD) in Normal Subjects Taking Salsalate 1,500 mg Twice Daily

Day of Study	TT_4 (nmol/L, n = 8)*	TT_3 (nmol/L, n = 8)*	T_4/T_3 (n = 8)*	rT_3 (nmol/L, n = 4)	THBR (n = 8)*	FTI (n = 8)*	FTD (pmol/L, n = 5)	TSH (mU/L, n = 8)*
0	90.1 ± 7.7	1.76 ± 0.20	51.7 ± 7.7	0.24 ± 0.05	1.08 ± 0.06	97.1 ± 8.3	19.8 ± 4.1	1.47 ± 0.47
1	82.9 ± 8.6	1.61 ± 0.16†	55.3 ± 7.0		1.08 ± 0.07	88.3 ± 7.4		0.91 ± 0.27†
3	68.6 ± 8.7‡	1.31 ± 0.27§	54.4 ± 13.7	0.18 ± 0.02†	1.09 ± 0.04	74.4 ± 7.5‡	19.5 ± 4.0	0.95 ± 0.49†

NOTE. Statistical analysis was performed using Student's *t* test for paired values, with differences *v* day 0.
Abbreviations: TT_4, total T_4; TT_3, total T_3.
*n = 6 on day 1.
†$P < .05$.
‡$P = .0001$.
§$P = .002$.

pressed on day 1 (1.61 ± 0.16 nmol/L, $P < .05$). By day 3, it had declined even further (1.31 ± 0.27 nmol/L, $P = .002$) and was subnormal in three subjects. Although total T_4 and total T_3 levels decreased significantly, the baseline T_4/T_3 ratio (51.7 ± 7.7) remained unchanged on both day 1 (55.3 ± 7.0, nonsignificant [NS]) and day 3 (54.4 ± 13.7, NS). Compared with an initial concentration of 0.24 ± 0.05 nmol/L, rT_3 declined to 0.18 ± 0.02 nmol/L on day 3 ($P < .05$) but stayed within the normal range at all times. The THBR was unchanged on both day 1 (1.08 ± 0.07, NS) and day 3 (1.09 ± 0.04, NS) of salsalate administration.

Free T_4 estimates varied depending on the assay. The FTI declined in parallel with total T_4, decreasing modestly on the first day (88.3 ± 7.4, NS) and to significantly less than baseline on the third day (74.4 ± 7.5, $P = .0001$), while the FTD (19.8 ± 4.1 pmol/L at baseline) was unchanged after 3 days of salsalate use (19.5 ± 4.0 pmol/L, NS).

Serum TSH concentrations decreased after the first 24 hours (0.91 ± 0.27 mU/L, $P < .05$) and remained suppressed for the duration of the study (0.95 ± 0.49 mU/L on day 3, $P < .05$).

DISCUSSION

It is widely recognized that salicylates decrease serum total T_4 and total T_3 levels, a characteristic they share with several other medications.[3,5,7] This is accomplished primarily through competition for low-affinity binding sites on carrier proteins, which forces a transient increase in unbound hormone levels and accelerates the clearance of thyroid hormones from the circulation.[4,5,8] They also inhibit hepatic 5′-monodeiodination of T_4, which could contribute to the decrease in serum T_3, and decrease TSH concentrations, which may decrease hormone production rates.[6,9,10] Finally, there is evidence that freed hormone is shunted away from the liver toward extrahepatic sites of metabolism.[11]

Compared with other nonsteroidal antiinflammatory agents, salsalate is particularly effective in depressing serum thyroid hormone concentrations.[1-3,12] During long-term administration, total T_4 decreases by almost 40% and total T_3 decreases into the hypothyroid range.[2] Although both the FTI and free T_4 by unbound analog assay also decline, this is likely an anomaly introduced by sample dilution, similar to that observed during therapy with anticonvulsants.[4,13,14]

The present study shows that serum total T_4 and total T_3 levels are significantly reduced during the first several days of salsalate administration. However, despite the decrease in total hormone concentrations, the T_4/T_3 ratio remains unchanged. Similar to the declines in total T_4 and total T_3, blood levels of rT_3 decrease by about 25% after 72 hours.

These proportional reductions in total hormone levels suggest that salsalate alters thyroid hormone metabolism primarily by interfering with hormone binding to carrier proteins and not by reducing hepatic 5′-monodeiodination. Furthermore, the decrease in rT_3 is opposite to what would be expected if hepatic 5′-monodeiodinase was significantly inhibited by the medication. An alternative explanation would be that salsalate both retards the disposal of T_3 and accelerates the disposal of rT3, but this possibility could not be tested.

These results differ from those derived from animal models. In rat liver homogenates, salicylates competitively block both the conversion of T_4 to T_3 and the outer-ring deiodination of rT_3 to 3,3′-T_2, compatible with the inhibition of 5′-monodeiodinase.[6] Short-term administration of sodium salicylate to rats decreases serum total T_4 and total T_3 within 30 minutes while significantly increasing the blood levels of rT_3.[15] The biliary excretion of T_3 transiently increases and then decreases dramatically after salicylate loading, suggesting interference with hepatic T_4 to T_3 conversion, while at the same time there is a prolonged increase in the excretion of both rT_3 and its deiodination product 3′,5′-T_2.[16] In contrast to the therapeutic doses of salsalate used in the present study, these rat models used high doses of salicylate, which on a weight basis were many times the doses given to our subjects. Also, the observed changes in thyroid hormone metabolism were those that occur acutely, within a few hours instead of over several days.

The addition of sodium salicylate to serum increases the free fractions of both T_4 and T_3, an effect attenuated by sample dilution, and salicylate loading in normal subjects abruptly increases the serum concentration of free T_4 measured in undiluted serum by either direct dialysis or ultrafiltration.[4,13] By comparison, the FTI decreases progressively during salsalate administration. This occurs because the THBR assay is performed in diluted serum, reducing the concentration of weakly bound salicylate to the point at which it no longer effectively competes with the tracer for low-affinity protein binding sites.[17] The THBR fails to increase as total T_4 decreases, and the FTI consequently underestimates the true free T_4 value.

Like other salicylates, salsalate depresses serum TSH levels, at least over the short-term, presumably by increasing free hormone levels.[13] During long-term administration, TSH levels are normal, arguing against a direct interference of the agent

with TSH assays.[2] Furthermore, although salicylates decrease both the uptake and release of radioactive iodine by the thyroid gland and blunt the TSH response to TRH, they are not significantly concentrated by the thyroid, pituitary, or hypothalamus.[8-10 18] The suppression of TSH over the first 3 days of salsalate administration despite an unchanged FTD suggests that the direct dialysis assay used in this study, like the FTI, underestimates the true free T_4 concentration.

Short-term administration of therapeutic doses of salsalate significantly alters routine thyroid function test results. Serum levels of total T_4, total T_3, and rT_3 decrease to about 75% of baseline levels after 3 days, the FTD remains unchanged, and there is a sustained suppression of TSH. The proportionate decrease in total hormone concentrations suggests that inhibition of hormone binding to serum proteins is more important than the effects of salsalate on hepatic 5′-monodeiodinase activity.

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