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Bromine and thyroid hormone activity

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Abstract

***Aims*—To examine the possible consequences of high plasma concentrations of bromine on thyroid hormone.**

***Methods*—Bromine was measured by inductively coupled plasma mass spectrometry in the plasma of 799 patients consulting for thyroid disorders. Because the mean (SD) bromine concentration in the plasma of healthy subjects is 4 (1) mg/l, concentrations above 6 mg/l were regarded as outside the normal range. Bromine, free thyroxine (FT4), and thyroid stimulating hormone (TSH) values were compared.**

***Results*—The percentage of patients with normal, low, and high FT4 and TSH plasma activities, measured separately, did not differ between patients with low and high bromine concentrations. The percentage of patients with high TSH but normal FT4 values was significantly higher in the group with bromine values of more than 6 mg/l than in the group with bromine concentrations below this ($p < 0.02$).**

***Conclusion*—An increase in plasma bromine could potentiate an increase in plasma TSH concentration, probably as a consequence of a minor inhibitory effect on thyroid activity.**

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The associations between plasma bromine concentration and thyroid function have been studied more exhaustively in rats than humans. Leeuwen *et al*,[1 2] Loeber *et al*,[3] Buchberger *et al*[4] have shown that an excessive intake of sodium bromide inhibits thyroid function in rats, as shown by the decrease of thyroxine and the increase of thyroid stimulating hormone (TSH) activities in plasma. In humans, on the other hand, Sangster *et al*[5] reported that high doses of sodium bromide taken by mouth in healthy volunteers for 12 weeks did not affect their thyroid function. Rather than studying the consequences on thyroid hormone activity of high doses of bromine given to healthy subjects, we investigated the consequences of high plasma bromine concentrations in patients examined for thyroid disorders.

Methods

Between June 1989 and December 1990, bromine plasma assays were made on 799 patients consulting for thyroid disorders, in addition to the usual investigations including free thyroxine (FT4) and TSH measurements.

Inductively coupled plasma mass spectrometry (ICPMS), used for quantifying bromine in plasma, has been described recently.[6] Briefly, sample preparation comprised a 10-fold dilution of 200 μl of plasma with 1800 μl of a diluent containing 1% nitric acid and 25 μg/l of Europium, used as an internal standard. The diluted plasmas were nebulised into the torch and bromine and Europium ions measured at $m/z = 79$ and 153, respectively, using an ICPMS prototype (Nermag). As this method permits simultaneous determination, iodine was also measured.

FT4 and TSH were measured using commercial kits (Amerlite, Amersham) based on enhanced luminescence immunoassays.

All the data were studied using an advanced statistical analysis program (Deltasoft PCSM; Grenoble, France). The χ^2 test was used for the analysis of the distribution of patients in the different groups and the Mann-Whitney U test for the comparison of bromine concentrations in plasma.

Results

The bromine plasma concentration in normal subjects was 4·1 (mean (SD)) (0·9) mg/l,[6] a value which accords with published results. Therefore, bromine concentrations above 6 mg/l—about 2 SD above the mean normal value, although not very high, could be regarded as outside the normal range.

When FT4 and TSH results were compared separately in both groups of patients with bromine concentrations above and below 6 mg/l, there was no significant difference.

Combinations of TSH and FT4 results compared with bromine concentrations are given in table 1. The only significant difference was the increase in the percentage of patients with high TSH but normal FT4 activities in the "high" bromine group (11%) compared with the "low" bromine group (6%).

To eliminate any possible skewing of results from abnormal iodine concentrations bromine concentrations in the plasma of patients with normal iodine and either normal TSH and FT4 activities or high TSH but normal FT4 activities were also compared

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Table 1 Number (%) of patients categorised according to concentrations of TSH, FT4, and bromine in plasma

TSH mIU/l	*FT4 pmol/l*	*Plasma bromine concentrations (mg/l)* Br < 6 g/l	Br ≥ 6g/l	*Total*
0·15 ≤ TSH ≤ 4	12 ≤ FT4 ≤26	281 (45%)	72 (40%)	353
	FT4 < 12	14 (2%)	4 (2%)	18
	FT4 >26	18 (3%)	5 (3%)	23
TSH < 0·15	12 ≤ FT4 ≤26	64 (10%)	18 (10%)	82
	FT4 < 12	2 (<1%)	1 (<1%)	3
	FT4 > 26	153 (25%)	44 (25%)	197
TSH > 4	12 ≤ FT4 ≤26	39* (6%)	20* (11%)	59
	FT4 < 12	48 (8%)	12 (7%)	60
	FT4 > 26	1 (<1%)	3 (2%)	4
Total		620 (78%)	179 (22%)	799

Normal values for FT4 and TSH are, respectively, 12–26 pmol/l and 0·15–4 mIU/l.
*Difference statistically significant at $p < 0·05$ between the groups with normal and high bromine concentrations χ^2 test)

(table 2). The mean plasma bromine concentration was 13 mg/l in patients with normal TSH and FT4 activities and 38 mg/l in patients with high TSH but normal FT4 activities, (p = NS). The percentage of patients with a bromine concentration above 6 mg/l, was however, significantly higher in patients with high TSH but normal FT4 values (35%) than in those with normal TSH and FT4 values (19%). An association between high plasma bromine concentrations and an increase in the incidence of a thyroid hormone disorder, characterised by high TSH but normal FT4 activities, therefore seems likely.

Discussion

Current methods for bromine analysis, based on colorimetric reactions, are not sensitive enough for reliable quantification of the normal concentrations in plasma. This probably explains why there are so few data on bromine concentrations in different pathologies. The use of an inductively coupled plasma mass spectrometer is a direct method, merely requiring a dilution; it is sufficiently sensitive, reproducible, and specific for this purpose. Moreover, this method permits the simultaneous determination of iodine. Its main disadvantage, however, is that it requires the use of an expensive instrument.

In this study 22% of the patients seen for thyroid disorders had plasma bromine concentrations above 6 mg/l. Why this should be is not well understood but excessive intake, or insufficient elimination, or both, could be the cause in these patients. According to Greve[7] and Rauws,[8] the average daily intake of bromine in the Netherlands is about 8 mg. In France in healthy people, the daily urinary elimination of bromine is about 4 mg[6] and because most bromine is excreted by the kidneys, this value should be about the same as the daily intake. Daily intake can be increased by various foods such as leafy vegetables, which, according to Greve,[7] contain a high quantity of bromine, and by the use of certain drugs containing bromine. That increased bromine concentrations could be attributed to drugs was established by questioning many patients in this study, but the role of drugs has certainly been underestimated, because many prescribed and over the counter drugs contain bromine. Moreover, as the plasma half-life of bromine is about 12 days[9] increased bromine concentrations can be found several days after a patient has stopped taking a drug containing bromine.

The second possible cause for an increase in bromine may be its reduced renal elimination. Even in the absence of renal insufficiency, this can occur when sodium chloride intake is low, as demonstrated long ago by Langley-Czerwinski *et al*[10] in both rabbits and dogs. Consequently, a diet low in salt could decrease the renal elimination of bromine and increase its plasma half-life. It is probably important, however, to distinguish between most of the values observed in this study and those reported in patients with clinical symptoms of excessive bromine, which were higher than 1 g/l[11 12]

The moderate increase in plasma bromine concentrations is probably a contributory factor to an increase in plasma TSH activities, because the incidence of high plasma TSH activities was significantly higher in patients with high rather than normal plasma bromine concentrations, even when patients with abnormal iodine concentrations were excluded. Moreover, it was the only significant difference found in this study.

Our results agree with those of Leeuwen *et al*,[2] who showed that, in rats, bromine inhibits iodine uptake by the thyroid gland, oxidation of iodide to iodine, incorporation of iodine into tyrosine residues, coupling of tyrosine to thyronine and, as a consequence, leads to increased TSH secretion. However, the inhibitory effect of bromine in patients is sufficiently slight as to be compatible with the absence of detectable effects of a high intake of bromine on the thyroid gland of healthy volunteers, observed by Sangster *et al*.[5]

Table 2 Number (%) of patients with normal plasma iodine classified according to plasma concentrations of TSH, FT4, and bromine

Iodine	*40 ≤ I ≤ 80 µg/l*	
Thyroid hormone value	*TSH normal + FT4 normal*	*TSH > 4 mIU/l + FT4 normal*
All patients	n = 273 x (ci) = 13 (159) m = 4·3	n = 46 x (ci) = 38 (400) m = 4·8
Patients with bromine of ≥6 mg/l	n = 51(19%) x (ci) = 52 (378) m = 8·1	n = 16 (35%)* x (ci) = 101 (678) m = 8·5
Patients with bromine of ≤ 6 mg/l	n = 222 (81%) x (ci) = 4 (2) m = 4	n = 30 (65%) x (ci) = 4 (2) m = 3·9

Mean ± confidence interval (x (ci)) and median (m) concentrations bromine in mg/l.
*Difference statistically significant at $p < 0·02$ (χ^2 test).

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1 van Leeuwen FXR, den Tonkelaar EM, van Logten MJ. Toxicity of sodium bromide in rats: effects on endocrine system and reproduction. *Food and Chemical Toxicology* 1983;21:383–9.
2 van Leeuwen FXR, Hanemaaijer R, Loeber JG. The effect of sodium bromide on thyroid function. *Arch Toxicol* 1988;**Suppl 12**:93–7.

3 Loeber JG, Franken MAM, van Leeuwen FXR. Effect of sodium bromide on endocrine parameters in the rat as studied by immunocytochemistry and radio immunoassay. *Food and Chemical Toxicology* 1983; **21**:391–404.
4 Buchberger W, Holler W, Winsauer K. Effects of sodium bromide on the biosynthesis of thyroid hormones and brominated/iodinated thyronines. *J Trace Elem Electrolytes Health Dis* 1990;**4**:25–30.
5 Sangster B, Blom JL, Sekhuis VM, *et al.* The influence of sodium bromide in man: a study in human volunteers with special emphasis on the endocrine and the central nervous system. *Food and Chemical Toxicology* 1983; **21**:409–19.
6 Allain P, Mauras Y, Douge C, Jaunault L, Delaporte T, Beaugrand C. Determination of iodine and bromine in plasma and urine by inductively coupled plasma mass spectrometry. *Analyst* 1990;**115**:813–5.
7 Greve PA. Bromide-ion residues in food and feedstuffs. *Food and Chemical Toxicology* 1983;**21**:357–9.
8 Rauws AG. Pharmacokinetics of bromide ion—An overview. *Fd Chem Toxic* 1983;**21**:379–82.
9 Vaiseman N, Koren G, Pencharz P. Pharmacokinetics of oral and intravenous bromide in normal volunteers. *Clin Toxicol* 1986;**24**:403–13.
10 Langley Czerwinski A. Bromide excretion is affected by chloride administration. *J Am Pharmacol Ass* 1958; **XLVII**:467–71.
11 Stewart RB. Bromide intoxication from a nonprescription medication. *Am J Hosp Pharmacol* 1973;**30**:85–6.
12 Trump DL, Hochberg MC. Bromide intoxication. *Johns Hopkins Med J* 1976;**138**:119–23.