Evidence that the Administration of Vitamin C Improves a Defective Cellular Transport Mechanism for Iodine: A Case Report

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Introduction

Orthoiodosupplementation is the daily amount of the essential element iodine needed for whole body sufficiency.[1] Whole body sufficiency for iodine is assessed by an iodine/iodide loading test.[2] The test consists of ingesting four tablets of a solid dosage form of Lugol (Iodoral®), containing a total of 50 mg iodine/iodide. Then urinary iodide levels are measured in the following 24-hour collection. The iodine/iodide loading test is based on the concept that the normally functioning human body has a mechanism to retain ingested iodine until whole body sufficiency for iodine is achieved. During orthoiodosupplementation, a negative feedback mechanism is triggered that progressively adjusts the excretion of iodine to balance the intake. As the body iodine content increases, the percentage of the iodine load retained decreases with a concomitant increase in the amount of iodide excreted in the 24-hour urine collection. When whole body sufficiency for iodine is achieved, the absorbed iodine/iodide is quantitatively excreted as iodide in the urine.[1-3]

In the first study of the loading test in six normal subjects, the percent of loading dose of iodine excreted in the 24-hour urine collection was 39±17.2 (mean ± SD) with a range of 14.2-66%.[2] In eight patients not receiving iodine supplementation, a mean value of 40% was reported.[4] Recently, more than 4,000 loading tests were performed in the US population by the Flechas Family Practice Laboratory using our procedure.[2] The amount of the iodine load excreted in the 24-hour collection averages 40%, covering a wide range of ages of both sexes.[5]

After three months of supplementation with 50 mg iodine/iodide per day, most non-obese subjects not exposed to excess goitrogens achieved whole body iodine sufficiency, arbitrarily defined as 90% or more of the iodine load excreted in the 24-hour urine collections.[2,6] Adult subjects retained approximately 1.5 gm of iodine when they reach sufficiency.[3] Baseline serum inorganic iodide levels 24 hours after last dose of iodine in eight normal subjects with normal body weight who achieved whole body iodine sufficiency had a mean ± SD of 1.1±0.18 mg/L.[3,7] We have arbitrarily defined as a normally functioning iodine retention mechanism, baseline serum inorganic iodide levels between 0.65 and 1.3 mg/L 24 hours after the last dose of iodine in a subject who excretes 90% or more of the ingested iodine.[7]

In patients with a normal gastrointestinal absorption of iodine but with a very defective iodine retention system, the absorbed iodine is quantitatively excreted in the urine with little or no retention. In these rare cases, the loading test will suggest whole body iodine sufficiency (90% or more excreted), but the serum inorganic iodide levels 24 hours after the iodine load will remain low (less than 0.13 mg/L). The inefficient iodine retention mechanism could be due to either a defective cellular iodine transport system or blockage of this iodine cellular transport by goitrogens that compete with iodide for the halide binding site of the symporter system. The defective iodine cellular transport mechanism could be due to genetic defects or oxidative damage to the halide binding site of the symporter.[6]

We previously reported a defective cellular transport system for iodine in two obese female subjects not responding to orthoiodosupplementation.[6] These individuals had low serum iodide levels (0.11 mg/L and less than 0.06 mg/L) combined with high urinary excretion of iodide following the loading test (96% and 102%). We would like to report a third case of cellular iodide transport damage in a non-obese female subject with a past history of hyperthyroidism followed by hypothyroidism treated with Synthroid 50 µg/day over the last four years. The other treatment modalities were added to the thyroid hormone therapy which served as baseline. The patient developed symptoms of hyperthyroidism following implementation of orthoiodosupplementation with 50 mg iodine/day. She titrated her iodine dose down to 12.5 mg every other day (6.25 mg average daily dose). She tolerated a daily average dose of 6.25 mg iodine well with increased energy. The iodine transport damage was corrected at least partially by administration of the antioxidant vitamin C in a sustained released form at 3 gm/day for three months.

Elevated bromide levels were observed in urine and serum samples, 20 times the levels reported in the literature in normal subjects.[8,9] Mild bromism may have been the cause of the oxidative damage to the iodine transport system and the side effects to orthoiodosupplementation. Chloride competes with bromide at the renal level and increases the renal clearance of bromide.[10,11] Sodium

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Table 1

Self-Assessed Effect of Treatment Modalities on Patient's Symptomatology

Symptoms	Synthroid (50 µg/day) 4 years	Iodine (6.25 mg/day) 1 year	Vitamin C (3 gm/day) 3 months	Chloride load (10 gm/day) 7 days
Tremor	Not Present	0/+1	0	0
Fatigue	+1	+1	0	-2
Exopthalmos	-1	*	0	0
Urine Frequency	-1	-1	0	+1
Effect on Overall Well-Being	+1	0/+1	0	0

0 = No effect; +1 = Some improvement; +2 = Marked improvement
-1 = Worse; -2 = Much worse
* Temporary improvement with alternating recurrence

chloride at 10 gm/day for one week resulted in a marked increase in urine bromide levels and a sharp drop in serum bromide. While on the chloride load, urinary frequency improves for the first time in five years, but fatigue worsened, and she experienced facial and body acne. No significant change in symptomatology was observed while on vitamin C. The responses of her symptoms to various treatments modalities by self-assessment are summarized in Table 1. The treatment modalities are cumulative and added sequentially in the patient's management. Measurements of serum and urine bromide and iodide levels reported in this manuscript were performed by ion-selective electrode assay, following chromatography on strong anion exchanger cartridges.[3,7]

Case Report

The patient is a 52-year-old, white, female nurse (height = 64 inches; weight = 140 pounds) with a past history of hyperthyroidism. Her medical history was unremarkable until five years ago when she presented with tachycardia, tremors, exopthalmos, and urinary frequency. Thyroid blood tests revealed slightly elevated total T_3 and elevated T_4 along with a suppressed TSH (TSH <0.02 IU/L; T_4 = 17.1 µg %; T_3 = 187 ng %). Her endocrinologist recommended treatment with radioiodide. After doing some research on this subject, the patient chose not to proceed with this treatment. She did not pursue any course of therapy at this point as she felt her symptoms were not severe enough to justify radioablation of the thyroid. She was followed with thyroid function tests. Her clinical history is summarized in Table 2.

Four years ago, she developed severe fatigue. Thyroid function tests revealed elevated TSH and with slightly lowered T_3 and T_4 levels (TSH = 28.1 IU/L; T_4 = 3.4 µg %; T_3 = 114 ng %). She was placed on 50 mcg/day of Synthroid. After two months on Synthroid, her fatigue improved markedly. Follow-up blood tests revealed a euthyroid state with normal TSH (TSH = 1.2 IU/L; T_4 = 8.7 µg %; T_3 = 128 ng %). However, urinary frequency was still present. During the next four years while on Synthroid, exopthalmos followed a relapsing/remitting course with symptomatic periods alternating with asymptomatic periods. The exopthalmos would be her guide to how her illness was progressing.

One year ago, orthoiodosupplementation was implemented following the iodine/iodide loading test with evidence of whole body sufficiency for iodine (90% of the load recovered in the 24-hour urine collection) but with a very low basal serum iodide level (0.016 mg/L). The patient experienced an exacerbation of all of her symptoms including exopthalmos following the loading test. However, she did feel an increase in energy and warmth after the first dose of iodine. Over the next few months, she titrated the iodine down from 50 mg to 12.5 mg every other day (average daily dose 6.25 mg/day). Although she felt better on orthoiodosupplementation, the relapsing/remitting course of exopthalmos was still present. However, the patient felt her exopthalmos was overall improving following orthoiodosupplementation. She was able to tolerate a daily average of 6.25 mg iodine during the year, while on Synthroid.

Approximately four months ago, she was placed on vitamin C sustained release (Optimox C-500) at 3 gm/day. She continued the every other day iodine 12.5 mg. Prior

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to vitamin C administration and three months after, the serum profile of inorganic iodide levels was obtained following a load of 50 mg iodine/iodide. The pattern of serum inorganic iodide levels prior to supplementation with vitamin C is displayed in Figure 1. The profile of serum inorganic iodide levels obtained in six normal female subjects is superimposed for comparison. The sharp peak of serum iodide at 32 mg/L at one hour post load, followed by a rapid drop suggests that the gastrointestinal absorption of iodine was very efficient but she was unable to transfer efficiently the serum iodide into the target cells. Following three months on vitamin C, the same test was repeated. The data presented in Figure 2 revealed a normal profile of serum inorganic iodide levels. Her baseline serum inorganic iodide increased from 0.016 mg/L to 0.42 mg/L, and she retained 50% of the iodine load (49.2% recovered in 24-hour urine collection), compared to 10% of the load prior to supplementation with vitamin C.

During the post vitamin C loading test, serum bromide was measured in the serum samples collected for the iodide profile displayed in Figure 2. Serum bromide levels were markedly elevated with a pre load level of 143 mg/L and values increased up to 202 mg/L post load (Figure 3). The 24-hour urine collection contained 192 mg bromide. Serum bromide levels reported in normal subjects 20 years ago ranged from 3-12 mg/L.[8,9] Since chloride increases renal clearance of bromide,[10,11] the patient was told to ingest 10 gm of sodium chloride/day (in the form of Celtic Sea Salt) for seven days.

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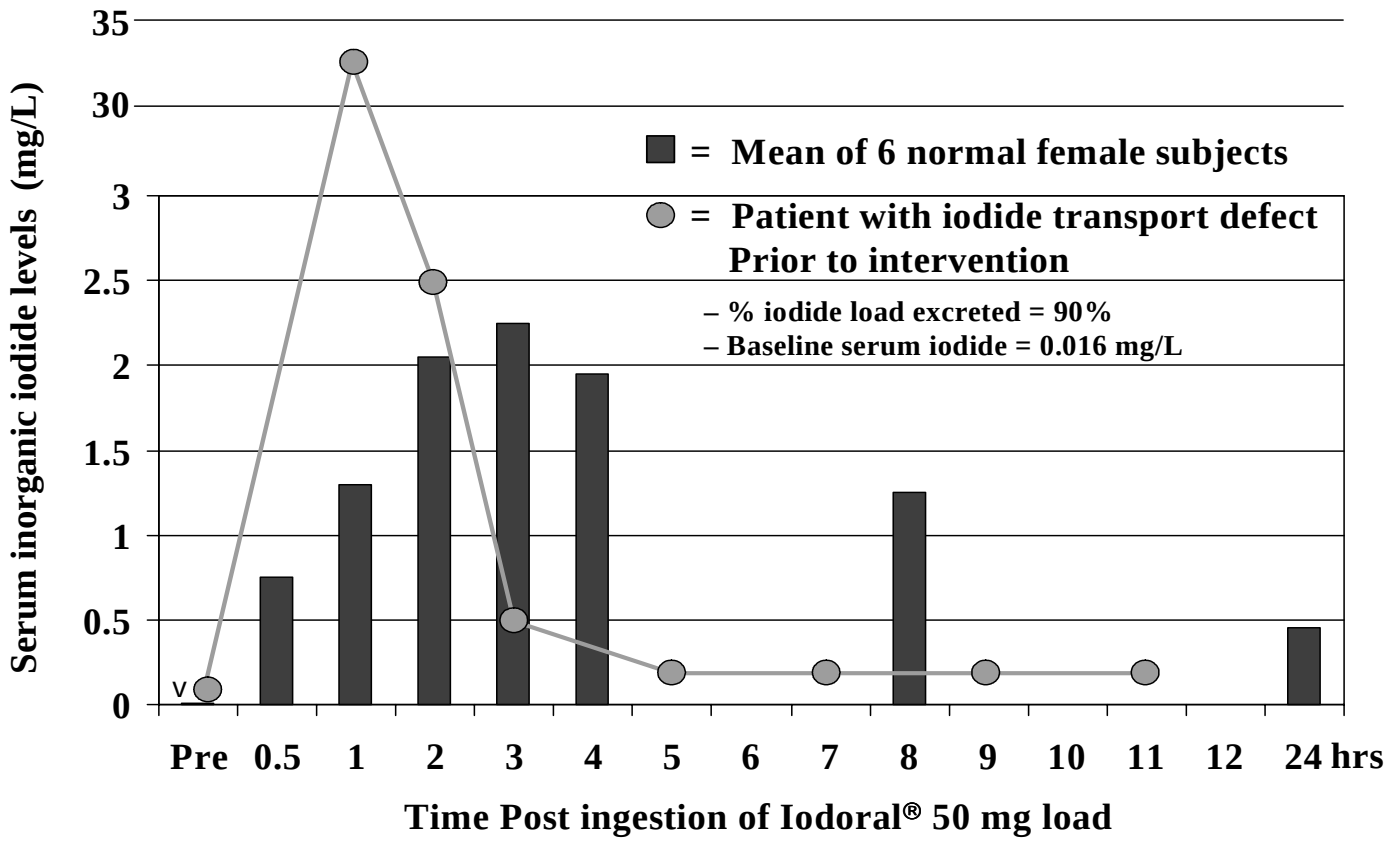
Table 2

Chronology of Patient's Medical History

Date	Signs, Symptoms, Blood Work, Diagnosis, Treatment, and Response
2000	Signs and symptoms = tachycardia + tremors + exopthalmus + urinary frequency TSH = <0.02 IU/L T_4 = 17.1 µg% T_3 = 187 ng% Diagnosis — Hyperthyroidism with exopthalmus Treatment — Endocrinologist proposed radioablation of the thyroid gland. Patient refused, since she felt symptoms did not interfere with her performance at home and at work to justify such drastic measures.
2001	Symptom = sever fatigue TSH = 28.1 IU/L T_4 = 3.4 µg% T_3 = 114 ng% Diagnosis — Hyperthyroidism Treatment — Synthroid 50 µg/day Response — Fatigue improved. Euthyroid — TSH = 1.2 IU/L T_4 = 8.7 µg% T_3 = 128 ng%
2001-2004	Treatment — Synthroid 50 µg/day Response — Patient exopthalmus fluctuated between periods of remission and periods of relapse concomitant with symptoms of urinary frequency
2004	Iodine/iodide loading test — 90% of oral load excreted in 24-hour urine collection but baseline serum iodide = 0.016 mg/L. Evidence of a defective iodine transport mechanism. — Orthoiodosupplementation implemented at 50 mg iodine/day (4 tablets Iodoral®). Exopthalmus, tremors and urinary frequency worsened. — Patient titrated intake down to 1 tablet every other day (daily average of 6.25 mg). — Average daily intake of 6.25 mg iodine was tolerated well during the year while in Synthroid. — Increased energy level. Some improvement in tremors and exopthalmus.
2005	Vitamin C = 3 gm/day for three months Loading test was performed before and after three months on vitamin C Serum profile pre-vitamin C was indicative of iodine transport defect (Figure 1) Serum profile after three months on vitamin C revealed a normal pattern (Figure 2)

Figure 1



The patient excreted 90% of the iodine load, but her basal serum inorganic iodide level was very low — 0.016 m/L. This pattern suggests a defect in the iodine retention mechanism.

This resulted in a bromide detoxification reaction. The patient became very fatigued. In addition, she developed facial and body acne, most likely due to mild bromism. However, one positive response to the chloride load was that urinary frequency decreased significantly during that week. This was the first time that frequency of urination became normal since the onset of Graves' disease five years ago.

Discussion

To our knowledge, this is the first case report of a patient with evidence of a very defective retention mechanism for iodine who was studied with serial serum iodide levels prior to and following intervention. A combination of orthoiodosupplementation in amounts of iodine the patients could tolerate and administration of the antioxydant vitamin C *via* the oral route improved the performance of the iodine retention mechanism. Repair of a defective iodine cellular transport mechanism following orthoiodosupplementation combined with a complete nutritional program may explain our observation that in some cases a repeat loading test three months after orthoiodosupplementation resulted in a decreased percentage load excreted instead of the expected increase. This explains why in some cases patients feel better on orthoiodosupplementation although the repeat loading test three months following orthoiodosupplementation reveals a greater retention of iodine and a drop in percentage load excreted. The milder forms of iodine retention defect will probably be overlooked until a more refined procedure is worked out to assess accurately the efficiency of the iodine transport mechanism. To be discussed later, the salivary/serum iodide ratio may be the test that will detect various levels of iodine transport defect, the greater the ratio, the more efficient the transport system.

We have previously observed that some patients who experienced side effects while on orthoiodosupplementation excreted large amounts of bromide in the urine. Orthoiodosupplementation induced and increased mo-

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bilization of bromine from storage sites with increased urinary excretion of bromide.[4,6,12] The halide, bromide, was measured in the serum and urine samples of the second loading test. Bromide levels were markedly elevated in the 24-hour urine collections, at 192 mg/24 hours, compared to 3-12 mg/24 hours reported in normal subjects.[8,9] Serum bromide levels were markedly elevated with a baseline of 141 mg/L, with post-iodine load values as high as 202 mg/L (Figure 3). The renal clearance of bromide in adult subjects not ingesting large amount of chloride is around 1 L/24 hr. Therefore, the 24-hour urine bromide levels at steady state conditions should be equal to the amount of bromide in one liter of serum. The levels of bromide in serum and urine were some 20 times higher than expected in normal subjects. Since chloride increases renal clearance of bromide,[10,11] she was placed on sodium chloride (Celtic Sea Salt) at 10 gm/day for one week. After one day on chloride, urine bromide levels increased to 530 mg/24 hours and after the seventh day to 760 mg/24 hours. With a daily average excretion of (530+760)/2 = 645 mg, she excreted 645 x 7 = 4,515 mg of bromide during that week. Her serum bromide level after seven days on the chloride load decreased markedly to 43.2 mg/L, from a pre-chloride load of 141 mg/L. Since orthoiodosupplementation increases markedly urine excretion of bromide,[4,6,12] it is likely that the patient's total body bromine content was much higher prior to starting the iodine supplementation. This patient was not taking a bromide-containing medication. Her elevated serum and urine bromide levels are most likely from a dietary source.

Some patients require up to two years of orthoiodosupplementation to bring post loading urine bromide levels below 10 mg/24 hours, if chloride load is not included in the bromine detoxification program. Rapid mobilization of bromine from storage sites with orthoiodosupplementation, combined with increased renal clearance of bromide with a chloride load, often causes side effects. Increasing fluid intake and adding a complete nutritional program to orthoiodosupplementation minimizes these side effects. In this patient, rapid mobilization of bromine from storage sites with iodine and increased excretion of bromide from chloride loading resulted in side effects of severe fatigue and facial and body acne, but urinary frequency improved significantly for the first time in five years. The patient was asked to score the effect of treatment modalities on her overall well-being, with a score of 1 being the worst and 10 being best. She gave a score of 3 while on Syntroid compared to a score of 5 following one year on orthoiodosupplementation at a daily average of 6.25 mg iodine; three months on vitamin C at 3 gm/day; and seven days on the chloride load.

We are currently preparing a protocol for the evaluation of

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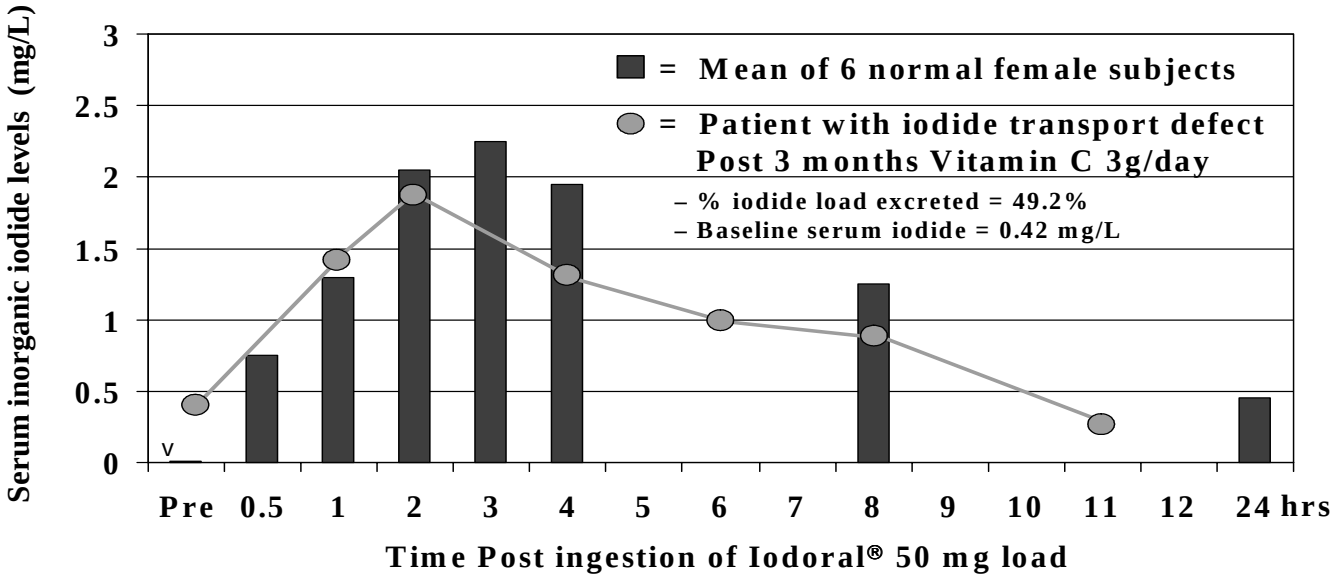
Figure 2

Serum Profile of Inorganic Iodide Levels Following the Iodine/Iodide Load (50 mg) in 6 Normal Subjects and in 1 Patient with Iodide Transport Defect Following 3 Months of Intervention with Sustained-Release Vitamin C at 3 mg/day



She excreted 49.2% of the iodine load and the baseline serum level was 0.42 mg/L, evidence of improved function of the iodine cellular transport mechanism.

patients not responding to orthoiodosupplementation and with evidence of a defective whole body iodine retention mechanism. The results of the loading test showing 90% or greater excretion of the iodine load combined with baseline serum iodide levels below 10^{-6}M (<0.13 mg/L). The evaluation of such patients ideally should include antibody titer to the sodium iodide symporter. Several organs in the human body beside the thyroid gland are capable of concentrating 20-40 fold peripheral iodide levels against a gradient.[13] The salivary glands have this capability, possessing a sodium iodide symporter system similar to the thyroidal iodide symporter.[13] The least invasive way to assess response to interventions in these patients would be to measure iodide levels in saliva and serum and to calculate the ratio of saliva iodide/serum iodide. A ratio near unity would indicate a severe defect/damage of the symporter function. An increase in the ratio following intervention would reflect an improvement in the symporter function. We are planning to measure this ratio in normal subjects in order to establish a normal range.

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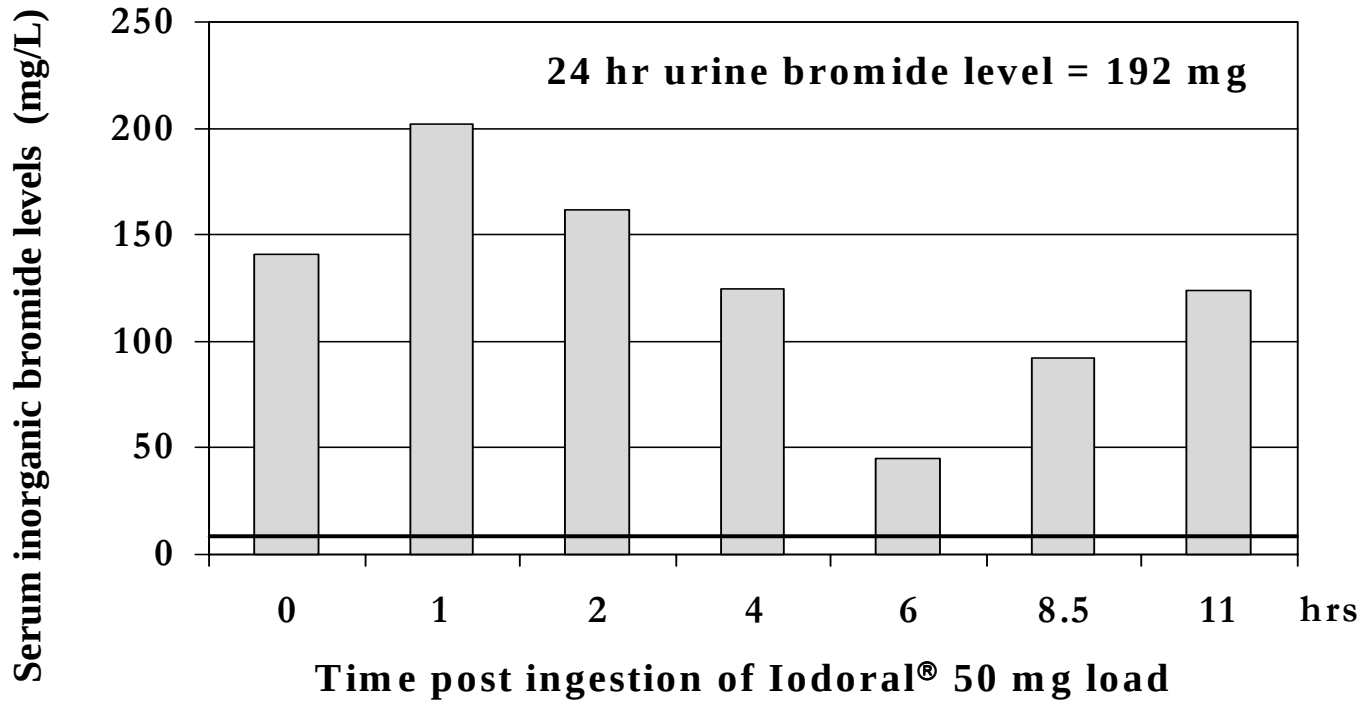
Figure 3



The heavy horizontal line represents the upper limit of serum bromide levels reported in normal subjects.