Serum Inorganic Iodide Levels Following Ingestion of a Tablet Form of Lugol Solution: Evidence for an Enterohepatic Circulation of Iodine

by Guy E. Abraham, MD

Introduction

The element iodine was discovered in 1811[1] and recognized as an essential element a century later in the early 1920s.[2,3] The recommended daily allowance (RDA) of elemental iodine by the Food and Nutrition Board of the United States National Academy of Sciences was not established until 1980, and it was not confirmed until 1989.[4] The World Health Organization made its own recommendations on iodine intake in 1996, taking into consideration age and physiological conditions.[5] However, the US RDA and WHO recommendations were not based on whole-body sufficiency for iodine, but on the minimum amounts of iodine required to prevent goiter and cretinism.[4,5] In 1930, Thompson, *et al*[6] stated, "The normal daily requirement of the body for iodine has never been determined." This statement is still true today, more than 70 years later. We still don't know the iodine/iodide requirements for whole-body sufficiency.

Based on an iodine loading test developed by the author to assess whole body sufficiency for iodine,[7] 100-400 times the US RDA (orthoiodosupplementation) is required to achieve whole-body sufficiency for iodine. The human adult body retains approximately 1.5 gm of iodine when iodine sufficiency is achieved,[8] an amount 100 times higher than reported in medical textbooks for the normal adult.[5] The amount of iodine present in the thyroid gland in an iodine-sufficient adult represents only 3.3% of the total body iodine,[8] not the 70-80% reported in medical textbooks.[5]

Several clinicians are now using the iodine loading test and implementing orthoiodosupplementation in their practices. They report a very good correlation between the results of the loading test and clinical response of their patients to iodine supplementation (for an example, see reference 9). As part of a project to study the metabolism of ingested Lugol solution in tablet form (Iodoral®), serum inorganic iodide levels following ingestion of Iodoral® were measured in two groups of normal volunteers evaluated with serial blood samples. The results obtained from this study are reported here. A double peak of serum inorganic iodide levels was observed in some subjects with a time interval of eight hours between the peaks. This double peak is typical of substances undergoing an enterohepatic circulation. This metabolic aspect of ingested inorganic iodine/iodide has not been previously reported.

Materials and methods

The procedure used to measure urinary iodide levels[10] was modified to measure serum inorganic iodide levels. The detection method by ion-selective electrode is the same as previously described.[10] But the chromatographic purification of iodide from the other halides by solid state partition on anion exchange resins was modified. First, instead of 500 mg column with a 10 ml reservoir (Alltech #309750), the 600 mg syringe cartridge was used (Alltech #21907). Both chromatographic systems contain the same strong anion exchanger SAX resin.[10] Second, the vacuum manifold connected to a vacuum pump previously used,[10] was replaced with Positive Displacement Manifolds (PDM-40, and PDM-20) capable of running 40 and 20 samples, respectively, in the same batch. The Positive Displacement Manifolds were designed by the author and built by a precision machining facility. Third, the elution of the halides was performed with increasing ionic strengths of sodium nitrate. Because the two chromatographic systems behaved differently regarding the sequence of elution of the halides, pilot studies were performed with standard materials of the halides to optimize the system. In the 500 mg column, fluoride was eluted with the biological fluid, while with the 600 mg cartridge, chloride came first with the eluted sample. The sequence of the elution procedure used for the cartridges is displayed in Figure 1. This elution sequence resulted in an excellent separation of the halides with less than 5% overlap. The sensitivity of the assay was 0.006 mg/L if a sample of 10 ml of serum was used. With a smaller volume of serum, the sensitivity decreased proportionally. All serum samples measured so far, prior to iodine supplementation, were below the sensitivity of the assay.

Subjects

Following informed consent, two groups of normal subjects were studied. Group I consisted of three normal women and two normal men with normal body weight. Subjects in Group I received an amount of three tablets of Iodoral® (37.5 mg total iodine) orally. Iodoral® is the tablet form of Lugol solution containing 12.5 mg elemental iodine per tablet.[11] Blood samples were obtained at time zero, 30 min, 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs, and

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24 hrs, (eight samples) following the ingestion of the preparation.

Group II consisted of six normal women with normal body weight. This group was studied twice: Before and after 1 month of iodine supplementation at 50 mg elemental iodine/day (four tablets Iodoral®). For the loading test, four tablets (50 mg) were ingested and blood samples were obtained at time zero, 10 min, 20 min, 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 8 hrs, and 24 hrs (10 samples). Serum samples obtained, following further processing, were frozen in plastic containers until assayed.

Results

The serum levels of inorganic iodide in Group I subjects receiving three tablets of Iodoral® are compared with the levels obtained pre-supplementation in Group II subjects who ingested four tablets (Figure 2). At time zero, the serum iodide levels were undetectable in both groups. Since 10 ml of serum was used in Group I and 3 ml in Group II, the sensitivity of the assay was 0.006 mg/L for Group I and 0.02 mg/L for Group II.

The serum levels obtained at 10 and 20 minutes in Group II were omitted from this figure for ease of comparisons since these two samples were not available in Group I. Also, Group I subjects did not have a three-hour blood sample, and Group II subjects did not have a six-hour blood sample. By 30 minutes post ingestion of three tablets (Group I) and four tablets (Group II), mean serum iodide levels were 0.4 mg/L and 0.7 mg/L respectively for Group I and Group II. Peak levels were achieved in both groups between two and four hours. Serum inorganic iodide levels were still detectable at 24 hours with 0.4 mg/L and 0.45 mg/L. The mean peak levels for Group I were around 1.5 mg/L; whereas, for Group II, the mean peak levels were between 1.8 mg/L and 2.2 mg/L. After one month of supplementation at 50 mg/day in Group II, four of six subjects reached peak levels at 10 minutes. These levels were maintained for 2-3 hours, forming a plateau, followed by a sharp drop, and a second peak at eight hours post ingestion.

The data on one of the subjects pre- and post-supplementation are displayed in Figure 3. Prior to supplementation, the iodide levels were below 0.02 mg/L at 10 minutes, became measurable at 20 minutes (0.2 mg/L), increased progressively to reach a peak 1.8 mg/L at two hours, and decreased afterward to levels of 0.4 mg/L at eight and 24 hours. Following one month of supplementation with four tablets of Iodoral® (50 mg), the peak levels were three times higher and shifted to the left by two hours. A plateau was maintained between 10 minutes and three hours with levels fluctuating between 4.6 mg/L and 5 mg/L. At four hours, the serum iodide level dropped sharply to 1.4 mg/L. No blood samples were obtained at six hours. A second peak of 3.2 mg/L was

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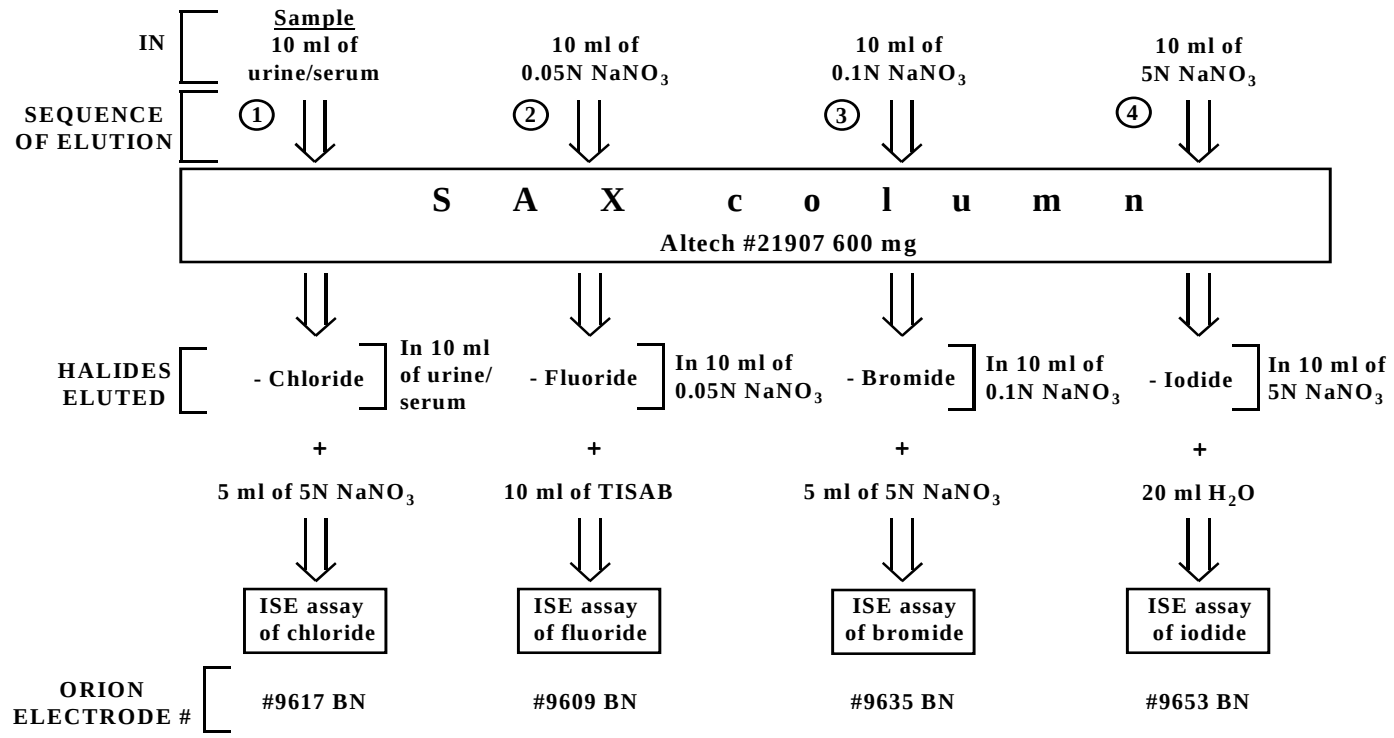
Figure 1



This flowchart describes the combined measurement of chloride, fluoride, bromide, and iodide in the same urine or serum sample, by prior chromatography on anion-exchange resin cartridges fitted with 10 ml plastic syringes, in a Positive Displacement Manifold (PMD).

observed at eight hours, suggesting an enterohepatic circulation of iodine. Following one month of supplementation, steady state conditions were achieved in this subject, and the serum iodide levels were 1.3 mg/L preloading and 1.2 mg/L 24 hours post-loading. As previously discussed,[8] at a daily intake of 50 mg iodine, expected serum levels at steady state would be equal to 50 mg/day divided by 43.5 L/day which computes to 1.15 mg/L. The renal clearance rate of iodide is 43.5 L/day.[8]

The second peak of serum iodide levels eight hours after the first peak, following supplementation with 50 mg iodine for one month, was confirmed in a female subject who collected urine samples individually without pooling for 24 hours following the loading test with 50 mg (four tablets). This subject excreted 42% of the oral amount of 50 mg. A total of eight samples of voided urine were collected over the 24-hour period (Figure 4). The values shown on Figure 4 are expressed as percentage of the total iodide excreted in 24 hours, recovered in the voided sample expressed per hour, therefore representing excretion rate. This value was computed by dividing the amount of iodide measured in the sample by the interval of time in hours between collections. For example, if 20% of the total iodide excreted was recovered in a sample with a time interval of two hours from the previous void sample, the excretion rate would be 10%/hr. The first peak of urine iodide excretion rate occurred in sample #2, collected at five hours post ingestion, representing a three-hour period (time interval 2-5 hours from ingestion of iodine). This peak at 2-5 hours coincides with the serum data with peaks observed between two and four hours post-iodine administration. Serum iodide is efficiently cleared by the kidneys. A second peak was observed in sample #6, obtained at 13 hours post ingestion with a 2-hour interval (11-13 hrs). The interval of time between the two peaks is approximately eight hours, confirming the peak observed at eight hours in serum samples when the first peak was at 10 minutes.

Discussion

The effect of orthoiodosupplementation on the profile and levels of serum iodide following a loading test is suggestive of an effect of iodine on the efficiency and rapidity of absorption of iodine. Possibly, this effect of iodine supplementation on iodine absorption may be applicable to the absorption of other nutrients.

The second peak of serum iodide following the loading test was not observed in the subjects prior to iodine supplementation (Figure 2) because such a peak would be expected eight hours after the first peak. Since the first peaks occurred 2-4 hours after ingestion of iodine in Figure 2, the second peak would have occurred at 10-12 hours after the iodine load. No blood sample was obtained between eight and 24 hrs in those subjects.

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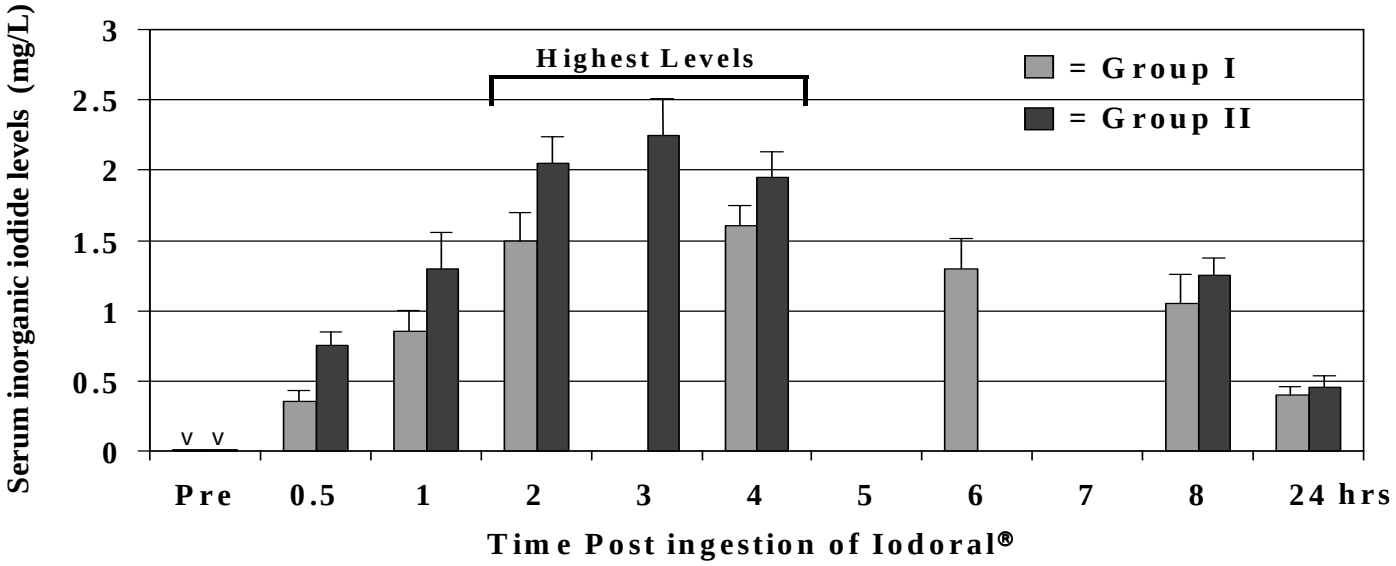
Figure 2



Serum inorganic iodide levels following ingestion of 37.5 mg (three tablets Iodoral®) in Group I and 50 mg (four tablets Iodoral®) in Group II. Peak level are observed between two and four hours. V is less than 0.006 mg/L for Group I and less than 0.02 mg/L for Group II.

An enterohepatic circulation of ingested inorganic iodine has not been previously reported. Such a metabolic pathway of iodine could result in elevated hepatic concentrations of iodine. We previously reported a significant effect of orthoiodosupplementation on serum liver enzymes.[11] What role iodine plays on liver functions and bile formation is, at the present, unknown. Some patients have reported improved digestion, even with fatty meals, and regular bowel movement following orthoiodosupplementation. It is possible that iodine improves the flow of bile from the liver to the gastrointestinal tract. Iodine deserves more attention from medical researchers and clinicians.

A careful review of published data on amiodarone suggests that this organic iodine-containing drug is a sustained release form of iodine. The iodine released is the active agent, with the drug itself being the cause of its toxicity.[12] If this is the case, inorganic non-radioactive iodine would be the treatment of choice in those clinical conditions currently treated with amiodarone. In their 2001 publication, Martino *et al*[13] reported a list of side effects and complications of amiodarone: corneal microdeposits in 100% of the cases; anorexia, nausea in 80%; skin photosensitivity and discoloration in 55-75%; neurological symptoms in 48%; abnormal liver tests in 25%; thyroid dysfunction in 14-18%; and lung dysfunction in 10-13%. The pulmonary toxicity is the most serious complication of amiodarone therapy, with a fatal outcome in 9% of the patients experiencing this side effect of amiodarone.[14]

It is hard to believe that such a drug is widely used by US physicians in medical conditions where inorganic non-radioactive iodine has never been tested. Connolly,[15] in his 1999 review of amiodarone efficacy and safety, reported, "On the basis of the number of prescriptions filled in retail pharmacies, amiodarone was the most often prescribed antiarrhythmic agent, accounting for 24.1% of the total antiarrhythmic prescriptions in 1998." He further commented that amiodarone accounted for 33-74% of prescriptions in Europe and North and South America, compared to 0.3% in Japan, which is 100 times less than the other countries mentioned. It is of interest that mainland Japanese consume at least 100 times the RDA for iodine.[16,17] That is at least 100 times more iodine than countries with 100 times more prescriptions for amiodarone. Regarding the evidence-based analysis of amiodarone efficacy and safety, Connolly stated, "The general view that amiodarone is the most useful drug for VT and VF, notwithstanding the rather modest evidence from randomized trials, led to its being adopted as the standard medical therapy in several recent randomized secondary prevention trials evaluating the ICD… A meta-analysis of these trials based on individual patient data yielded a relative risk reduction in all-case mortality of 13% to 15%, which was of borderline statistical significance (P=0.03 or 0.06 depending on analytical method used)."

To make matters worse with amiodarone, thyroidologists have become so destructive that some of them recom-

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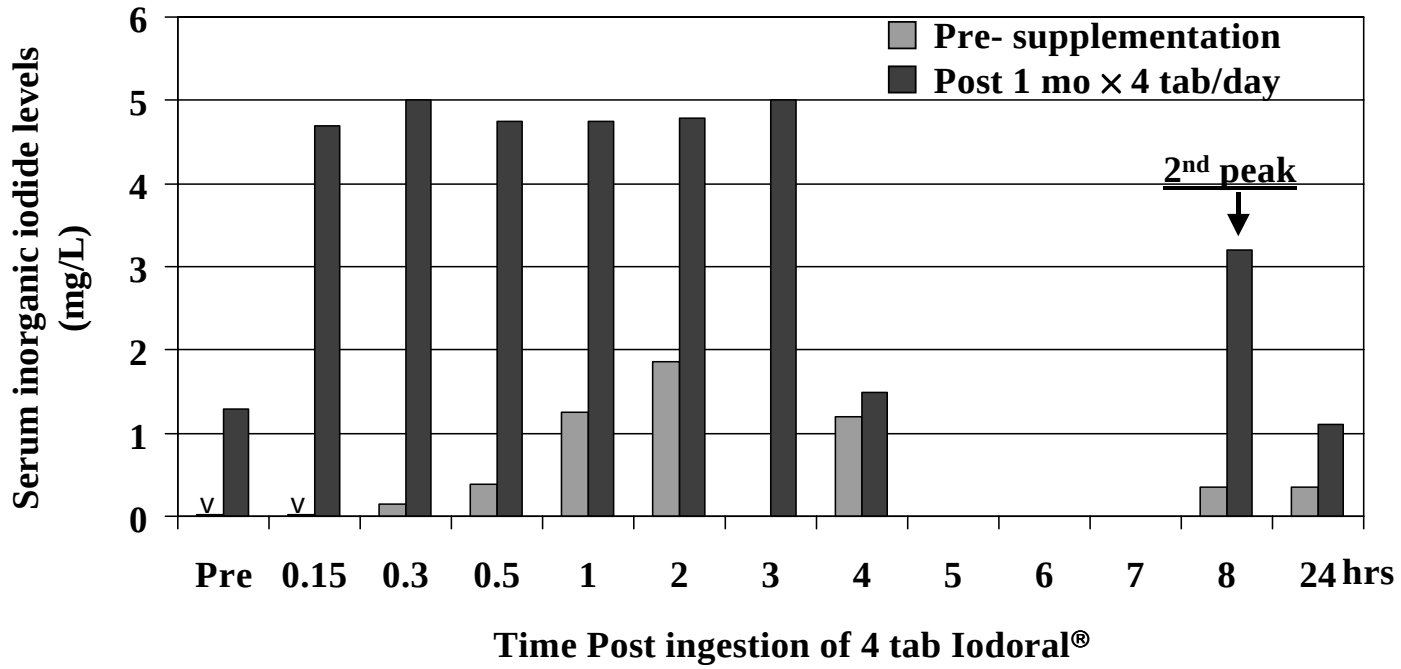
Figure 3



Serum inorganic iodide levels in a 48-year-old woman following 50 mg elemental iodine: presupplementation and after one month on 50 mg (four tablets Iodoral®)/day. V is less than 0.02 mg/L.

mend radioiodine ablation of the thyroid to allow the reintroduction of amiodarone treatment in patients with a prior history of amiodarone-induced thyrotoxicosis.[18] To quote Hermida, *et al*,[18] "However, hypothyroidism should be viewed as a goal, rather than a complication, of treatment in these patients." They have gone berserk!

Implementation of orthoiodosupplementation in the above cases would be appropriate, not as a treatment for cardiac arrhythmias, but as a means of supplying these patients with adequate amounts of an essential nutrient for whole body sufficiency. Who knows? Orthoiodosupplementation and whole body iodine sufficiency may be the answer to several clinical conditions currently treated with toxic drugs.

An enterohepatic circulation of amiodarone has been reported by Andreasen, *et al.*[19] Since we have observed an enterohepatic circulation for inorganic iodine, could the iodine present in amiodarone and released from amiodarone play a role in this enterohepatic circulation? Broekhuysen, *et al,*[20] using balance studies of amiodarone and the iodine released from amiodarone, reported the following. In two subjects treated with 300 mg of amiodarone/day, the total amount of iodine measured in urine and feces was very low during the first three days, with a mean of 19% and 7% of the total iodine ingested suggesting that 80-90% of the iodine ingested was retained in the body. After 25-27 days of therapy with 300 mg/day, the mean percentage excretion of combined urine plus feces in these two subjects increased 48% and 75%. Therefore, after approximately one month, the percentage of iodine retained by the body had decreased to 25% and 50%. No inorganic iodine/iodide was found in feces, only the organic form, amiodarone; whereas, in urine, inorganic iodide was excreted.

In two other subjects treated with 300 mg/day for seven weeks, balance studies revealed at the end of the study that the total excreted iodine in urine and feces averaged 97.4% and 96.9%. The authors commented, "These results suggest that iodine is retained in the body until a mechanism is triggered that adjusts the excretion of iodine to balance completely the intake." They estimated that the body retained 1.5-2.0 g of iodine before the ingested iodine in amiodarone is completely excreted, and before therapeutic efficacy.

In three patients who died following long-term treatment with amiodarone, the levels of inorganic iodine present in various organs and tissues were measured. The total body iodine content was estimated at approximately 2 g with the greatest amount found in fat tissues (700 mg) and striated muscle (650 mg). Iodine was present in every tissue examined. The highest concentrations of

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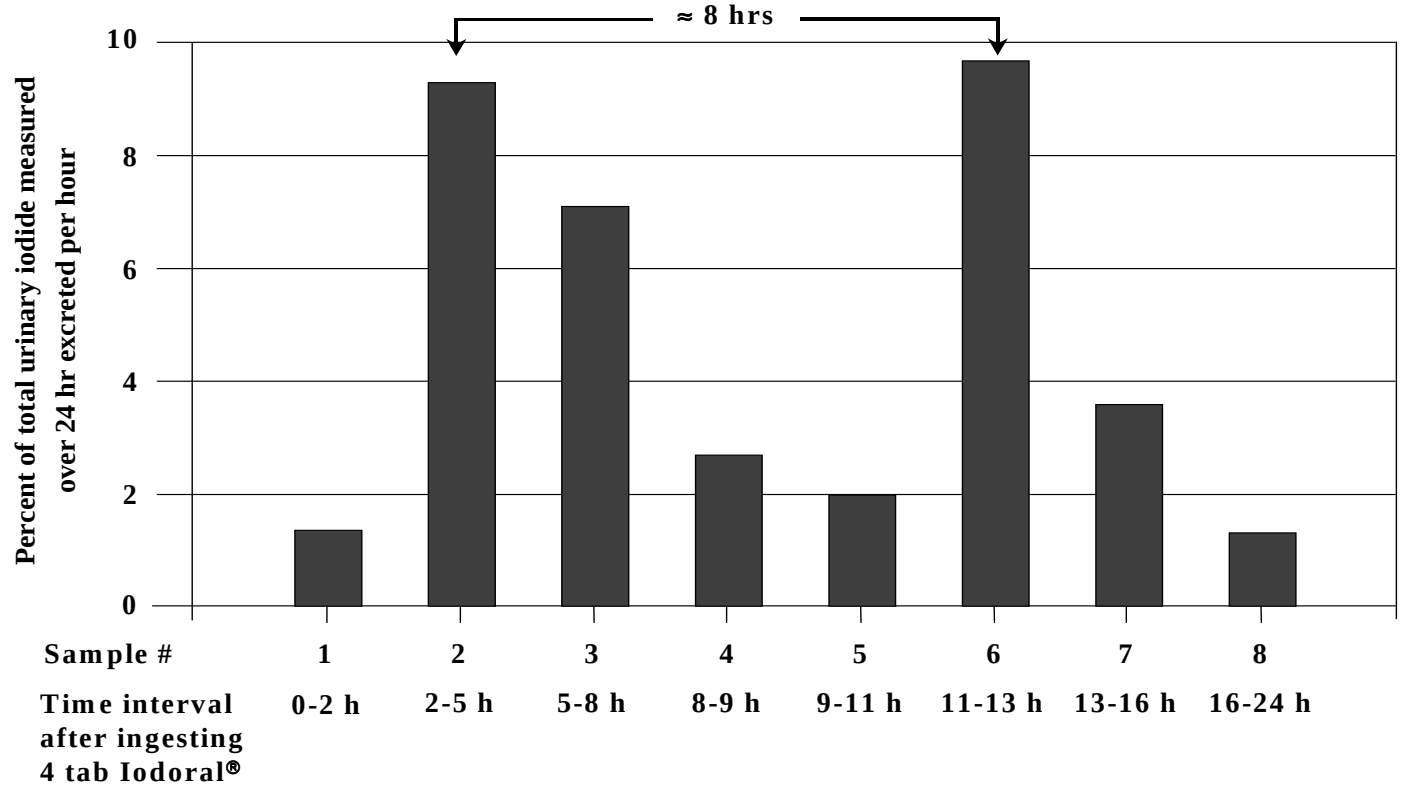
Figure 4



Urinary excretion of iodide per hour in consecutive samples of urine collected over 24 hours after ingestion of four tablets of Iodoral® in a female subject.

iodine were found in descending order in the thyroid gland, liver, lung, fat tissues, adrenal glands, and the heart.

When a tablet form of Lugol solution (Iodoral®) is ingested at a daily amount of 50 mg elemental iodine, whole body sufficiency is achieved in approximately three months; and the estimated amount of iodine retained in the body is approximately 1.5 g.[8] This is the same amount of iodine retained in patients on amiodarone following 4-7 weeks at 300 mg/day. Clinical response to amiodarone is observed after the same period of time (4-7 weeks) on amiodarone therapy. These data are suggestive of an important role of inorganic iodine released from amiodarone in the therapeutic effect of this drug; and that whole body sufficiency for iodine is a requirement for optimal cardiac function. If amiodarone is a toxic form of sustained release iodine, and inorganic iodine is the active ingredient, why not give inorganic iodine to these unfortunate patients, saving them from the toxicity of the amiodarone molecule?[12]

Inorganic non-radioactive iodine/iodide is an essential nutrient, not a drug. Therefore, the body has the metabolic mechanism for using inorganic iodine beneficially, effectively and safely. Iodine is the safest essential nutrient, with a track record of 180 years of use in medicine.[7] Published data confirms its safety even when used in pulmonary patients in amounts four orders of magnitude greater than the US RDA.[8]

About the Author

Guy E. Abraham, MD, is a former Professor of Obstetrics, Gynecology and Endocrinology at the UCLA School of Medicine. Some 35 years ago, he pioneered the development of assays to measure minute quantities of steroid hormones in biological fluids. He has been honored as follows: General Diagnostic Award from the Canadian Association of Clinical Chemists, 1974; the "Medaille d'Honneur" from the University of Liege, Belgium, 1976; the Senior Investigator Award of Pharmacia, Sweden, 1980.

The applications of Dr. Abraham's techniques to a variety of female disorders have brought a notable improvement to the understanding and management of these disorders. Twenty-five years ago, Dr. Abraham developed nutritional programs for women with premenstrual tension syndrome and post menopausal osteoporosis. They are now the most commonly used dietary programs by American obstetricians and gynecologists. Dr. Abraham's current research interests include the development of assays for the measurement of iodide and the other halites in biological fluids and their applications to the implementation of orthoiodosupplementation in medical practice.

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