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Are there Side Effects when Using Supraphysiologic Levels of Iodine in Treatment Regimens?

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Abstract

Potential pharmacological use of iodine unrelated to thyronine chemistry is a current area of interest for researchers. This chapter examines the side-effects associated with chronic daily oral administration of molecular iodine (I_2) at levels above the recommended dietary tolerable upper intake level (UL), using controlled studies in mastalgia patients whose symptoms are associated with fibrocystic breast tissue. The recommended dietary allowance (RDA) for iodine in adult men and women in the United States is 150 μg/day; the dietary UL suggested for the general population is 1100 μg/day (1.1 mg/day). The thought process that underlies the RDA and UL incorporates safety considerations and adequacy of thyroid function. Iodide oxidation in tissues known to concentrate iodide (thyroid, mammary) yields at least two different iodine species that can iodinate biomolecules. Several researchers have suggested an antiproliferative activity for I_2. Tissue distribution of iodine atoms from orally administered I_2 is distinct from that for iodide, as a significant percentage of iodine from I_2 is associated with lipids. The antiproliferative activity of some iodinated lipids is essential for thyroid autoregulation. The thyrotoxicity of orally administered iodide and I_2 are distinct; iodide has been shown to be more thyrotoxic than I_2. Nevertheless, controlled data in female patients treated chronically with daily I_2 suggests a dose–response relationship with respect to subclinical thyroid findings.

Abbreviations

AE	Adverse event
FBC	Fibrocystic breast condition
FT_3	Free triiodothyronine
I_2	Molecular iodine
IL	Iodinated lipid
LPO	Lactoperoxidase
MCF-7	Human breast adenocarcinoma cell line
NIS	Sodium iodide symporter
OTC	Over the counter
RDA	Recommended daily allowance
T_3	Triiodothyronine
T_4	Thyroxine
Tg	Thyroglobulin
TH	Thyroid hormone
TPO	Thyroid peroxidase
TPOAb	Antibodies to TPO
TSH	Thyroid-stimulating hormone
UL	Tolerable upper intake level

Introduction

It has been suggested that treatment with supraphysiologic levels of iodine has potential therapeutic uses beyond thyronine function (Miller, 2006). Some clinicians believe that all tissues in the human body should be saturated with iodine (Flechas, 2005). Maintenance of the equilibrium between thyroidal and extrathyroidal iodine is estimated to require about six times the tolerable upper intake level (UL) (Berson and Yalow, 1954). Controlled chronic safety data for daily iodine intake at these levels are difficult to find even though physicians prescribed daily iodine therapy at doses that ranged from 10 to 100 times the UL during the first half of the twentieth century (Kelly, 1961).

Thyronine–receptor complexes stimulate or inhibit gene expression in almost every tissue in the human body, and therefore necessarily command our focus. The result is a thyroid hormone (TH)-centric perspective of iodine physiology that persuades us to avoid consideration of nonthyronine pharmacologic activity associated with iodine. The role for so-called *extrathyroidal iodine* has been discussed in the literature as iodide uptake in the majority of breast cancers has aroused the interest of several researchers (Venturi *et al.*,

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2000; Venturi, 2001). The question of extrathyroidal iodine is worthy of consideration as the path to understanding the relationship between dietary iodine intake and conditions, such as autoimmune thyroid disease, may lie outside TH biochemistry.

There is no suggestion that iodine intake above the UL is required to maintain tissue-specific TH concentrations, although tissue-specific regulation of THs via the action of deiodinases plays an important role in mild and moderate iodine deficiency (Obregon *et al.*, 2005; Pedraza *et al.*, 2006). The pharmacological activity of supraphysiological levels of iodine is putatively associated with the antioxidant activity of iodide (Winkler *et al.*, 2000; Schmut *et al.*, 2004; Berking *et al.*, 2005)and/or the antiproliferative activity of molecular iodine (I_2) (Zhang *et al.*, 2003, 2006; Shrivastava *et al.*, 2006). Wolff (1989) describes the *paradoxical* relationship between iodination of tyrosyl groups leading to THs versus the iodination of *alternate substrates* that leads to formation of antiproliferative agents. Antiproliferative activity unrelated to THs has been demonstrated in several model systems, and has led some to suggest the use of I_2 as an adjuvant therapy for breast cancer patients (Torremante, 2004). This chapter provides an overview of the safety of daily I_2 administration and provides data on its potential clinical application with mastalgia patients.

Iodine Chemistry

Iodine can adopt a range of oxidation states, and various iodine species exist in an aqueous environment: −1 to +5, e.g., −1 (iodide, I^-); + 1 (hypoiodous acid, HOI); +5 (iodate, IO_3^-). The oxidation of iodide by reactive oxygen species, such as H_2O_2, has been studied since the early 1920s. Two of the primary variables that determine the concentration and distribution of iodine species formed during the oxidation of iodide are pH and iodide. The effect of pH is dramatic; the effect of iodide is nonlinear in that the rate of formation of I_2 or hypoiodous acid (HOI) can increase or decrease as iodide is increased, depending on the precise experimental conditions (Gottardi, 1999).

The oxidation of iodide is a perquisite to the formation of bioactive molecules that contain iodine. The reaction products from thyroid peroxidase (TPO) and lactoperoxidase (LPO) catalyzed iodide oxidation are known to be a function of iodide concentration. I_2 is formed and released by these enzymes at elevated iodide concentrations (Magnusson *et al.*, 1984). Taurog (1970) suggested that the formation of I_2 could be responsible for some aspects of iodide regulation. This suggestion by Taurog preceded a complete description of aqueous iodine equilibria, which was only made possible by computer modeling. A material mathematical description of iodine equilibria was first published in 1981 (Gottardi, 1981). The model was further refined, and a complete description of the underlying effect of pH and iodide concentration on the formation of more than eight different iodine species has been published (Gottardi, 1999). The medical literature exploring iodide oxidation in biological systems has not fully incorporated these results that demonstrate that I_2 and HOI cannot be formed independently in an aqueous environment. The formation of I_2 necessarily leads to the formation of HOI under physiological conditions, and this has potential consequences for iodination of biomolecules.

The mechanism of thyroglobulin (Tg) iodination has been intensely debated and remains an open question; the specific controversy focuses on whether or not iodination of Tg tyrosyl groups occurs via an enzyme-bound intermediate, or by freely diffusing iodination equivalents released from TPO. It is clear, however, that TPO actuates nonspecific iodination reactions in the thyroid. The two chemical species of iodine that can iodinate biomolecules under physiologic conditions are HOI and I_2. Dunford and Ralston (1983) demonstrated that HOI, not I_2, is the primary species that iodinates tyrosine in aqueous environments that contain both I_2 and HOI. I_2 is likely to be the species that is responsible for the iodination of lipids. The distinct pharmacological and toxicological properties of iodide and oxidized iodide (I_2) have been a topic of some interest in the literature, as some activity not associated with THs has been ascribed to I_2.

Nonthyronine Pharmacologic Activity

A large number of clinical and nonclinical studies demonstrate that iodine exerts pharmacological activity unrelated to thyronine. The most thoroughly examined area relates to the mechanism underlying the autoregulatory effect in the thyroid. A second area of research that has received attention is the effect of iodine on the mammary tissue. These two areas are briefly reviewed here as they provide insight into the clinical data that will subsequently be discussed.

Iodinated lipids

Iodinated lipids (ILs) play an important role in thyroid autoregulation (Boeynaems *et al.*, 1995; Dugrillon, 1996; Gartner *et al.*, 1996). Boeynaems and Hubbard (1980) demonstrated the conversion of arachidonic acid into iodinated metabolites such as 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid by LPO, iodide and H_2O_2. The formation of this iodinated lipid is inhibited by methimazole, suggesting the requirement for iodide oxidation. Four different ILs have been identified in mammalian thyroid cells: 6-iodo-5-hydroxy-8,11,14-eicosatrienoic acid (δ-iodolactone); α-iodohexadecanal (IHDA); 5-iodo-7,10,13,16,19-docosapenta-enoic acid (γ-lactone); and 14-iodo-l5-hydroxy-5,8,11-eicosatrienoic acid (ω-lactone). Two of the four identified iodinated lipids are known to

express biological activity. The fact that only two of the four identified lipids express activity is consistent with a nonspecific iodination mechanism, i.e., not an active site mediated biosynthetic reaction directed to a specific end product.

Research of the past 25 years demonstrates that the pharmacological activity of nonthyronine mediators plays an essential role in thyroid autoregulation (Panneels *et al.*, 1994; Dugrillon and Gartner, 1992; Langer *et al.*, 2003). The data suggests that ILs are formed in the thyroid via nonspecific iodination reactions catalyzed by the release of oxidized iodide species from TPO (Kessler and Hooge, 2007).

Mammary tissue

Studies with Iodide The uptake of iodide in the ductal tissue of the mammary gland has been studied for over five decades (Honour *et al.*, 1952). Potter *et al.* (1959) showed that the lactating mammary gland of the rat actively secretes iodine, and that this is a major pathway for iodine elimination, with up to 50% of circulating radioactive iodine recovered in milk after 24 h. Strum (1978, 1979) studied the ability of the mammary gland to take up and organically bind radioiodide in nonpregnant, pregnant and lactating rats, and in nonpregnant animals on an iodine-deficient diet. Tissues from control (nonpregnant) animals showed a low *in vivo* uptake of iodine. Uptake in animals given estradiol was more pronounced in iodine-deficient animals than in controls.

Several investigators studied the effect of iodine deficiency on the mammary gland, and reported that when rats are kept iodine deficient, the structure of the mammary gland is altered (Eskin *et al.*, 1967; Aquino and Eskin, 1972). Iodine deficiency is associated with atrophic changes, as well as areas of dysplasia and atypia. The gland also becomes highly sensitive to stimulation by estradiol, which makes the gland hyperplastic and leads to the formation of cysts. Japanese investigators reported a suppressive effect of iodine on 7,12-dimethyl benzanthracene-induced mammary tumors in rats, and a marked suppression when iodine and medroxyprogesterone acetate were given together (Kato *et al.*, 1994; Funahashi *et al.*, 1996). Eskin *et al.* (1974) reported that uptake of iodine in abnormal breast tissue is increased. Data from subsequent studies support the suggestion that the concentration of iodine in fibrocystic breast tissue is higher than in histologically normal tissue (Kilbane *et al.*, 2000).

Dr Keisuke Iwamoto used genetically-modified human breast adenocarcinoma cell line (MCF-7) cells to overexpress sodium iodide symporter (NIS) and/or LPO, to test the hypothesis that the survival advantage conferred by iodide to human breast cancer cells requires the suppression of LPO, i.e., iodide, but not oxidized iodide (I_2) (Iwamoto and Kim, 2005). The model used ionizing radiation (IR) to demonstrate that overexpression of NIS conferred radioresistance on MCF-7 cells. This effect was apparently due to iodide intake as perchlorate eliminated radioresistance. However, overexpression of LPO was associated with: (1) a decrease in plating efficiency; (2) reduction in the absolute number of surviving cells; (3) growth rates below those of control cells and unirradiated cells; and (4) a reduction in invasiveness. This study underscores the dichotomy that exists in our understanding of iodine physiology as it relates to thyroid function, as opposed to the pharmacology of iodine not associated with THs.

Iodide versus Molecular Iodine (I_2) The disparate pharmacological and toxicological activity associated with iodide as compared to I_2 has been explored by a number of researchers in a range of model systems. The reader is cautioned that the literature must be read with care, as some studies that purport to examine I_2 suffer from inappropriate handling of this idiosyncratic species (Robison *et al.*, 1998). I_2 reacts with water and therefore cannot be stored in an aqueous environment for a prolonged time; the instability is exacerbated at basic pH as I_2 will rapidly convert into HOI and other species (Wyss and Strandskov, 1945).

Changes in thyroid and mammary tissue in iodine-deficient rats were studied after exposure for 10 days to either iodide or I_2 in drinking water (Eskin *et al.*, 1995). Drinking water with iodide eliminated thyroid gland hyperplasia, but I_2 did not. Lobular hyperplasia of the mammary gland was reduced with I_2, but increased with iodide. The authors concluded that these two forms of iodine have different tissue specificities.

The relative toxicological and pharmacological properties of iodide versus I_2 were examined in a series of studies. Acute exposure of iodide in fasted rats resulted in rapid distribution of iodine into the thyroid. In comparison, thyroid uptake of iodine from I_2 was depressed, and retention of iodine in thyroid at 72 h was about 30% less (Thrall, 1990). A statistically different association of radioactive iodine was observed in the whole blood, blood cells, lipids, albumin, globulin and serum water when iodine was administered as I_2 as compared to iodide. A larger percentage of the iodine administered as I_2 was retained in the stomach contents and ultimately was covalently bound to a lipid material (Thrall *et al.*, 1992). The percentage of iodine retained in thyroid 72 h after I_2 administration was 70% and 58% of the amount observed from iodide (Thrall, 1990). I_2 in drinking water was less effective than iodide in suppressing thyroid uptake of a challenge dose of ^{125}iodide in dosing studies conducted for 100 days. Significant increases in thyroid size were observed in male rats treated with iodide, but not with I_2 (Sherer *et al.*, 1991). Subsequent studies (Garcia-Solis *et al.*, 2005) examined the influence of perchlorate on iodine incorporation from orally administered I_2 or iodide.

Table 82.1 Mastalgia trials with an I_2 dosage form

Study number	*Size*	*Duration (months)*	*Trial type*	*I_2 dosage form*
MX02-CLN-04	92	7	Efficacy iodine-naive patients[a]	Aqueous I_2
MX02-CLN-05	923	36	Safety iodine-adapted patients[b]	Solid I_2
MX02-CLN-09	136	6	Safety iodine-naive patients[a,c]	Solid I_2
MX02-CLN-07	389	6	Safety iodine-naive patients[a,c]	Solid I_2
SYM-CL-02	111	6	Efficacy iodine-naive patients[a,c]	Solid I_2

Note: Abbreviation: I_2, molecular iodine.
[a]Placebo-controlled, double-blind, randomized.
[b]Uncontrolled, single-center.
[c]Multicenter trial, double-blind, randomized.

The administration of I_2 resulted in half as much iodine uptake in the thyroid as iodide; perchlorate (6 mg i.p., 2 h predosing) reduced thyroidal uptake from iodide by more than 90%, as compared to 40% with I_2.

All studies that have used a valid I_2 dosage form have concluded that iodide and I_2 have distinct pharmacokinetic and toxicological properties. The antioxidant and antiproliferative activities of I_2 are further elaborated in this text and in Chapter 26 authored by Dr Carmen Aceves, whose studies with I_2 have greatly expanded our understanding in this area.

The mere presence of peroxidase, H_2O_2, and iodide are not necessarily sufficient to ensure formation of I_2. Tissues must be capable of concentrating iodide at a sufficient threshold such that the iodide anion can itself compete for binding to the enzyme-bound hypoiodous acid intermediate to yield I_2. Currently no evidence exists outside of thyroid and mammary tissue to support the formation of iodinated by-products, although both the salivary gland and ovaries concentrate iodide and express a peroxidase.

While there is direct experimental evidence indicating that I_2 is less thyrotoxic than iodide, little safety data exists exploring the safety of orally administered I_2 in humans. The results of all controlled human clinical trials conducted with I_2 are reported below.

Clinical Trials with I_2

Fibrocystic breast condition (FBC)-associated mastalgia is a common pain disorder characterized by periodic, cyclic, pain, breast tenderness and nodularity, and quite limited treatment options. The etiology and pathophysiology of FBC and mastalgia remain unclear. Current hypotheses suggest subtle hormonal imbalances in the hypothalamic–pituitary axis. Uncontrolled studies in over 1000 women (Ghent *et al.*, 1993) provided clinical support for the efficacy and safety of I_2 in the treatment of mastalgia patients. This chapter will provide data from subsequent studies with I_2 that can be segmented into: (1) studies that treated clinically impacted patients to explore efficacy; or (2) studies that examined safety by exposing (a) iodine-adapted patients to I_2 or (b) iodine-naive patients with normal physiologic breast pain to I_2. A list of the studies conducted with I_2 is provided in Table 82.1.

Placebo-controlled human efficacy trials with molecular iodine (I_2)

MX02-CLN-04 – Aqueous I_2 (5 mg/day) Aqueous I_2 was used in the first randomized, double-blind, placebo-controlled study (MX02-CLN-04) to examine the clinical effects of I_2 in women with mastalgia associated with fibrocystic breast changes. The study was conducted at the Virginia Mason Clinic in Seattle, WA. All patients were euthyroid and demonstrated clinical and mammographic findings consistent with the diagnosis of fibrocystic breast changes. Patients were required to have a history of severe mastalgia (cyclic or noncyclic). Physicians rated breast tenderness on a scale of 0–20, with 0 representing no pain and 20 as exquisite pain; over 70% of the enrolled patients were scored as 20 out of 20 at baseline.

Exclusions included a history of thyroid disease (e.g., Graves' disease or adenoma), pregnancy, or cosmetic breast reduction. Patients ranged in age from 25 to 64 years. Data were collected on a total of 92 patients: 46 in placebo and 46 in the active arm. The active and placebo groups were similar in age (25–64) and weight (45–112 kg) characteristics. In the course of the trial, patients experienced an interruption of the drug due to a lack of supply. Of the 92 patients, 54 were compliant (daily dosing for 7 months) and 38 experienced a treatment interruption (i.e., noncompliant) due to nonavailability of the drug. In the active arm 23 patients were compliant, and 23 experienced a dosing interruption (noncompliant). This interruption in dosing led to a study with an additional treatment arm that allows comparison between the two treated groups, i.e., compliant and noncompliant.

The screening phase was followed by a 7-month treatment phase; safety and efficacy assessments were made after 1, 3, and 7 months. Clinical laboratory assessments included TH tests. Adverse events (AEs) were evaluated

Table 82.2 Mean breast examination scores by treatment group (aqueous I_2)

Population	*Treatment group*	*Baseline score (SD)*	*Post treatment score (SD)*	*Change (SD)*
All	I_2 ($n = 46$)	37.3 (16.4)	13.5 (12.7)	−23.9 (18.1)[a]
	Placebo ($n = 46$)	35.3 (16.4)	32.7 (16.7)	−2.6 (8.9)[a]
Compliant	I_2 ($n = 23$)	42.0 (14.4)	12.9 (12.6)	−29.1 (18.2)[b]
Noncompliant (dose interruption)	I_2 ($n = 23$)	32.7 (17.2)	14.0 (13.1)	−18.7 (16.7)[b]

Notes: Patients were dosed daily for 7 months with 5 mg aqueous I_2 (molecular iodine). Breast examination scores were calculated by summing the rating for five symptoms (tenderness, nodularity, fibrosis, hyperactivity and macrocysts) in each breast. The "compliant" population did not experience interruption of dosing. The "non-compliant" group experienced a dosing interruption of about 1 month on average.

[a]Indicates a statistically significant difference ($p < 0.001$).

[b]Indicates a statistically significant difference ($p < 0.01$).

using a structured instrument that included known symptoms of iodine therapy: rash, diarrhea, acne, nausea, hypothyroidism, hyperthyroidism and hair loss. Efficacy was assessed by: (a) scoring breast tenderness on a scale from 0 to 20; (b) scoring nodularity on a scale from 0 to 20; (c) scoring fibrosis on a scale from 0 to 20; (d) rating breast hyperactivity (a cone shaped density behind the areola) from 0 to 6; and (e) counting the number of macrocysts. The total score for each breast was computed individually.

The breast examination scores are shown in Table 82.2. At baseline the mean breast scores for the placebo (35.3 ± 16.4) and the I_2 treatment group (37.3 ± 16.4) were not statistically different. At the end of the trial, patients on I_2 exhibited a statistically significant ($p < 0.001$) reduction in the mean breast examination score of −23.9, as compared to a change of −2.6 for the placebo group. A reduction in the mean breast examination score of ≈70% (29.1/42.0) was demonstrated in the compliant I_2 treatment group. A statistically significant change ($p < 0.01$) was also observed when comparing the I_2 compliant group (no dosing interruption) with the I_2 noncompliant group; likewise, statistical significance ($p < 0.01$) was reached in a comparison between the noncompliant I_2 treatment group and placebo. No difference ($p = 0.99$) between the compliant and the noncompliant placebo treatment groups was observed.

No serious AEs were reported in this study. The I_2 treatment group reported 5 (11%) AEs as compared to 10 (22%) in the placebo group. The AEs in the I_2 group were acne, constipation, weight loss, loose stools and polyuria; the placebo group reported three instances of acne in addition to headache, gas (n=2), dry mouth and nausea. No overt or subclinical thyroid conditions were observed.

I_2 reacts with water to yield a complex mixture of iodine species including iodide, iodate and triiodide, and this complicates the evaluation of safety data from this trial. The total dose of iodine provided to these patients probably exceeded the estimated upper limit of 5 mg/day. Symptoms associated with hyper- or hypothyroidism were observed, but no statistically significant differences between the placebo and treated groups were measured. It should be noted that the significant clinical benefit observed in this specific population in no way implies that elevated I_2 intake would be beneficial in reducing normal physiologic breast pain or fibrosis not associated with clinical mastalgia. The concept of normal versus clinical breast pain has been defined in parts of Europe, but no standard of care exists in North America.

SYM-002 – Solid I_2 SYM-002 was a multicenter, randomized, double-blind, placebo-controlled study that dosed patients for 6 months with 0.0, 1.5, 3.0 and 6.0 mg I_2 in a ratio of 1:1:2:2. Healthy euthyroid mastalgia patients between the age of 18 and 50 who were unresponsive to conservative treatments, such as over-the-counter (OTC) analgesics, were eligible for the study. Subjects needed toidentify a history of at least 6 months of moderate or severe breast pain, and to document at least 6 days per cycle of a score ≥5 cm with VAS pain daily. Patients presented at least several diffuse nodules or increased thickness of breast tissue involving at least 25% of both breast surfaces. Subjects with a history of thyroid disease or positive TPO antibodies (TPOAb) were excluded, as well as those who started or stopped hormonal therapy within 6 months of enrollment. Laboratory assessment included a chemistry profile, hematology analysis, urinalysis and thyroid function tests (T_3, T_4, TSH, FT_3).

Investigators performed categorical assessments of pain, tenderness and a breast examination using structured instruments. Physicians scored pain and tenderness as none, mild, moderate, or severe. Each symptom or finding was assessed separately for each breast. In subjects whose symptom intensity differed between breasts, symptoms were graded on the basis of the breast having the greatest degree of involvement. The Lewin group's validated breast pain scale (Bloor *et al.*, 1997) was completed by patients at baseline and after 3 and 6 months of treatment.

There was a statistically significant (Spearman's correlation coefficient = 0.962, $p < 0.001$) correlation at baseline

between the categorical pain assessments made by physicians and patient self-assessment for the Lewin overall breast pain scale; this relationship was maintained even as subjects moved between categorical rankings, month 3 (Spearman's correlation coefficient = 0.973, $p < 0.001$) and month 6 (Spearman's correlation coefficient = 0.966, $p < 0.001$).

At baseline the placebo (mean overall pain = 37.7) and pooled treatment groups (mean overall pain = 38.4) reported scores that were not significantly different. After 3 months of therapy, the pooled treatment group differed significantly from the placebo group with respect to the four symptoms that comprise the Lewin breast pain scale: dull aching pain ($p < 0.02$); sharp shooting pain ($p < 0.05$); pain during movement ($p < 0.02$); pain from pressure ($p < 0.05$); and overall pain ($p < 0.02$). After 3 and 6 months of double-blind therapy, subjects on placebo reported a slight increase, 20% and 8%, respectively, in Lewin overall breast pain scale, as compared to a reduction reported in all treatment groups. The magnitude of pain reduction increased with dose in a statistically significant manner at both month 3 ($p < 0.01$) and month 6 ($p < 0.01$). The majority of change in the Lewin overall pain scale occurred by month 3 for the three treatment groups and all of the benefit in the 6.0 mg/day group was observed by month 3, i.e., 45.4% and 45.0%, respectively.

Of the 111 patients enrolled and randomized, 24 participants discontinued early: 2 (11.8%) were in the placebo group; 5 (31.3%) in the 1.5 mg/day group; 7 (18.4%) in the 3.0 mg/day group; and 10 (25.0%) in the 6.0 mg/day group. The concentration of I_2 was not associated with increases in incidence, severity, or causality of treatment-emergent adverse events. No clinically significant changes in laboratory parameters or vital signs were observed as compared to placebo. The 10 most frequently reported treatment-emergent AEs were as follows: upper respiratory tract infection ($n = 29$; 26%); headache ($n = 23$; 20%); sinusitis ($n = 14$; 12%); nausea ($n = 11$; 9.9%); acne ($n = 10$; 9.0%); back pain ($n = 10$; 9.0%); diarrhea ($n = 10$; 9.0%); dyspepsia ($n = 9$; 8.1%); rash ($n = 9$; 8.1%); and abdominal pain ($n = 7$; 6.3%). Headaches were the only AE that occurred in a different proportion among the treatment groups; 41% of the placebo group reported headaches as compared to 6.3% in the 1.5 mg/day group, 26% in the 3.0 mg/day group, and 12% in the 6.0 mg/day group ($p < 0.05$). There was no statistically significant difference in the dropout rate for patients on placebo (11.8%), 1.5 mg/day (31.3%), 3.0 mg/day (18.4%), or 6.0 mg/day (25%).

No statistically significant change was observed in any of the five thyroid function tests (T_3, FT_3, T_4, T-uptake, TSH) for any treatment group, as the mean changes were all within the normal range. No significant shifts either up or down in change from baseline to minimum or maximum were observed. No statistically significant differences among treatment groups were observed for mean change from baseline to minimum, except for T ($p < 0.05$). The largest mean change (1.2 mU/ml) from baseline to the maximum value in TSH at any time point was observed in the 6.0 mg/day treatment group. Low TSH values were observed for eight subjects receiving I_2.

Safety trials with I_2

A solid dosage form of I_2 provides the ability to examine safety in chronic dosing studies at discrete exposure levels. Two different patient populations were studied: (1) women without previous exposure to iodine therapy (iodine naive); and (2) women already receiving aqueous I_2 therapy. The latter group may serve as an approximate model of those populations known to consume (Yamada *et al.*, 1986) and excrete (Konno *et al.*, 1993) iodine at levels that are 5–10 times above the current recommended UL. An open-label study (MX02-CLN-05) of 36 months was used to evaluate safety in women with prior chronic exposure to iodine.

Patients already receiving aqueous I_2 therapy were enrolled in study MXCL02-05 and dosed at I_2 levels that ranged from 3 to 12 mg/day. More than 900 patients were enrolled; the average age was 47.4 years and ranged from 17 to 78 years. No dose adjustment was made in 736 patients; 184 received multiple doses (up or down) from the baseline. At the baseline the number of patients assigned to each dose level was 311 at 3 mg/day, 603 at 6 mg/day, 5 at 9 mg/day, and 1 at 12 mg/day.

The general population can tolerate high levels of dietary iodine (Pennington, 1990), but discrete populations of patients are known to be at increased risk for thyroid-related AEs as a result of iodine therapy (Braverman, 1994). The inclusion–exclusion criteria for the safety studies of I_2 in iodine-naive subjects eliminated patients known to be at risk. Euthyroid patients with (a) no history of thyroid disease, (b) no previous exposure to I_2, and (c) no concomitant iodine-containing medications, were eligible for inclusion in these safety trials (MX02-CLN-07 and MX02-CLN-09). The first placebo-controlled study was conducted for 6 months and the second for 12 months.

The first study of I_2 exposure in iodine-naive patients (MX02-CLN-07) enrolled 389 patients: placebo ($n = 67$); 0.3 mg/day ($n = 66$); 2.0 mg/day ($n = 63$); 3.0 mg/day ($n = 66$); 6.0 mg/day ($n = 65$); and 9.0 mg/day ($n = 62$). The average age was 42.4 years and ranged from 20 to 55 years. The second study in iodine-naive patients (MX02-CLN-09) enrolled 136 patients into a 12-month crossover trial using placebo and 6 mg/day of I_2; 49 patients crossed over from placebo to active or vice versa, and therefore safety data is reported for these patients in each category. Safety data on placebo ($n = 61$) and 6.0 mg/day ($n = 105$) was gathered in the study. The total I_2 exposure is shown for each of these trials in Table 82.3.

Variations in treatment emergent thyroid status were evaluated based on TSH and T values. Patients were categorized

Table 82.3 Months of exposure in safety studies with a solid I_2 dosage form

	Months of exposure to I_2						
Study number	*<1*	*1*	*3*	*6*	*12*	*24*	*30–36*
MX02-CLN-05[a]	920	920	920	911	812	709	572
MX02-CLN-07[b]	322	310	280	231	0	0	0
MX02-CLN-09[c]	105	102	92	76	4	0	0
Total	1350	1333	1293	1218	816	709	572

[a]MX02-CLN-05 was a 3-year open-label study with daily doses from 3 to 12 mg/day.
[b]MX02-CLN-07 was a placebo-controlled 6-month study with daily doses from 0.3 to 9.0 mg/day.
[c]MX02-CLN-09 was a placebo-controlled 12-month study with a 6.0 mg/day daily dose.

as subclinical hyperthyroid if TSH was below the normal range (0.35–5.00 mU/l) and T values were within the normal range (60–155 nmol/l); patients that exhibited depressed TSH and elevated T values were scored as overtly hyperthyroid. Patients were categorized as subclinical hypothyroid if TSH was elevated and T values were normal; patients with depressed T values were considered as overtly hypothyroid. Overt hypothyroidism occurred in 0.2, 1.3 and 1.2% of the patients in studies MX02-CLN-05, MX02-CLN-07 and MX02-CLN-09, respectively, which is comparable to the estimated prevalence (2%) of overt hypothyroidism in adult women. Overt hypothyroidism occurred in 0.5, 1.6 and 1.2% of the patients in studies MX02-CLN-05, MX02-CLN-07 and MX02-CLN-09, respectively, also comparable to the estimated prevalence (2%) of overt hyperthyroidism in adult women.

Subclinical hyperthyroidism was more common than overt disease occurring in 5.5, 2.3 and 2.3% of the patients in studies MX02-CLN-05, MX02-CLN-07 and MX02-CLN-09, respectively. These values are comparable to those previously reported (Wang and Crapo, 1997; Lind *et al.*, 1998). The highest incidence of thyroid abnormality was that of subclinical hypothyroidism, which occurred in 15% of patients in study MX02-CLN-05; iodine-naive patients experienced subclinical hypothyroidism at rates of 8.9 and 10.5% in studies MX02-CLN-07 and MX02-CLN-09, respectively.

The incidence of abnormal thyroid function in the placebo and the treatment groups for iodine-naive patients did not demonstrate statistical significance using Fisher's exact test: subclinical hyperthyroidism ($p = 0.216$; 0/107 vs. 9/388); overt hyperthyroidism ($p = 0.590$; 0/107 vs. 5/388); subclinical hypothyroidism ($p = 0.326$; 6/107 vs. 36/388); overt hypothyroidism ($p = 1.00$; 1/107 vs. 6/388); subclinical hyper- or hypothyroidism ($p = 0.0745$; 6/107 vs. 45/388). The comparison of subclinical and overt categories versus placebo ($p = 0.032$; 7/107 vs. 56/388) demonstrates statistical significance. A comparison of subclinical conditions in placebo versus patients exposed at 6 mg/day or more also demonstrates a statistically significant difference ($p = 0.045$; 6/107 vs. 26/203), as does the 9 mg dose group alone ($p = 0.042$; 6/107 vs. 9/57).

The minimum acute dose of iodide that perturbs TSH (within the normal range) is about 1.5 mg; therefore, the response to daily therapy at doses ≥2 mg/day is of interest. As compared to placebo, a statistically significant difference in subclinical and overt thyroid conditions for iodine-naive patients exposed at ≥2 mg/day ($p = 0.007$; 6/107 vs. 49/323) was demonstrated. These observations should be of interest to physicians who suggest iodine therapy for the general public.

Comparison of treatment emergent thyroid function variations between iodine-adapted and iodine-naive patients is problematic, as the average exposure to drug MX02-CLN-05 (1.45 ± years) was much greater than that in the studies with iodine-naive patients. The overall incidence of treatment-emergent subclinical hyper- or hypothyroidism was 20.6%. This incidence is higher than that reported in earlier studies. In iodine-adapted patients there was a statistically significant difference ($p = 0.0019$; 40/300 vs. 109/490) between the 3 mg and 6 mg treatment group. The pattern of data presented in Table 82.4 suggests that therapy with supraphysiological levels of iodine in adapted and iodine-naive patients is associated with an increase in subclinical thyroid conditions, but not overt thyroid disease.

The clinical symptoms of hypothyroidism include weight gain, constipation, hair loss, menorrhagia and decreased heart rate. The clinical symptoms of hyperthyroidism include fatigue, irritability, weight loss, increased sweating, amenorrhea, diarrhea and an increased heart rate. The placebo and the treatment group did not demonstrate a statistically significant difference in the incidence of any of these symptoms.

Possible sensitivity reactions to I_2 were reported in up to 4% of the patients in these trials, but no statistically significant rates were observed as compared to the placebo group (Table 82.5).

Overt thyroid disease is not observed at a rate that differs from controls or the normal population. However, patients receiving therapy should be under the care of a physician who monitors their thyroid status periodically, as subclinical hypothyroidism is a concern. For over three decades the Institute of Medicine (IOM), an operating agency of the Untied States National Academy of

Table 82.4 Number and percentage of iodine-adapted[a] and iodine-naive[b] patients on daily I_2 therapy with treatment emergent variations in TSH and T_4 laboratory values

		Hyperthyroidism		*Hypothyroidism*					
		Subclinical[c]	*Overt*	*Subclinical*[c]			*Overt*		
Dose I_2 (mg/day)	Patients with lab values	↓TSH	↓TSH ↑T_4	↑TSH (5–10)	↑TSH (10–20)	↑TSH (>20)	↑TSH (5–10) ↓T_4	↑TSH (10–20) ↓T_4	↑TSH >20) ↓T_4
3.0[a]	300	16 (5.3)	1 (0.3)	27 (9.0)	10 (3.3)	2 (0.7)	2 (0.4)	0 (0.0)	0 (0.0)
6.0[a]	490	28 (5.7)	1 (0.2)	70 (14)	10 (2.0)	1 (0.2)	0 (0.0)	2 (0.4)	2 (0.4)
9.0[a]	16	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
12[a]	4	1 (25)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Iodine-naive patients									
0	63	0 (0.0)	0 (0.0)	3 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
0.03	65	1 (1.5)	0 (0.0)	3 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2.0	58	2 (3.4)	0 (0.0)	3 (5.2)	2 (3.4)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
3.0	62	0 (0.0)	2 (3.2)	5 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6.0	60	2 (3.3)	0 (0.0)	6 (10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
9.0	57	2 (3.5)	2 (3.5)	8 (14)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	1 (1.8)
0	44	0 (0.0)	0 (0.0)	3 (6.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)
6.0	86	2 (2.3)	1 (1.2)	8 (9.3)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

[a]Patients previously adapted to I_2 (molecular iodine) before entry in study MX02-CLN-05 a 3-year open-label study.
[b]Iodine-naive patients were euthyroid and had no history of thyroid disease before entering placebo-controlled studies MX02-CLN-07 and MX02-CLN-09.
[c]Subclinical patients had normal T_4 values.

Table 82.5 Acute and sensitivity reactions possibly related to I_2 exposure in safety trials (percentage of patients)

Trial	*MX02-CLN-05*[a]				*MX02-CLN-07*							*MX02-CLN-09*[b]
Maximum exposure	*36 months*				*6 months*							*12 months*
Dose (mg I_2/day)	3	6	9	12	0	0.3	2	3	6	9	0	6
No. of patients	336	563	20	4	67	66	63	66	65	62	61	108
Acne	3	2	5	0	3	6	2	2	2	3	5	4
Puritus	1	1	0	0	1	6	0	0	2	2	3	3
Rash	4	2	5	0	4	5	6	0	2	5	3	2
Urticaria	0	1	0	0	1	0	0	0	2	2	0	1
Fever	0	<0.5	0	0	1	0	0	0	0	0	2	2
Abnormal vision	0	<0.5	0	0	0	0	2	2	0	0	0	2
Cardiac/heart failure	0	0	0	0	0	0	0	0	0	0	0	0
Seizure/convulsion	<0.5	0	0	0	0	0	0	0	0	0	0	0
Asthma	1	1	0	0	0	0	0	0	0	2	2	1

[a]In study MX02-CLN-05 dose adjustments were allowed. Patients are included in the group that represents their most frequent dose.
[b]Study MX02-CLN-09 was a crossover study. Some patients (n = 49) crossed over to a subsequent treatment and are included in both active and placebo-treatment categories.

Science, has assembled a group of eminent physicians and researchers who carefully consider both the minimum dietary requirement and safe upper limit for dietary iodine (IOM, 2000). This group has concluded that the UL for iodine is *not meant to apply to individuals under medical supervision* since the majority of the normal population can tolerate a high level of daily iodine. While the majority of the general public can tolerate elevated dietary intake of iodine, the data from controlled trials in euthyroid women with no risk factors suggests that there is an increased rate of thyroid-related subclinical findings associated with iodine intake above the UL. The safety profile observed in these studies is entirely consistent with this recommendation from the IOM. The data supports periodic monitoring for individuals dosed daily with iodine above the UL.

Summary Points

- Individuals who consume iodine at levels above the recommended UL (1.1 mg/day) should do so under the care of a physician and have their thyroid status monitored periodically.
- The pharmacological and toxicological profiles of orally administered iodide and I_2 are distinct; iodide is more thyrotoxic than I_2.
- Several model systems support an antiproliferative role for I_2 but not iodide.
- Daily I_2 treatment of women at doses up to 5½ times the UL is not associated with an increase in overt thyroid disease.
- Elevated rates of subclinical hypothyroidism are likely in iodine-naive women treated with I_2 at levels higher than the recommended UL.
- The incidence of subclinical thyroid conditions in iodine-adapted patients increases with dose above 3 mg/day of I_2.
- Two double-blind, randomized, placebo-controlled studies indicate a beneficial effect of I_2 in patients with severe mastalgia dosed daily at levels that are at least three times above the UL.

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