Contrast Material Iodides: Potential Effects on Radioactive Iodine Thyroid Uptake

Andrew J. Laurie, Sandra G. Lyon, and Elliott C. Lasser

Department of Radiology 0632, University of California, San Diego, School of Medicine, La Jolla, California

The levels of contaminant, free inorganic iodide and iodine were determined in several commonly used ionic and nonionic intravenous contrast media to gain a better understanding of the roles of these compounds in radioactive iodine uptake inhibition. The method, which involved a reduction-oxidation reaction using sodium nitrite, yielded accurate and precise data for the iothalomate based ionic contrast media as well as the nonionic contrast media. There was no free iodine in any of the contrast media tested. There was considerable variation in free iodide levels, ranging from 1.38 μg/ml to 20.84 μg/ml among the different contrast media, although significant differences between the ionic and nonionic media were not found. These levels of contaminant iodide are thought to play a role in the short-term inhibition of radioactive iodine uptake.

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Radioactive iodine uptake (RAI) examinations play an important role in evaluating thyroid function and disease. It has been appreciated for many years that RAI exams are depressed following the administration of intravenous contrast media (*1–5*), and it has been speculated that free inorganic iodides in the contrast media (CM) are responsible for the decreased uptake (*1*).

Levels of contaminant iodine and iodide in ionic CM have not been reported for over 15 years (*6*). Further, no such data has been published in the literature for the newer nonionic CM. Thus, we assayed free iodine and iodide levels in some current and frequently used intravenous CM to further study the role of contaminant inorganic iodides in the suppression of RAI uptake.

MATERIALS AND METHODS

The following CM were studied: the ionic CM, Vascoray (iothalamate meglumine and iothalamate sodium), Conray 400 (iothalamate sodium) and Conray 60 (iothalamate meglumine) and the nonionic CM, Optiray 320 (ioversol), Isovue 300 (iopamidol) and Omnipaque 350 (iohexol). The assay procedure was a modification of the USP (*7*) for the determination of free iodide and iodine levels. To a 50.0-ml polyethylene centrifuge tube was added 2.0 ml of CM, 2.5 ml of 2N sulfuric acid and 4.0 ml of toluene. The solution was mixed vigorously using a vortex mixer for 1 min and centrifuged at 1600 g for 10 min. The presence of a pink color in the turbid toluene layer was indicative of free iodine. Following centrifugation, 0.50 ml of a 2% sodium nitrite solution was added and again the entire mixture was vortexed for 1 min and then centrifuged at 1600 g for 10 min. The presence of a pink color in the toluene layer was indicative of free iodide. The toluene layer was carefully extracted and analyzed colormetrically with a Beckman DU-64 spectrophotometer at 500 nm against a toluene blank. A standard curve was prepared using the above procedure, substituting 2.0 ml of a 10.0, 25.0, 50.0, and 100.0 μg KI/ml solution for the CM. Assay controls were carried out by adding a known amount of free KI to the CM and analyzing for recovery.

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For reprints contact: Elliott C. Lasser, MD, Department of Radiology 0632, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0632.

RESULTS

The bottled CM had levels of inorganic iodide between 1.48 μg/ml and 20.84 μg/ml. No free iodine was found in any bottles. The values for the various CM are listed in Table 1. Free KI added to CM vials could be recovered at a level of 95%–100%. There was minimal inter-bottle variation as signified by the standard deviation values and essentially no variation on repeat assays of the same bottle (<0.5 μg/ml).

DISCUSSION

Based upon the reproducibility among same bottle samples, as well as near complete recovery of added free KI, both the precision and accuracy of the assay are satisfactory (Table 1).

The mechanism by which CM inhibits RAI uptake has not been clearly demonstrated. However, it is believed that free inorganic iodides are of primary importance. Fradkin and Wolff (*8*) indicated that acute increases in inorganic iodide will raise organic iodine formation until a critical level of serum or thyroid iodide is reached after which an autoregulatory turn-off of organic iodine formation occurs. It is unknown if the inorganic iodide per se acts as the "turn-off" signal. Although the precise levels of iodide necessary to induce autoregulatory turn-off in euthyroid individuals are not known, Childs (*9*) demonstrated that intravenous exposure to a minimum of 100 μg of iodide could suppress thyroid uptake in hyperthyroid exophthalmic patients.

TABLE 1
Levels of Free Inorganic Iodide in Contrast Media

Contrast Media	Free Iodide (μg/ml)*
Ionic	
Vascoray	20.84 ± 1.20
Conray 400	1.48 ± 0.74
Conray 60	14.52 ± 1.38
Nonionic	
Optiray 320	7.95 ± 0.51
Omnipaque 350	7.74 ± 0.45
Isovue 300	3.17 ± 0.65

* The concentrations of free iodide are given as an average and standard deviation of duplicate assays of five different bottles of CM, except Omnipaque 350 in which only two bottles were assayed.

Contrast media are known to cause other effects on thyroid function. St. Germain (*10*) described a complex regulatory effect of CM on the 5′ deiodinase enzyme in an attempt to further elucidate the well known phenomena of decreased T4 to T3 conversion following CM. The effect of this on RAI uptake is unclear. Furthermore, while biliary contrast media inhibit canine thyroidal deiodinases, this is not true of current urographic media (*12*). Jaffiol et al. (*2*) demonstrated that thyroid hormone levels were only minimally decreased and TSH levels were unchanged following intravenous CM—indicating that hormonal feedback inhibition is probably not responsible for depressed RAI uptake. Rather, Jaffiol suggested that CM have an inhibitory effect on the iodine pump mechanism. Finally, since the molar concentration of free iodide in CM is at least several orders of magnitude greater than the radiolabeled iodide in the RAI uptake study, suppression may be due in part to competitive inhibition. This will depend considerably on the time interval between the administration of the CM and the RAI test.

The potential sources of inorganic iodide following CM are two-fold: (1) deiodination of the CM molecule and (2) free iodide contamination products. Although in vivo deiodination has been described (*11*), its effects on RAI uptake are unclear. It is believed that the extent of deiodination is dependent partially on the duration that the CM remains in the body. This may well explain the extended (over one year) (*3*) RAI uptake inhibition following myelography using the older lipid-based CM, which remained in the spinal canal for long periods of time. It may also explain the longer uptake inhibition following cholecystographic CM which are subject to partial reabsorption (*3*). The extended duration of RAI uptake inhibition makes it unlikely that iodide contaminants per se are responsible for long-term inhibition. However, most of the contrast agents that we analyzed, when given in routine procedural doses (50–200 ml), may well produce levels above that described by Childs as capable of suppressing RAI uptake. Thus, contamination iodide products may help explain short-term RAI inhibition following intravenous CM (*5*). The extent of RAI suppression over time is not well defined from the available literature. However, the average free iodide value from Table 1 (9.2 μg/ml) administered in a 150-ml intravenous dose to a hyperthyroid patient appears capable of producing about a 50% reduction in RAI uptake at 48 hr if one applies the data of Childs et al. (*9*).

Although the phenomena of CM-induced inhibition of RAI uptake is well described, there is still much to be learned. The duration and intensity of the suppression are not well defined and clearly will vary with CM dosage and the content of free iodide in a given CM vial, as well as with undefined biological variables. The mechanism while not clearly identified is likely secondary to increased levels of inorganic iodide. This study demonstrated the presence of contaminant inorganic iodides in both ionic and nonionic CM in levels significant to induce short-term RAI inhibition. The mechanism for long-term inhibition, however, is less clear and perhaps deiodination of the CM plays some role.

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