



GRAVES' DISEASE & THYROID FOUNDATION

*Educate * Encourage * Empower*

P.O. Box 2793 • Rancho Santa Fe, CA 92067 • (877) 643-3123 • www.gdatf.org • info@gdatf.org

Treatment of Graves' Disease by the "Atomic Cocktail" by Malcolm R. Powell, M.D., F.A.C.P, F.A.C.N.P

The so-called "atomic cocktail" became available after World War II for the treatment of thyroid disease. Today radioactive iodine is in common use to suppress the hyperthyroidism that accompanies Graves' disease. Hyperthyroidism is due to an oversupply of thyroid hormone which serves to regulate the metabolic rate of diverse tissues and systems in the body. As a consequence of the oversupply of thyroid hormone in hyperthyroidism, there is hyperactivity of the central nervous system manifested by nervousness, irritability, restlessness and hyperactivity, increased heart rate and force of heart contraction, rapid gastrointestinal transit with increased frequency of bowel movements, and even a general increase of metabolic activity causing tendency to weight loss with heat intolerance and increased perspiration. These diverse symptoms can be relieved by simply reducing the excessive levels of thyroid hormone to more normal

levels. Suppression of hormone production accomplishes this.

Radioiodide can be administered by mouth either in a capsule or in liquid form. It is absorbed rapidly from the gastrointestinal tract and is carried by the bloodstream to various organs in the body that concentrate iodide. Because iodide is an important constituent of thyroid hormone, a large proportion of ingested iodide is accumulated in the normal thyroid. With hyperthyroidism, an even greater fraction is accumulated in the abnormal thyroid where it is used to manufacture thyroid hormone. If radioactive iodine is given in a sufficient dose, it will irradiate the thyroid cells that remove the iodide from the bloodstream and can deliver thousands of times the radiation dose to these cells that is delivered to any other region of the body. This not only suppresses the thyroid cellular function but also can remove other cells from the

thyroid that seem to participate in the Graves' disease process. Cells called lymphocytes are important mediators of immune response and are invariably found to be increased in glands involved by Graves' disease. Part of the favorable effect of thyroid suppression by radioiodide is undoubtedly due to suppression of the lymphocytic infiltration of the thyroid, as well as suppression of the thyroid cells. Graves' disease is a disease with very significant involvement of the immune system, both in its development and in its continuation.

What are the theoretical risks of radioiodide treatment? These risks are in three general areas:

- * Risk of Development of Malignancy
- * Risk of Premature Aging
- * Reproductive Risk.

There is no doubt that radiation exposure can induce cancer in any animal exposed. However, to cause an

appreciable risk of cancer, there must be a relatively large radiation exposure. We are constantly exposed to low levels of radiation in our day to day lives. All animals have radiation repair mechanisms that actually repair the small amounts of cellular damage induced by background radiation. Although there is theoretical risk of induction of cancer, especially leukemia, with radiation exposure of humans, it takes a far larger radiation exposure than is used to suppress thyroid overactivity for there to be an appreciable risk of cancer as a result of the radiation exposure. Radioiodide is used to treat thyroid cancer in doses approximately twenty times the dosage used to treat overactive thyroids. Even in the patients treated for thyroid cancer, there is only a very small and completely acceptable risk of subsequent development of cancer. In persons treated for overactive thyroids, the risk was not detectable after observation of large numbers of patients in studies conducted by the U.S. Public Health Service.

The second area of concern is premature aging. This occurs only after relatively large radiation exposures to the whole organism. Radioiodide involves a very small radiation exposure, one that

is completely without any premature aging effect on the total organism. However, the thyroid receives a large radiation exposure and most certainly does undergo premature aging effects. The stem cells which produce new generations of thyroid cells are preferentially injured by the radiation exposure and tend to disappear prematurely which causes early aging of the thyroid. If the patient is left with a normally functioning thyroid after the initial effects of radiation exposure, this aging effect is likely to cause late thyroid failure. Therefore, a high proportion of people treated with radioiodide will develop late hypothyroidism and require treatment with replacement doses of thyroid hormone.

The reproductive risks of radiation exposure occur in two areas. First, radiation exposure can induce genetic changes which may cause mutations to appear in offspring of radiation exposed animals. Genetic material in the reproductive cells is most susceptible to induction of such damage at a time when the reproductive cell is maturing. For this reason, patients treated with radioiodide are advised not to conceive a child within six months of their treatment. The reproductive cells which are

in the final stages of development prior to conception are exquisitely sensitive to radiation whereas the resting reproductive cells that have not transformed into mature reproductive cells are quite radiation resistant. By waiting for six months after radioiodide therapy before fertilization of reproductive cells, cells that might have been damaged by radiation exposure are no longer present and fertilization will occur of cells which were in a resting phase and radiation resistant at the time of radiation exposure. The other reproductive risk is of actual damage to an embryo exposed to radiation. Embryos are much more sensitive to radiation exposure than mature animals. Obviously, radioiodide therapy is never given intentionally to a pregnant woman.

If we accept that the risks of radioiodide treatment are essentially negligible or at least so small that they have not yet been detected or quantified in the enormous number of patients that have been treated with these lower dose ranges of radioiodide since 1948, what are the risks of alternative treatments? There are two alternative treatments, medical suppression of the thyroid gland with the hope that the thyroid function will remain within normal ranges when

suppressive medical therapy is stopped at least six months later, or subtotal removal of the thyroid gland by surgery. The surgical option requires brief medical therapy before surgery so that the patient is rendered euthyroid, reducing the risk of a “thyroid storm” or other problems due to lack of control of the hyperthyroidism prior to embarking upon a surgical procedure. The two medical therapies most commonly used for prolonged suppression of overactive thyroid glands are treatment with methimazole or with propylthiouracil. Both these medical treatments are associated with risks of drug reactions, some serious. The most threatening drug reactions are agranulocytosis where the bone marrow stops making polymorphonuclear granulocytes, an important blood cell that protects against infection, and toxic hepatitis, a chemically induced inflammation of the liver. In unusual circumstances, either of these reactions can be fatal. Since as many as 5% of people treated with the medical suppressive drugs do have at least minor drug reactions, and the major reactions are encountered in a few cases per thousand, the risks of drug therapy are certainly much higher than the risks of radioiodide therapy.

Likewise, the risk of a surgical anesthesia accident, even in our best hospitals, varies between 1 in 10,000 and 1 in 100, 000. Again, the theoretical risks of radioiodide therapy at the lower dose ranges are certainly far below this risk.

Radioiodide is administered either as a capsule or as a drink, on an empty stomach. There are no patient observable radiation side effects in these lower dose ranges. The radio iodide suppressive effect upon the thyroid is observed in terms of reduction of patient symptoms between ten days and one month post therapy with most patients becoming completely normal in six to eight weeks. Depending on the size therapy used, a proportion of patients who become normal will progress to hypothyroidism and require immediate thyroid hormone replacement therapy while others may remain in normal ranges for many months to many years. The proportion that remain normal varies. Depending upon the size of radioiodide dose used in the treatment. Some patients will require re-treatment with a second dose of radioiodide, but usually in this circumstance the hyperthyroidism is considerably less of a symptomatic problem for the

patient at the time of the second treatment and the second treatment is merely a nuisance requiring further testing and delay of a complete response of the major symptoms.

Some other patient concerns that we encounter in counseling patients about radioiodide therapy should be mentioned. The radioiodide that is used in the treatment is radioiodide-131. It has a physical half life of eight days, meaning that every eight days half of the administered dose disappears, whether it is in the patient or elsewhere. At the end of ten half lives or eighty days, there will be virtually no detectable traces of the original dose left. However, if we try to measure residual radioactivity in a patient at two months, it is already very difficult to detect any residual activity at sixty days since the patient also has a biologic loss of radioactivity, principally in the urine. Thus, the biologic half life of radioactivity in the body is much shorter than the physical half life and the effective half life which is the combination of the biological and physical half life is only about four days for patients treated with radioiodide-I131.

There are some other cells in the body which receive substantial radiation doses, though not of the magnitude

of the doses received by the thyroid cells. These other cells are the secretory cells of the salivary glands, the acid-forming cells of the lining of the stomach, and the cells lining the urinary tract. The salivary and gastric cells receive larger radiation doses than the rest of the body because they concentrate iodide like the thyroid cells do, but fail to hold on to the iodide that they accumulate. The cells lining the urinary tract receive their larger doses simply because the principal excretory pathway of iodine is in the urine. These three areas all have no real long range risk from the radiation exposure, because the cells that are affected are sloughed off into the saliva, the gastric juices, and into the urine as cells age in each location and new cells take their places. This lessens the potential for any long term effect of the radioiodide exposure upon the three areas which receive larger than average iodide radiation exposures during radioiodide therapy.

A common concern is “Will I glow in the dark after treatment?” We always assure our patients that they won’t unless they did before they were treated.

Last, it should be explained that there are some variations

in radioiodide therapy planning. The discussion heretofore has been about suppression of overactive thyroid function. Suppression is achieved by a variety of dosage schedules which are in use in various parts of the country and of the world. Some physicians prefer to treat with thyroid suppressive therapy prior to radioiodide therapy while others prefer to treat first with radioiodide. We prefer the latter in most cases since suppressive therapy can result in a variety of populations of cells functioning differently within the thyroid. The non-uniformity of cellular function somewhat complicates subsequent radioiodide therapy. However, this probably is not a major effect with short term therapy with suppressive agents. Some therapists use relatively larger and some relatively smaller radioiodide doses, the former causing more early hypothyroidism and the latter accepting the need to re-treat more frequently.

Treatment to remove the thyroid requires a larger dose of radioiodide. Many nuclear medicine physicians treat more aggressively when there is significant eye involvement, referred to as ophthalmopathy. We prefer to attempt to completely remove (ablate) the thyroid with a

larger dose of radioiodide whenever there is significant eye involvement, since the inflammatory infiltration of the eye muscles in Graves’ disease ophthalmopathy is an immune reaction and it is established that the thyroid gland and the eye muscles share common antigens. Antigens are the substances which stimulate an immune response and we believe that if the thyroid antigens are completely removed, there is less risk of continuation of the immune disease involving the eye muscles. In practice, ablation of the thyroid with radioiodide seems to be followed by a very low incidence of progressive eye disease or progressive ophthalmopathy that would require other treatment such as radiation therapy of the eye orbits or orbital surgery to enlarge the orbital space to accommodate the enlarged eye muscles. When people are treated with thyroid ablation therapy with radioiodide, there is a theoretical risk that the ablation therapy will stimulate or aggravate the immune disease by releasing antigens from the thyroid. However, this doesn’t seem to happen in practice, probably because the lymphocytes that participate in the immune process are the first cells affected by the radiation therapy of the thyroid and are removed from the thyroid prior to significant

local release of thyroid antigens by the radiation injury to the thyroid cells. What seems to be observed in long term follow-up of people who have had their thyroid removed by radioiodide therapy is that their eyes “plateau” with little or no further progression of the inflammatory immune disease. After many months or a year or two, the immune process seems to subside with reduction of the irritative eye symptoms. When a radioiodide treated patient continues to have progression of ophthalmopathy, it will usually be found that there is significant functioning thyroid tissue remaining. This function will usually be observed even if the patient is on thyroid replacement therapy since it will be “autonomous function” that is totally unresponsive to the amount of the thyroid hormone present. Autonomous function is a hallmark of Graves’ disease activity. Thus, repeat radioiodide treatment can usually be given to these patients, even while they are on full replacement therapy with thyroid hormone. It is absolutely essential that during the radioiodide treatment of patients with active ophthalmopathy, they should at no time be allowed to become hypothyroid, since this can stimulate a

progression of the eye disease. For this reason, it is quite common to re-treat these patients with radioiodide while they are on treatment with thyroid hormone.

[Editor's update: new guidance was released in 2011 regarding the use of radioiodine treatment in patients with mild and moderate-to-severe ophthalmopathy. For more info, please see "*Hyperthyroidism and Other Causes of Thyrotoxicosis: Management Guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists*" by Bahn, et. al at thyroidguidelines.net.]

After radioiodide therapy, there are some minimal radiation precautions to prevent exposure of your family to unnecessary amounts of radiation. These will be explained to you by your physician. Almost all patients treated either for thyroid suppression or for thyroid removal (ablation) are treated as outpatients. They can therefore expose those around them to radiation emitted from their own bodies. While this would cause no observable harm, we try to limit population radiation exposures to as low levels as practicable. In particular, we are concerned

about persons under the age of 40, especially children, infants, and fetuses. Simple measures can be used to reduce their exposure essentially to zero. This can be accomplished since radiation absorption falls off very rapidly with distance from the radiation source and a distance of six feet is in most circumstances sufficient to make any radiation exposure insignificant. Your doctor will further discuss this with you at the time of any radiation therapy.

In summary, the “atomic cocktail” used to treat Graves’ disease is a safe, effective, and relatively low cost way of treating thyroid disease. Looked at another way, if a person were able to select his illness, hyperthyroidism is not a bad one to pick since the treatment is so simple and effective.

Used with permission of the author:

Malcolm R. Powell, M.D., F.A.C.P., F.A.C.N.P., San Francisco, California, August 28, 1991

© Copyright Graves’ Disease & Thyroid Foundation. All rights reserved.