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Potassium iodide and the Wolff-Chaikoff effect: Relevance for the dermatologist

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The inhibition of organic binding of iodide in the thyroid gland by excess iodide, resulting in the cessation of thyroid hormone synthesis, is known as the Wolff-Chaikoff effect. This review explores the nature of the Wolff-Chaikoff effect, both in terms of its potential mechanisms and its relevance to dermatologists who use potassium iodide as a therapeutic agent. (J Am Acad Dermatol 2000;42:490-2.)

The management of most inflammatory dermatoses focuses on the use of corticosteroids or other immunosuppressive agents. On occasion, the clinician may find that these drugs are contraindicated or are responsible for intolerable side effects, necessitating the use of other treatment. Potassium iodide (KI) is a drug whose major indications are for inflammatory conditions in which the neutrophil may be pathogenic. Dermatologists need to be cognizant of the Wolff-Chaikoff effect (WCE), the cessation of thyroid hormone synthesis subsequent to the administration of iodide, if KI is part of their therapeutic armamentarium.

KI has been used successfully in a myriad of inflammatory dermatoses, including erythema nodosum, subacute nodular migratory panniculitis (erythema nodosum migrans), nodular vasculitis, erythema multiforme, and Sweet's syndrome.[1] Although KI may be effective in cutaneous[2] and lymphocutaneous sporotrichosis,[3] it is not effective in pulmonary[4] or systemic sporotrichosis, in which itraconazole has supplanted its use.[5]

Although KI has been used therapeutically for more than 150 years,[1] it was repopularized by Schultz and Whiting,[6] who reported that 24 of 28 patients with erythema nodosum and 16 of 17 patients with nodular vasculitis responded to treatment with KI. Relief of symptoms occurred within 2 days, with most lesions clearing within 2 weeks. The average course of therapy was 3 weeks. Horio et al[7] confirmed these findings by observing relief of subjective symptoms such as lesional tenderness, fever, and arthralgias within 24 hours. Complete remission of lesions 10 to 14 days after administration of KI was noted in 11 of 15 patients with erythema nodosum, 7 of 10 with nodular vasculitis, and 1 of 4 with Behçet's disease. The best response was noted in patients with erythema nodosum associated with systemic symptoms and a positive C-reactive protein, to whom the medication was administered shortly after the onset of illness.[7] Despite the fact that the systemic symptoms tend to be less frequent in cases of subacute nodular migratory panniculitis (erythema nodosum migrans), a rapid response to KI has also been reported in this disorder.[8]

The dosages of KI used by Schulz and Whiting[6] ranged from 360 to 900 mg/day. They found that the mixture was bitter, so they subsequently compounded a powder dispensed in a gelatin capsule. Horio et al[7] used an oral dose of KI 300 mg 3 times daily. KI is also available in a saturated solution (SSKI) at a dose of 47 mg/drop.[9] This can be added to juice to improve its palatability.[3] Although KI is usually well tolerated, adverse reactions may include cutaneous findings (ie, erythematous, purpuric, urticarial, acneiform, nodular, pustular, carbuncular, and vegetative lesions) or gastrointestinal symptoms (ie, nausea and vomiting).[1]

The precise mechanism by which KI exerts its therapeutic effect is unknown. It has been speculated that because most of the disorders for which KI is indicated display neutrophils in the early stages of the disease, modulation of neutrophil chemotaxis could be affected. Honma et al[10] studied the effect of KI on neutrophil chemotaxis in 15 healthy subjects by means of a modified Boyden chamber method. Oral KI (15 mg/kg daily for 3 days) significantly inhibited neutrophil chemotaxis in peripheral blood.

Other than the dermatologic indications detailed above for the use of KI, it has been administered to

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protect the thyroid gland during radioactive iodide studies[11] and is recommended as a thyroid blocker in the event of a nuclear emergency.[12] Iodide administration may also occur inadvertently, such as by the ingestion of iodide-containing expectorants, or the injection of iodized radiopaque dyes.[13] Amiodarone, an antiarrhythmic agent, is 37% organic iodine (by weight), and has been reported to induce thyrotoxicosis, or hypothyroidism via the WCE. Because of the fat solubility and long half-life (22 to 55 days) of amiodarone, both amiodarone-induced thyrotoxicosis and amiodarone-induced hypothyroidism may be persistent.[14]

Although this article focuses on the WCE, it should be realized that iodine excess may lead to thyrotoxicosis (Jod-Basedow effect). This appears to be caused by loss of normal autoregulatory mechanisms that are the seat of autonomous foci as occurs in toxic multinodular goiters. Rarely, iodine excess may cause an acute thyroiditis manifested by a painful, enlarged thyroid gland.[9]

Iodine is an essential requirement for the production of the thyroid hormone L-thyroxine (T4) and L-triiodothyronine (T3). By definition, iodine generically refers to the iodine molecule in any inorganic form, molecular iodine refers specifically to I2, and the term *iodide* is used to refer to the ion I-.[15] The biosynthetic pathway and control mechanisms of thyroid hormone synthesis have been reviewed by Heymann.[16] The minimum daily requirement of iodine is approximately 50 µg. Unless an individual is in an endemic region of iodine deficiency, most people ingest a far greater quantity of dietary iodine. Dietary iodine is reduced to the oxidation level of iodide before absorption, which occurs throughout the intestine, but principally in the small intestine.[15] Therefore, iodine actually enters the thyroid gland in the form of inorganic or ionic iodide, whose source is iodide derived either from deiodination of thyroid hormones or from the iodide ingested in food, water, or medication.[17]

Regulatory mechanisms of the thyroid gland must be in place to maintain the homeostasis of thyroid hormone secretion. The thyroid gland possesses two such mechanisms. First, the thyroid gland participates in a classic negative feedback mechanism via the pituitary secretion of thyroid-stimulating hormone (TSH) in response to thyrotropin-releasing hormone (TRH) from the hypothalamus.[9,16]

The second regulatory mechanism resides within the thyroid gland itself, and is called autoregulation. This serves to maintain a pool of organic iodine within the thyroid gland. Thus, autoregulation serves as an initial defense against the fluctuations of the iodine supply. If autoregulation is unable to maintain a normal rate of thyroid hormone synthesis, activation of the hypothalamic-pituitary axis will ensue. Conversely, autoregulation allows escape from the inhibition of hormone synthesis induced by large quantities of iodine.[9] The inhibition of organic binding of iodide in the thyroid gland by excess iodide, resulting in the cessation of thyroid hormone synthesis, is the WCE.[18] If the autoregulatory mechanisms are absent or deficient, escape from the WCE cannot occur and hypothyroidism results.[9]

Iodide-induced hypothyroidism has been observed in patients with Hashimoto's thyroiditis, euthyroid patients previously treated by thyroid surgery or ^{131}I treatment for Graves' disease, patients receiving certain drugs (ie, sulfonamide derivatives, lithium), patients previously treated by a lobectomy for euthyroid multinodular goiter, and occasionally individuals with an apparently normal thyroid gland. Roti et al[19] studied the effects of the administration of pharmacologic quantities of iodide on thyroid function in 18 patients with a previous history of painful subacute thyroiditis, compared with 12 euthyroid patients with a previous history of thyroid surgery for benign nodular disease. They found that euthyroid patients with a previous history of subacute thyroiditis were predisposed to iodide-induced hypothyroidism. They concluded that subtle abnormalities in the thyroid organification and subsequent thyroid hormone synthesis persist years after the episode of subacute thyroiditis. It is unclear whether this finding is the result of autoimmunity per se, or other as yet undefined effects of autoimmunity, because autoantibodies to thyroglobulin or microsomal enzymes were not detected in patients with a history of subacute thyroiditis. Similar findings have been reported in patients with postpartum thyroiditis and a previous history of amiodarone-induced thyrotoxicosis.[20]

if hypothyroidism is defined in these studies solely by increased TSH, the study is wrong!

The exact mechanism by which the WCE transpires remains speculative. Chiraseveenuprapund and Rosenberg[18] have demonstrated that at elevated intrathyroidal iodide concentrations there may be decreased availability of hydrogen peroxide for iodination reactions. Whether this apparent decreased availability of hydrogen peroxide, induced by excess iodide, is the result of increased usage of hydrogen peroxide via competing reactions, such as I2 formation in the presence of excess I–, or the result of decreased formation of hydrogen peroxide through inhibition of the intrathyroidal hydrogen peroxide-generating system, remains an enigma. Yamamoto and DeGroot[21] studied the effects of varying doses of stable iodide on thyroid peroxidase function and NADPH-cytochrome-*c* reductase in rats. The easier induction of the WCE in intact thyroid tissue com-

pared with an acellular preparation suggests that inhibition of other factors in the iodinating system, such as hydrogen peroxide generation, may be more important than inhibition of peroxidase. Corvilain et al[22] contend that the WCE is probably mediated through an inhibition of the inositol triphosphate response to TSH and the hydrogen peroxide response to calcium.

For dermatologists who use KI, knowledge of the WCE is imperative. Before KI is prescribed, it would be prudent for the physician to inquire about any history of thyroid disease, autoimmune or otherwise. It is also essential to determine whether a patient is taking other medications, such as amiodarone, that could affect thyroid function. Unless there is a suspicion of underlying thyroid disease, baseline thyroid function studies (ie, TSH, T4, antithyroglobulin, and antimicrosomal antibodies) are not indicated. Fortunately, with the dermatoses for which KI is currently indicated, it is likely that any therapeutic effect will be apparent within a few weeks. This is within the time frame that thyroid autoregulatory processes will ordinarily allow for escape from the WCE. If therapy with KI is continued for more than 1 month, however, a screening TSH would be prudent to ensure that iodide-induced hypothyroidism does not ensue. If iodide-induced hypothyroidism is detected, these changes are reversible by discontinuing the administration of KI. In a study of 7 patients with iodide-induced hypothyroidism, serum T4, T3, and TSH concentrations returned to normal within 1 month of iodide withdrawal.[23]

REFERENCES

1. Horio T, Danno K, Okamoto H, Miyachi Y, Imamura S. Potassium iodide in erythema nodosum and other erythematous dermatoses. J Am Acad Dermatol 1983;9:77-81.
2. Cabezas C, Bustamante B, Holgado W, Begue RE. Treatment of cutaneous sporotrichosis with one daily dose of potassium iodide. Pediatr Infect Dis J 1996;15:352-4.
3. Lesher JL Jr, Fitch MH, Dunlap DB. Subclinical hypothyroidism during potassium iodide therapy for lymphocutaneous sporotrichosis. Cutis 1994;53:128-30.
4. Gerding DN. Treatment of pulmonary sporotrichosis. Semin Respir Infect 1986;1:61-5.
5. Kauffman CA. Old and new therapies for sporotrichosis. Clin Infect Dis 1995;21:981-5.
6. Schulz EJ, Whiting DA. Treatment of erythema nodosum and nodular vasculitis with potassium iodide. Br J Dermatol 1976; 94:75-8.
7. Horio T, Imamura S, Danno K, Ofuji S. Potassium iodide in the treatment of erythema nodosum and nodular vasculitis. Arch Dermatol 1981;117:29-31.
8. Rostas A, Lowe D, Smout MS. Erythema nodosum migrans in a young woman. Arch Dermatol 1980;116:325-6.
9. Woeber KA. Iodine and thyroid disease. Med Clin North Am 1991;75:169-78.
10. Honma K, Saga K, Onodera H, Takahashi M. Potassium iodide inhibits neutrophil chemotaxis. Acta Derm Venereol (Stockh) 1990;70:247-9.
11. Wilkin JK, Strobel D. Iododerma occurring during thyroid protection treatment. Cutis 1985;36:335-7.
12. Halperin JA. Potassium iodide as a thyroid blocker—Three Mile Island to today. DICP 1989;23:422-7.
13. Heidemann PH, Stubbe P, Schurnbrand P, Prindull G. Iodine-induced hypothyroidism and goiter following lipiodol lymphography. Eur J Pediatr 1982;138:82-3.
14. Harjai KJ, Licata AA. Effects of amiodarone on thyroid function. Ann Intern Med 1997;126:63-73.
15. DeGroot LJ, Larsen PR, Hennemann G. Thyroid hormone synthesis and secretion. In: DeGroot LJ, Larsen PR, Hennemann G, editors. The thyroid and its diseases. New York: Churchill Livingstone; 1996. p. 33-60.
16. Heymann WR. Cutaneous manifestations of thyroid disease. J Am Acad Dermatol 1992;26:885-902.
17. Wartofsky L. Diseases of the thyroid. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al, editors. Harrison's Principles of internal medicine. 14th ed. New York: McGraw-Hill; 1998. p. 2012-35.
18. Chiraseveenuprapund P, Rosenberg IN. Effects of hydrogen peroxide-penetrating systems on the Wolff-Chaikoff effect. Endocrinology 1981;109:2095-102.
19. Roti E, Minelli R, Gardini E, Bianconi L, Braverman LE. Iodine-induced hypothyroidism in euthyroid subjects with a previous episode of subacute thyroiditis. J Clin Endocrinol Metab 1990; 70:1581-5.
20. Roti E, Minelli R, Gardini E, Bianconi L, Gavaruzzi G, Ugliotti G, et al. Iodine-induced subclinical hypothyroidism in euthyroid subjects with a previous episode of amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 1992;75:1273-7.
21. Yamamoto K, DeGroot LJ. Function of peroxidase and NADPH cytochrome c reductase during the Wolff-Chaikoff effect. Endocrinol 1973;93:822-8.
22. Corvilain B, Laurent E, Lecompte M, Vansande J, Dumont JE. Role of the cyclic adenosine 3',5'-monophosphate and the phosphatidylinositol-Ca2+ cascades in mediating the effects of thyrotropin and iodide on hormone synthesis and secretion in human thyroid slices. J Clin Endocrinol Metab 1994;79:152-9.
23. Jubiz W, Carlile S, Laperquist LD. Serum thyrotropin and thyroid hormone levels in humans receiving chronic potassium iodide. J Clin Endocrinol Metab 1977;44:379-82.