Thyroid blockade in ^{123}I -mIBG cardiac imaging: A common sense approach

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The effect of iodine excess as a suppressor of thyroxine synthesis in the thyroid was first reported more than 65 years ago.^{1,2} With subsequent introduction of nuclear imaging techniques using compounds labeled with radioactive iodine, it became a common clinical practice to pretreat patients to protect the thyroid gland from unnecessary radiation exposure.^{3,4} Large quantities of non-radioactive iodide (saturated solution of potassium iodide (SSKI) or Lugol's solution) or other anions (usually perchlorate) that saturate the iodide transport system, if administered in advance of the radiopharmaceutical, can block entry of >95% of available radioiodine into the thyroid gland.^{5,6} In the case of long half-life isotopes such as iodine-131, practice guidelines often recommend use of additional doses of the thyroid blocking agent for up to 7 days after the radiopharmaceutical is administered.⁴

The biodistribution of an administered radiopharmaceutical determines to a great extent the radiation dose received by individual organs. The largest fraction of the dose to an organ usually is caused by isotope within that organ, with surrounding tissues contributing the remainder. Because of the specific iodine-concentrating capability of the thyroid, this organ is particularly susceptible to receiving increased radiation doses from radioiodine-containing preparations. However, it is important to distinguish between the radioiodine-labeled compound, which may have no special affinity for the thyroid gland, and free iodine (usually in the form of

ionic iodide), which is specifically concentrated there. Thyroid blockade should be effective at reducing radiation dose from the latter while having little or no effect on the former. In practice, however, it is often difficult to characterize in vivo radioactive counts as being due to decay of bound or unbound isotope.

For most radioiodinated compounds, the greatest contributor to radiation dose to the thyroid is the free iodine present in the preparation. While the US Pharmacopeia requires a minimum of 90% of radioiodine to be in the form of the labeled compound,⁷ most commercially produced radiopharmaceuticals contain at most 1-3% unbound iodine. While initial radioiodine thyroid uptake usually reflects the amount of free iodine in the administered product, over time there is a contribution from a secondary source, in vivo deiodination of the original labeled compound and its metabolites. While the iodine content of the administered product can be accurately determined from appropriate quality control tests, in vivo determination of the fate of the original radiolabeled molecules is more difficult. External measurements of activity levels in different organs are typically the most effective means to monitor radioiodine biodistribution, irrespective of the origin of the isotope.

In the current issue of the Journal, Guibbini and colleagues present cardiac and thyroid uptake data from 57 clinical patients (42 cardiology, 15 neurology) who underwent cardiac ^{123}I -mIBG imaging at 3 centers, 2 of which used thyroid blockade pretreatment and 1 which did not.⁸ There were differences in thyroid and cardiac uptake patterns between the cardiology and neurology patients but no difference in thyroid parameters (thyroid/mediastinum ratio and washout) between patients who did and did not receive thyroid blockade. The authors conclude that thyroid uptake on ^{123}I -mIBG imaging is primarily a reflection of sympathetic neuronal activity and therefore use of thyroid blockade pretreatment to prevent uptake of free iodide may not be justified.

This article raises several interesting questions. For an iodinated radiopharmaceutical for which there is

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specific uptake by the thyroid, is there a threshold of free radioiodine quantity below which protection of the gland from additional radiation exposure is unnecessary or even futile? While the free iodine content of the injectate can be analyzed for this purpose, in vivo there is no convenient means to estimate the relative contribution of bound and unbound iodine to measured imaging counts, so only indirect measures such as presented by Giubbini can be used to judge the utility of thyroid blockade. In addition, should the age of the patient (and medical co-morbidities) be considered in deciding whether the potential longterm effects of a small additional thyroid radiation dose warrant inclusion of thyroid pretreatment as part of the ^{123}I -mIBG imaging protocol? Given that clinical assessments are often used in decision-making for therapeutic interventions, especially those with side effects or potential morbidities, should similar reasoning be applied to diagnostic procedures? Particularly when the risks are demonstrably low (as would be the case for the additional small thyroid radiation dose in a 70-year-old heart failure patient), is even the minor inconvenience of pretreatment with Lugol's or perchlorate necessary?

The question should not be whether iodide or perchlorate pretreatment substantially reduces thyroid uptake of free iodine, because there is overwhelming research and clinical evidence that it does.⁹ The comparisons in the paper of Giubbini, using parameters (thyroid/mediastinum ratios and thyroid wash-out) which are not standardized and provide no absolute quantitation, cannot be used to support the contrary position. In addition, although Giubbini et al cite the results from 15 ADMIRE-HF study subjects¹⁰ with thyroid probe measurements that appear to support the lack of a statistical difference found in their study, they fail to mention the results from a much larger group of 669 ADMIRE-HF subjects that demonstrated a highly significant 61% reduction in average thyroid counts on late planar images with use of blockade.¹¹

An intriguing observation by Giubbini and colleagues is the apparent difference in thyroid uptake between patients studied for cardiac vs neurological disease. This finding can be seen as an extension of the rationale for the use of cardiac ^{123}I -mIBG imaging to identify patients with Parkinson's disease,¹² in that the mechanism of peripheral sympathetic neuronal degeneration is probably the same in both the heart and thyroid. This finding also supports the reasonable conclusion that a significant proportion of thyroid activity seen on ^{123}I -mIBG images reflects uptake in nerve terminals rather than unbound iodine present in the injectate or produced by in vivo deiodination.^{11,13} The possibility that measures of peripheral neuronal uptake of ^{123}I -mIBG in organs other than the heart could be

useful in assessing neurodegenerative diseases may warrant further investigation.

Whenever possible, decisions concerning use of diagnostic procedures should include a benefit/risk assessment applied to the individual being studied. While procedure guidelines and professional society recommendations are valuable adjuncts, it should be remembered that many "standard of care" practices have a historical basis and were never proven in controlled clinical trials. Even for those practices that have a sound physiological basis, such as thyroid dose reduction by pretreatment that prevents transport and uptake of radioactive iodine, clinical judgment and common sense should be used to insure that the best interests of the patient are served. While the large majority of patients who receive Lugol's or SSKI tolerate these agents, some patients find them unpleasant and a few could potentially become ill or manifest an allergy that was not previously known or suspected.^{14,15} Particularly in older patients undergoing cardiac ^{123}I -mIBG imaging using radiopharmaceutical produced under Good Manufacturing Practice standards, both the risk from use of thyroid blockade and the benefit from limiting thyroid radiation dose are small. The clinician should consider individualizing use of thyroid blockade with ^{123}I -mIBG imaging to meet the needs of the patient, whether this involves use of such pretreatment or not.

Disclosures

None.

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