Guidance for Industry

KI in Radiation Emergencies —

Questions and Answers

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2002
Procedural

Revision 1

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I. INTRODUCTION

This guidance provides answers to questions that FDA has received as state and local governments develop emergency response plans involving the use of potassium iodide (KI) to protect against the effects of radioactive iodine accidentally or intentionally released into the atmosphere. KI is recommended for use as an adjunct to other emergency measures, such as evacuation and control of the food supply to avoid ingestion of contaminated foodstuffs. When used correctly, KI can prevent or reduce the uptake of radioiodine by the thyroid gland. KI provides optimal protection when administered immediately prior to or in conjunction with passage of a radioactive cloud. The incorporation of KI into radiation emergency response plans is at the discretion of state and local governments.

This is a revision of the question and answer guidance published in April 2002. The revision incorporates two additional questions (question 4 and question 7) raised about KI intervention and makes minor editorial changes to the previous questions and answers.

II. BACKGROUND

In a guidance entitled *Potassium Iodide as a Thyroid Blocking Agent in Radiation Emergencies* (December 2001), the Food and Drug Administration (FDA) updated its 1982 recommendations for the safe and effective use of KI to prevent or reduce the uptake of radioiodine by the thyroid gland. The current recommendations are based on conclusions reached after reviewing data on radioiodine exposure and thyroid cancer risk gathered after the Chernobyl nuclear reactor accident in 1986. The data suggest that the risk of thyroid cancer is inversely related to age. Fetuses, infants, and young children are at greatest risk and may be harmed by small amounts of radioiodine.

[1] This guidance has been prepared by the Division of Metabolic and Endocrine Drug Products in the Center for Drug Evaluation and Research (CDER) .

Although special precautions should be taken when administering KI to pregnant women and newborns within the first month of life (adherence to the recommended dose, avoidance of repeat dosing, and monitoring of thyroid function in neonates), the benefits of short-term administration of KI as a thyroid blocking agent far exceed the risks of administration to any age group. For complete information, please refer to FDA's December 2001 guidance.

III. QUESTIONS AND ANSWERS

Q1: Does FDA have specific recommendations about radiation emergency preparedness plans and the use of KI?

A1: No. Decisions about the details of their preparedness plans are up to state and local authorities. FDA's guidance provides ***general*** recommendations about the use of KI prophylaxis in the event of a radiological emergency. These recommendations are discussed in Section V. of the guidance.

Q2: Is the graded dosing scheme recommended by FDA the only safe and effective way to take KI?

A2: No. FDA has made recommendations on the lowest effective dose. Higher doses (e.g., up to 130 mg) would be equally effective and, particularly among school-age children, extremely safe (see also question 9).

Q3: If a graded dosing approach is considered, how does FDA suggest that fractional doses (i.e., 65, 32, 16 mg) be administered?

A3: KI tablets can be dissolved in liquids and the appropriate volume administered. For example, if a 130 mg tablet were dissolved in 8 ounces of liquid, one ounce would contain about 16 mg of KI. FDA has conducted studies of the palatability, solubility, and stability of KI dissolved in a number of different liquids, including juice and formula. (See the *Home Preparation Procedure for Emergency Administration of Potassium Iodide Tablets to Infants and Small Children* .[2]) Emergency planners and others should understand that absolute precision in dosing is generally not critical to safety or efficacy (see also question 4).

Q4. FDA guidance recommends graded dosing by age, with neonates receiving the lowest dose (16 mg daily) and adults receiving the highest (130 mg). FDA approved KI tablets are available in two dosage strengths: 65 and 130 mg. At a minimum, dosing based on FDA guidance would require either splitting tablets or dissolving tablets in liquids. This may be impractical while responding to a radiological emergency. In this context, what is the impact of uniform dosing across all age groups eligible for KI prophylaxis?

[2] This is available at http://www.fda.gov/cder/drugprepare/default.htm.

A4. The FDA's guidance on dosing KI in radiation emergencies adheres to principles of minimum effective dose and therefore recommends graded dosing according to age (and thus, in effect, body size). There is ample evidence that the recommended doses, as well as higher doses (e.g., up to 130 mg), will effectively block thyroidal uptake of radioactive iodine if taken in advance of exposure. Furthermore, particularly among school-age children, higher milligram doses are extremely safe.

We also realize that a scheme of graded dosing may be difficult to implement during a radiological emergency involving large numbers of people. However, we continue to emphasize attention to KI dosing in infants. Excess iodine intake can lead to transient iodine-induced hypothyroidism. As we have said in our guidance, individuals who are intolerant of KI at protective doses, as well as neonates, pregnant, and lactating women, should be given priority with regard to other protective measures (i.e., sheltering, evacuation, and control of the food supply).

In summary, if local emergency planners conclude that graded dosing is logistically impractical, FDA believes that for populations at risk for radioiodine exposure, the overall benefits of taking up to 130 mg of KI instead of the lower doses recommended for certain age groups far exceed the small risks of overdosing. However, where feasible, adherence to FDA guidance should be attempted when dosing infants.

Q5: Will dosage strengths of KI below 130 mg be available in the United States?

A5: Yes. An FDA approved 65-mg KI tablet is being marketed now in the United States.

Q6: Are there plans to update the labeling for marketed KI products to conform to the revised FDA recommendations on dosing?

A6: Yes. FDA is working with manufacturers to amend the "Drug Facts" labeling for KI products, which are sold over the counter, to incorporate the new dosing recommendations.

Q7: How critical to public health is adherence to FDA's recommendations with regard to projected thyroid radioactive exposure thresholds for intervention by risk category? Specifically, the existence of different thresholds for neonates, children through age 18, and pregnant or lactating women ($\underline{\geq}$ 5 cGy) versus adults aged 18 through 40 years ($\underline{\geq}$ 10 cGy) versus adults over age 40 ($\underline{\geq}$ 500 cGy) are confusing and logistically complex to follow in responding to a radiological emergency.

A7. The FDA recommendations for KI intervention encompass different threshold thyroid radioactive exposures for different groups within the population. Several factors were involved in this approach:

- During the Chernobyl accident, younger people exposed to radioactive iodine (especially children 0 to 4 years old) were most sensitive to its carcinogenic effects.

In the years following the accident, most children who subsequently developed thyroid cancer apparently received internal thyroid radioactive exposures of less than 30 cGy, and the best dose-response information supports increased risk in children receiving 5 cGy or more.

- As age increases, the risk of thyroidal side effects following excess (i.e., nonradioactive) iodine ingestion increases. This is due to the increasing prevalence of underlying thyroidal illness with older age (e.g., Graves' disease, thyroid nodules, Hashimoto's thyroiditis).
- Thyroid irradiation in older adults (e.g., over 40 years of age) is associated with an extremely low incidence of cancer. Therefore, KI is only recommended if a very large internal radioactive dose to the thyroid is projected. In such a situation, KI would be ingested to prevent destruction of the thyroid gland, which, if it occurred, would lead to lifelong dependence on thyroid hormone replacement therapy.

In short, the recommended stepped intervention approach to KI use during radiation emergencies is based on differences in overall benefit versus risk in different population groups. Specifically, the benefits from thyroid blockade with KI predominate in the young in whom the risks of thyroid cancer from radioiodine are the greatest. The risks of KI take on more prominence in older adults in whom the risks of thyroid cancer are very small.

Notwithstanding the above, it is important to note that among 7 million adults who took stable iodine in Poland following Chernobyl, only two severe adverse reactions were reported, both in persons with known allergy to iodine. Based on these data, we have concluded that even if the risks associated with excess stable iodine are greater in adults than in children, the risk of serious adverse reactions overall is exceedingly small.

In summary, FDA understands that a KI administration program that sets different projected thyroid radioactive exposure thresholds for treatment of different population groups may be logistically impractical to implement during a radiological emergency. If emergency planners reach this conclusion, FDA recommends that KI be administered to both children and adults at the lowest intervention threshold (i.e., $\geq$ 5 cGy projected internal thyroid exposure in children).

As a rule, however, individuals with known allergy to KI or with pre-existing thyroid disease (e.g., Graves' disease, thyroid nodules, Hashimoto's thyroiditis) that might predispose them to adverse reactions should avoid KI. Most likely these will be adults, who have little or no risk of developing thyroid cancer from radioactive exposure to the thyroid and who may, in these cases, incur substantial risks from taking KI.

Q8: **Does the FDA guidance apply to residents outside of the 10-mile emergency planning zone for nuclear poser plants?**

A8: Yes. KI administered in advance of an exposure will successfully block thyroidal uptake of radioiodine, wherever one may reside.