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Environmental Advances 9 (2022) 100293

Contents lists available at ScienceDirect

Environmental Advances

journal homepage: www.sciencedirect.com/journal/environmental-advances

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Marc Benderitter [a], Francois Caire-Maurisier [b], Caroline Crambes [b], Thierry Pourcher [c], Jean-Charles Martin [d], Jacques Darcourt [e], Maâmar Souidi [a,*]

[a] Institut de Radioprotection et de Sûreté Nucléaire (IRSN), PSE-Santé, Fontenay-aux-Roses, 92260, France
[b] Pharmacie Centrale des Armées (PCA), Direction des Approvisionnements en produits de Santé des Armées, Fleury-les-Aubrais, 45404, France
[c] Laboratoire BIAM, Commissariat à l'Energie Atomique et aux énergies alternatives (CEA), Institut Joliot, 06107, Nice, France
[d] UMR INRA 1260/INSERM 1062/AMU « NORT », 13385, Marseille, France
[e] UMR TIRO-MATOs, Université Côte d'Azur (UCA), School of Medicine, 06107, Nice, France

ARTICLE INFO

Keywords:
Potassium iodide
Thyroid
Nuclear accident
Iodine thyroid blocking

ABSTRACT

Prophylaxis by "KI 65 mg, breakable tablet" is a pharmacological countermeasure of radiological protection adapted for the prevention of thyroid cancer after exposure to radioactive iodine. A first modification of the marketing authorization of "KI 65 mg, breakable tablet" for repeated prophylaxis for adults and children above 12 years old was obtained in France in 2020. At this point in time it is recommended to exclude the repeated intake of "KI- 65 mg, breakable tablet" by pregnant and breastfeeding women and children below 12 years old, who should consequently be subjected to a priority evacuation from the contaminated zone. Regulatory toxicology studies are underway in order to support an upcoming proposal of modification of the marketing authorization of "KI- 65 mg, breakable tablet" for repeated prophylaxis for pregnant women and children below 12 years old.

1. Introduction

The population protection strategy in the case of a threat or a real radioactive emission during a nuclear accident aims to limit population exposure to a level as low as possible. In an emergency phase, this strategy is based on three main measures: evacuation, sheltering and uptake of a single dose of stable iodine. In France, its application is under the authority of the government, represented by the local "Prefect. In the absence of adapted protective measures, the exposure of the population to radioactive iodine could generate the occurrence of thyroid cancer as shown by the increase of the incidence of thyroid cancer in the regions contaminated by the emissions of radionuclides from the Chernobyl accident. Such increase was observed in victims who at the time of the accident were children or young adults (Ron, 1995). In Japan, the real incidence of thyroid cancer after the Fukushima accident will not be known for several if not many years.

2. Iodine pharmacokinetics

2.1. Oral and pulmonary absorption

Present in organic and mineral forms, iodine is absorbed as iodides. Its oral absorption is fast and complete in approximately two hours. In the event of an accidental nuclear emission, radioactive iodine can penetrate the organism by oral and pulmonary absorption (organic and particulate). Hence, molecular iodine is able to pass within minutes to the systemic circulation via the respiratory tract. This shows that the "stable" or "radioactive" forms of iodine easily penetrate the organism and that there are no metabolic or permeability barriers that would limit their absorption.

2.2. Distribution and thyroid capture

Once absorbed, the iodides are distributed in the extracellular compartment and are promptly captured in tissues expressing the membrane transporter "Na-I-symporter" (NIS), which is able to assure the transport of iodides into the intracellular compartment, and more

* Corresponding author.
E-mail address: MAAMAR.SOUIDI@IRSN.FR (M. Souidi).

https://doi.org/10.1016/j.envadv.2022.100293
Received 18 August 2021; Received in revised form 16 August 2022; Accepted 23 September 2022
Available online 23 September 2022

particularly in the thyroid gland (Dayem, 2006). This transport protein plays a key role in the accumulation of thyroid iodine. If the thyroid is the main organ in terms of iodide accumulation, they are distributed due to the presence of NIS among others, to the mammary and salivary glands, the gastric mucosa and the placenta. An extremely fine regulation of iodide capture allows the thyroid to adapt to temporary or constant changes in the concentration of circulating iodine (Verger, 2001). This regulation mechanism, named the "Wolff-Chaikoff effect" is characterized in one hand by an inhibition of the iodine accumulation capacity of the thyroid, and on the other hand by a temporary inhibition of the secretion of thyroid hormones. Such inhibition is also responsible for the retention of radioactive iodine already incorporated in the hormonal precursors of a previously exposed individual, thus increasing the radioactivity dose received by the thyroid and potentially the onset of thyroid carcinogenesis.

2.3. Clearance

Total body clearance of iodides is essentially renal (Berson, 1952). After iodine ingestion, renal excretion of the pool not fixed by the thyroid and other organs reaches a plateau between 24 and 48 hours. Iodine is also eliminated in feces after the hepatic catabolism of thyroid hormones. In addition, inorganic iodine can concentrate in breast milk up to 48 hours after ingestion. These clearance mechanisms contribute to externalize iodides and thus to reduce internal radiation exposure at the tissue level. On the contrary, thyroid clearance, quantitatively as important as renal clearance, constitutes the stage at which iodides are internalized into thyroid tissue. In fact, it represents the main origin of thyroid radio-induced cancers because exposure time is largely increased. Therefore, the therapeutic strategy of thyroid protection is to limit, or if possible, block the stage of iodine capture and organification by the thyroid as to prevents of radio-induced carcinogenesis risk.

3. Population protection measure: iodine prophylaxis

Administration of KI tablets to the population allows the saturation of the thyroid by non-radioactive iodine, thus preventing the fixation of radioactive iodines released in the atmosphere. In fact, iodine is the substrate of thyroidal hormones and allows their synthesis. Once radioactive iodine enters the thyroid, it forms a complex with thyroglobulin. This accumulation of radioactive iodine is consequently responsible for the irradiation to thyroid tissue, which increases the probability of the appearance of thyroid cancer at long term. In any case, to be completely efficient, KI ingestion must take place ideally 1 to 2 hours before exposure to the radioactive plume (see Fig. 1), as the efficiency decreases sharply when the KI administration is delayed (Verger, 2001).

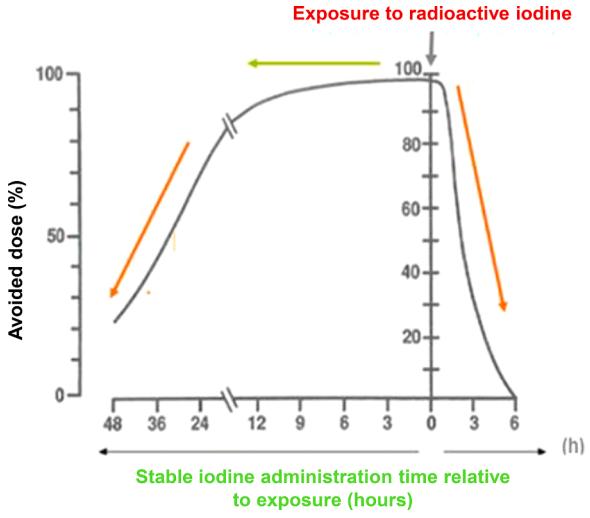

Fig. 1. thyroid protection efficiency given by a single dose of KI.

Protection of the thyroid function from radioactive iodines results mainly from the induction of a physiological thyroid regulation, the "Wolff-Chaikoff effect", which reduces its capacity to capture iodine (Wolff, 1948). It is clearly established that the "Wolff-Chaikoff effect" plays a central role in the regulation of thyroid function and that its control depends on its modulation. Ideally performed right before exposure to a radioactive release, the objective of the intake of KI tablets is to saturate the thyroid gland with non-radioactive (stable) iodine and to prevent the radioactive iodines carried by the plume to penetrate and be fixed in the thyroid (Verger, 2001). The speed at which this countermeasure takes place is of utmost importance considering the short half-life of released iodines (8 days for iodine-131 for example), as they can quickly elicit a high level of radiotoxicity to the thyroid from the moment they are fixed. In fact, the main benefit from such a population protection method is to limit the appearance of thyroid pathologies, particularly cancer in children years or decades following exposure. In France, in line with the WHO recommendations, the "iodine doctrine" dictates that all the population that could potentially be exposed to the radioactive release should benefit from this protective measure, with a priority given to pregnant women and those below 18 years old. In addition, it foresees the administration of a single dose according to a dosage program compatible with the recommendations of the WHO (World Health Organization, 2017). In consequence, the populations affected by this preventive measure will ingest stable iodine in the form of 65 mg KI tablets produced in France by the central pharmacy of the armed forces (Pharmacie Centrale des Armées, France).

3.1. The limitations of prophylaxis with a single dose of stable iodine

The "iodine doctrine" has until now been based on the theory that the different populations would be exposed to radioactive emissions during a brief time, as they would be rapidly protected. This, notably because of the different synergistic protection measures, such as evacuation or sheltering. Nonetheless, the natural and nuclear disaster of Fukushima Dai-ichi has brought up again questions on the conditions of the application of KI prophylaxis. In fact, this accident showed that the "iodine doctrine" that currently proposes one single dose of KI tablets could not satisfactorily protect populations that are repeatedly exposed to radioactive iodine emissions. Furthermore, even if the current doctrine considers the eventuality of a second dose, in case of an impossibility of a rapid evacuation, it does not precise the conditions of how and when the subsequent doses should be taken. In addition, from a regulatory point of view, the current marketing authorization of KI tablets does not allow repeated administration, as it was awarded based on the results of efficacy and toxicology studies with a single stable iodine dose. The administration modes of a single KI dose are thus known with precision; however, it is uncertain as to how the health authorities should proceed in a situation where the repeated intake of stable iodine is needed. Lastly, the WHO recently recognized a research need in order to objectify a positive benefit-risk ratio for a repeated KI prophylaxis (World Health Organization, 2017).

3.2. Since 2020, a new marketing authorization is available for a prophylaxis of repeated intake of stable iodine

A research program named PRIODAC (Repeated stable iodine prophylaxis in accidental situation and coordinated by the IRSN started in 2014 (Benderitter, 2018). Its initial objectives were to determine the modalities of repeated administration of stable iodine and to evaluate the potential side-effects on the diverse physiological functions of the organism. For this purpose, pharmacokinetic studies, efficacy and toxicity studies on animal models representative of the different population categories (adult, pregnant woman, fetus, infant, and elderly

adult) were proposed. Pre-clinical studies allowed to determine a positive benefit-risk ratio for the repeated intake of KI during 8 consecutive days. Indeed, an optimal effective dose for daily administration of potassium iodide (KI) over a period of 8 days was defined on the basis of preclinical studies conducted in rats and mice (Phan, 2018) This experimental work demonstrated the absence of significant side effects in an adult Wistar rat model for the selected dosing regimen. Side effects were examined on various organs, including the thyroid, cardiovascular, central nervous, immune and renal systems (Lebsir, 2018; Lebsir, 2020; Rosique, 2020). Regulatory toxicology studies using Good Laboratory Practice (GLP) on two animal species, rats and dogs, were performed. The safety factors used for this study were satisfactory. These GLP studies have recently led to an initial modification of the marketing authorization of KI for the repeated intake in adults and children above 12 in France-French Agency for the Safety of Health Products- (Agence nationale de sécurité du médicament et des produits de santé, 2021). This will allow to propose future operational solutions to the health authorities for the prevention of repetitive exposure to radioactive iodine.

3.3. Updated clinical data

Potassium iodide is a medicine (antidote) which prevents the accumulation of radioactive iodine in the thyroid. The intake of this treatment is done under the instruction of the competent authorities. Radioactive emissions can be short-lived or prolonged. This antidote is part of a well-defined global radiological protection program defined at the government level. The protection level is 80% after 2 hours and 40% after 8 hours from the start of contamination in iodine-rich regions, and of 65% and 15% respectively in regions with a deficiency in iodine. Treatment length can vary from a single dose to a daily dose during a maximum of 7 days, depending on the kinetics and the characteristics of the accident. To date it still recommended to exclude the repeated intake of potassium iodide by pregnant and breastfeeding women and children below 12 years old, who should consequently be subjected to a priority evacuation from the contaminated zone (see Table 1 below). For the follow-up of the populations treated with potassium iodide (65 mg, brakable tablet), a clinical surveillance by a physician is recommended. In France, the marketing authorization holder is the central pharmacy of the armed forces. The potassium iodide tablets are to be stockpiled in their original packaging, away from humidity, at a temperature below 25°C. Conservation limit is 10 years.

3.3.1. Dosage

Children > 12 years old and adults: One dose of 130 mg of potassium iodide per day repeated up to 7 days, which corresponds to 2 tablets of 65 mg per day for 7 days, except if the competent authorities consider otherwise. The tablets can be dissolved in a drink (water, milk or fruit juice).

Pediatric population (children from 36 months to 12 years old): Single dose of 65 mg of potassium iodide, which corresponds to 1 tablet that can be dissolved in a drink (water, milk or fruit juice).

Infant/toddler (from 1 to 36 months old): Single dose of 32.5 mg of potassium iodide, which corresponds to ½ tablet that can be dissolved in a drink (water, milk or fruit juice). Newborn (< 1 month): Single dose of 16 mg of potassium iodide, which corresponds to ¼ tablet that can be dissolved in a drink (milk bottle for example).

To date it is still recommended to exclude the repeated intake of potassium iodide for pregnant and breastfeeding women and children below 12 years of age, who should consequently be subjected to a priority evacuation from the contaminated zone.

Table 1
New dosage of potassium iodide (KI) prophylaxis according to age.

Age	Iodine (mg)	KI (mg)	Length of treatment
Newborn (up to 1 month)	12,5	16	Single dose
Infant / toddler (1 month to 3 years)	25	32	Single dose
Child (3 to 12 years)	50	65	Single dose
Adult and child above 12	100	130	Dose with possible renewal during 7 days
Pregnant / breastfeeding woman	100	130	Single dose

3.3.2. Special considerations and precautions

The drug notice recommends consulting a physician as soon as possible after intake of potassium iodide in the following cases:

Pregnant women and fetus exposed after the 12th week of gestation (fetal thyroid hormone production): fetal ultrasound surveillance until the end of pregnancy, then follow-up of the newborn to rule out goiter formation. Control of thyroid function (levels of TSH, free T4) is recommended.

Exposed infants below 1 year old and breastfeeding women: a control of thyroid function (levels of TSH, free T4) should be performed 2 weeks after administration. If hypothyroidism is diagnosed, a thyroid hormone treatment should be considered.

Individuals with a history of goiter or thyroid pathologies: clinical surveillance by a physician is recommended.

3.3.3. Warnings, drug interactions and side-effects

Few, very rare immunologic pre-existing pathologies (dermatitis herpetiformis or certain types of hypocomplementemic vasculitis).

4. Conclusions

In France, a first modification of the marketing authorization of potassium iodide for a repeated prophylaxis was obtained in March 2020. As of now, the product notice mentions the new dosage for adults and children above 12 years old as follows: one dose of 130 mg of potassium iodide per day up to 7 days, which corresponds to 2 tablets of 65 mg per day until day number 7, except if the competent authorities consider otherwise. These new data were shared with the World Health Organization (World Health Organization, 2017), which in its last version of recommendations concerning iodine prophylaxis had identified a research need to better define repeated prophylaxis and that according to the different population categories. Several research projects concerning the repeated prophylaxis of potassium iodide in pregnant women, the fetus, and children under 12 and their validation through Good Laboratory Practice (GLP) studies are underway and will allow us to cover all the population categories by the end of 2022. Depending on the obtained results, a novel modification of the marketing authorization to include all population categories could then be considered.

CRediT authorship contribution statement

Marc Benderitter: Conceptualization, Writing – original draft, Validation, Writing – review & editing, Visualization, Supervision, Project administration. **Francois Caire-Maurisier:** Conceptualization, Writing – original draft, Validation, Writing – review & editing, Visualization, Supervision, Project administration. **Caroline Crambes:** Conceptualization, Writing – original draft, Validation, Writing – review & editing, Visualization, Supervision, Project administration. **Thierry Pourcher:** Conceptualization, Writing – original draft, Validation, Writing – review & editing, Visualization, Supervision, Project administration. **Jean-Charles Martin:** Conceptualization, Writing – original draft, Validation, Writing – review & editing, Visualization, Supervision, Project administration. **Jacques Darcourt:** Conceptualization, Writing – original draft, Validation, Writing – review & editing, Visualization, Supervision, Project administration. **Maâmar Souidi:** Conceptualization, Writing – original draft, Validation, Writing – review & editing, Visualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors from the IRSN, CEA, AMU, UCA and PCA do not report any conflict of interests regarding the publication of this paper

Acknowledgments

This work was co-funded by the French Government under the 'Investments for the Future' program (Nuclear Safety and Radioprotection Research (RSNR) action), managed by the French National Research Agency (ANR- 11-RSNR-0019)". The authors thank the ANR program manager Dr Antony Lebeau for his support and confidence and Dr Juan Martinez-Guerrero for grammatical correction and proofreading of the manuscript.

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