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► To cite this version:

Jean-Charles Martin, Thierry Pourcher, Guillaume Phan, Julien Guglielmi, Caroline Crambes, et al.. Review of the PRIODAC project on thyroid protection from radioactive iodine by repeated iodide intake in individuals aged 12+. *European Thyroid Journal*, 2024, 13 (1), pp.e230139. 10.1530/ETJ-23-0139 . irsn-04467514

HAL Id: irsn-04467514

<https://irsn.hal.science/irsn-04467514v1>

Submitted on 20 Feb 2024

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REVIEW

Review of the PRIODAC project on thyroid protection from radioactive iodine by repeated iodide intake in individuals aged 12+

Jean-Charles Martin¹, Thierry Pourcher², Guillaume Phan³, Julien Guglielmi², Caroline Crambes⁴, François Caire-Maurisier⁴, Dalila Lebsir³, David Cohen³, Clément Rosique¹, Lun Jing², Maha Hichri², Lisa Salleron², Jacques Darcourt², Maamar Souidi³ and Marc Benderitter³

¹Centre de recherche en CardioVasculaire et Nutrition (C2VN), Institut national de recherche pour l'agriculture, l'alimentation et l'environnement (INRAE), Institut National pour la Santé Et la Recherche Médicale (INSERM), Aix Marseille Université (AMU), Marseille, France

²Transporter in Imaging and Radiotherapy in Oncology Laboratory (TIRO), Direction de la Recherche Fondamentale (DRF), Institut des sciences du vivant Frederic Joliot, Commissariat à l'Energie Atomique et aux Energies alternatives (CEA), Université Côte d'Azur (UCA), School of Medicine, Nice, France

³Institut de Radioprotection et de Sûreté Nucléaire (IRSN), PSE-Santé, Fontenay-aux-Roses, France

⁴Pharmacie Centrale des Armées (PCA), Direction des Approvisionnements en produits de Santé des Armées, Fleury-les-Aubrais, France

Correspondence should be addressed to M Souidi: maamar.souidi@irsn.fr

Abstract

Background: Intake of potassium iodide (KI) reduces the accumulation of radioactive iodine in the thyroid gland in the event of possible contamination by radioactive iodine released from a nuclear facility. The World Health Organization (WHO) has stated the need for research for optimal timing, appropriate dosing regimen, and safety for repetitive iodine thyroid blocking (ITB). The French PRIODAC project, addressed all these issues, involving prolonged or repeated releases of radioactive iodine. Preclinical studies established an effective dose through pharmacokinetic modeling, demonstrating the safety of repetitive KI treatment without toxicity.

Summary: Recent preclinical studies have determined an optimal effective dose for repetitive administration, associated with pharmacokinetic modeling. The results show the safety and absence of toxicity of repetitive treatment with KI. Good laboratory practice level preclinical studies corresponding to individuals >12 years have shown a safety margin established between animal doses without toxic effect. After approval from the French health authorities, the market authorization of the two tablets of KI, 65 mg/day, was defined with a new dosing scheme of a daily repetitive intake of the treatment up to 7 days unless otherwise instructed by the competent authorities for all categories of population except pregnant women and children under the age of 12 years.

Conclusion: This new marketed authorization resulting from scientific-based evidence obtained as part of the PRIODAC project may serve as an example to further harmonize the application of KI for repetitive ITB in situations of prolonged radioactive release at the European and international levels, under the umbrella of the WHO.

Keywords: iodine thyroid blocking; nuclear emergency; population over 12 years; potassium iodide; radioactive iodine contamination; repetitive prophylaxis

Introduction

The Repeated Stable Iodide Prophylaxis in Accidental Situations project (PRIODAC) (<https://en.irsrn.fr/research/priodac-project>) was launched by Institute for Radiation Protection and Nuclear Safety in 2014 for a duration of 8 years (1). It aimed to define the conditions for repetitive administration of potassium iodide (KI) in order to protect the population undergoing prolonged exposure to radioactive iodine in a nuclear or radiological accidental situation. The results obtained in a series of studies conducted as part of this project are reported here as a review, with a special focus on an application to the adult population. Besides an obvious interest with regard to the previous Chernobyl and Fukushima nuclear accidents, our results dedicated to population protection against radioactive iodine spreading can also be contextualized in the shadow of the war in Ukraine with the threat on Ukrainian nuclear power plants.

The main threat observed after radio-iodine contamination concerns papillary thyroid cancer, the most frequent histologic type of thyroid cancer that has been observed in such a situation (2). The World Health Organization (WHO) recommends the implementation of iodine thyroid blocking (ITB) in the event of radiological and nuclear emergencies (3), and it is advisable to do so in response to the prevailing geopolitical context (4). The protective effect of KI against exposure to radioactive iodines results mainly from the saturation of iodide transport, the dilution of circulating iodide, and the increased excretion of iodide. However, the regulation of thyroid function (including Wolff–Chaikoff effect) must also be taken into account (5). Indeed, iodide-induced thyroid regulation leads to the inhibition of several steps of thyrocyte function such as iodide uptake and its organification as well as thyroid hormone secretion. These effects increase the protection of the thyroid, though by inhibiting hormone secretion, radioactive iodine that has been previously incorporated could be retained. Although thyroid regulation by iodide was first described in the 1940s, little is known about the underlying molecular mechanisms which still need to be better characterized (5, 6). The recommended single dosage of KI according to age group was proposed by the WHO, i.e. 130 mg KI for adults and adolescents (over 12 years), 65 mg for children (3–12 years), 32 mg for infants (1 month–3 years), and 16 mg for neonates (birth to 1 month). The key factor for the effectiveness of this countermeasure effectiveness is a rapid and timely implementation. Indeed, the physical half-lives of radioactive iodine are quite short (8 days for iodine-131, 6.57 h for iodine-135) and thus require administration preferably in the few hours preceding the exposure or, failing that, as quickly as possible in the first hours afterward. If taken too long before exposure, this medication loses all its protective effects. If taken too late after exposure, the thyroid is no longer protected,

as the radioactive iodine has already accumulated in the thyroid. When ITB is initiated in the optimal time window, thyroid protection is greater than 80% during the first 2 days of unique KI administration (7).

In 2017, the WHO Guideline Development Group identified the need for more data on the dosage, optimal timing, regimen, and safety for repetitive ITB in the case of protracted releases of radioactive iodine (8). A review of the medical and scientific literature revealed a lack of knowledge concerning the side effects of repetitive administration of KI, both in humans and in animals. However, some early clinical studies in the adult population showed transient changes in blood thyroid hormone levels following KI administration (9, 10, 11, 12). The objective of the present paper is to present new knowledge recently published covering scientific evidence based on pharmacokinetics, bio-distribution, efficacy, and toxicology of repetitive ITB in preclinical models. KI is an antidote, used in the context of an exceptional health emergency following a nuclear accident, therefore it does not fall within the register of a conventional drug for therapeutic management. As this is a special application (nuclear emergency), it is not conceivable to carry out conventional clinical studies for its use in humans. These new data were challenged against a unique ITB, leading to the development of a secure and effective prescription extending up to 7 days for individuals aged 12 years and above.

Pharmacokinetics of repetitive ITB

A correlation between KI concentrations in the plasma and a blockade of the uptake of iodine radioisotopes into the thyroid has already been suggested in early studies (9, 10), but it has never been fully characterized experimentally or by pharmacokinetic–pharmacodynamic modeling. Part of our work was to revise and complete the data on KI prophylaxis using pharmacological approaches.

First, an optimal single dose of 1 mg/kg KI has been determined from dose-response preclinical experiments in rodents and was selected based on the level of thyroid protection against iodine-125 incorporation as well as on the thyroid distribution and urinary elimination of KI (11). Then, the pharmacokinetic parameters of KI were determined after oral and intravenous administration of this specific dose of 1 mg/kg in order to assess the duration of the thyroid protective effect and to propose an optimal dose regimen for repetitive KI prophylaxis (12). In terms of thyroid protection, it has been reported in the literature that in humans the percentage of avoided dose to the thyroid is between 50% and 75% even if the exposure occurs 48 h after a single oral administration of 100 mg to 200 mg of KI (i.e. 1.8 to 3.7 mg/kg KI) (7). Such levels of thyroid protection could serve as target values of minimal efficacy and were

selected for the assessment of the KI dose regimen in our study. Hence, the pharmacokinetic parameters of KI were determined in order to model a dose regimen consisting of daily administration of the dose of 1 mg/kg over 8 days. We confirmed the previously described good correlation (9, 10) between the effect of KI administration against the incorporation of iodine-125 into the thyroid and stable KI plasma concentrations, which allowed us to verify the efficacy of the proposed repetitive prophylaxis. The results showed that this dose regimen would provide over 75% thyroid protection for 14 h after the first KI administration and over 60% protection before subsequent KI dosing (12). These results showed that KI doses superior to 1 mg/kg should be considered for optimal thyroid protection in protracted prophylaxis and that the currently recommended dose in humans should be suitable, provided that no adverse effect is induced with 1.8 mg/kg/day KI for 7 days. Other experiments using SPECT (single-photon emission computed tomography) imaging were performed (13). The addition of radioactive iodine-123 to the KI dose (1 mg/kg) allowed us to determine the behavior of iodine in the thyroid and the other organs. It also confirmed the rapid elimination of the excess iodide within 12 h. SPECT imaging also allowed the determination of the kinetics of radioactive iodine and modeling of the thyroid protection at different time points in between two KI doses. Daily KI (1 mg/kg) administrations led to very effective protection (90%) against iodine-125 exposure after the last KI dose. This protection decreased to less than 60% 23 h after the last KI dose (Fig. 1). The overall protection was calculated to be about 85% for acute exposure at any time between two KI doses (13).

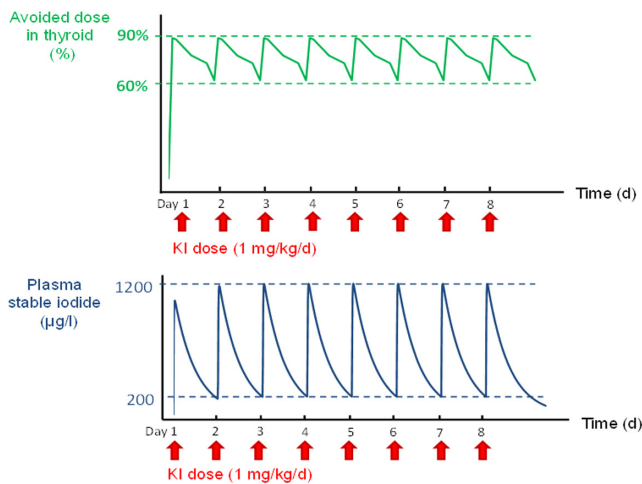


Figure 1

Correlation between thyroid protection against radioactive iodine isotope incorporation and plasma stable iodide concentrations as a function of time after repeated doses of KI (1 mg/kg/day) for 8 days in rats: the percentage of thyroid protection or avoided dose (green curve) and plasma stable iodide (blue curve) were simulated by pharmacodynamic/pharmacokinetic modeling of data obtained after oral administration of stable KI 1 h before iodine-125 intravenous injection (23).

In conclusion, these studies were useful in predicting the duration and efficacy of daily KI administration as a function of the pharmacokinetic parameters and in suggesting an operational dosing regimen for repetitive KI prophylaxis. From a fundamental point of view, these studies also provided further data on thyroid iodine metabolism and its regulation by iodide.

Standard, preclinical safety studies of repetitive ITB

The ability of the thyroid gland to concentrate iodide is essential for the synthesis of thyroid hormones through a complex mechanism involving several functional proteins (14, 15). The levels of circulating thyroid hormones are tightly regulated in physiological processes and have a major impact on the homeostasis of the body. Excess iodide can cause a transient downregulation of thyroid hormone levels, the so-called Wolff–Chaikoff effect (16, 17, 18, 19).

Repetitive administration of KI could be used as an option for prolonged exposure to radioiodine, but there is a real lack of knowledge on health outcomes about repetitive ITB.

Thus, as stated earlier, to experimentally mimic repetitive prophylaxis, a dose of 1 mg/kg/day for 8 days has been used in preclinical studies, as this has been shown to be an optimal dose in terms of efficacy (11). Urine iodine concentration was measured 10 days and 30 days after the end of treatment to assess iodide status, and no significant difference for any phenotypical outcomes was observed between the treatment and control groups (20). These results are in agreement with other preclinical studies where excess iodide for a relatively long period of time did not alter the overall body weight of Wistar rats (21, 22). In addition, given the importance of thyroid function on physiological homeostasis, a preclinical study showed that plasma and urinary biochemical parameters did not differ between rats given repetitive doses of iodide and controls (21). Yoshida and his colleagues also demonstrated that after administration of iodide at more than 3 mg/day to rats for 4 weeks, no change was observed in specific biochemical parameters (alanine aminotransferase, aspartate aminotransferase, total cholesterol, and triglycerides) (21), reflecting the harmlessness of this treatment on metabolism, particularly that of the liver. Finally, we showed that repetitive treatment with stable iodide for 8 days had no biological effects on the cardiovascular system (23).

To assess thyroid function 30 days after ending repetitive administration, blood levels of thyroid-stimulating hormone and free thyroid hormones were assessed as relevant biomarkers. No difference was observed between the treated and control groups, which may suggest that thyroid function was not affected by the repetitive setting (20). These findings align with the

outcomes of other clinical and preclinical studies conducted in repetitive settings, which consistently report no discernible impact of iodide on pituitary–thyroid axis activity (10, 22, 24, 25, 26, 27, 28, 29, 30).

In preclinical studies, histological analysis of the thyroid showed no changes attributable to the repetitive iodide supplementation. Follicle shape and size and cell proliferation index showed no difference between treated and control rats (20). This is in contrast with previous studies in rats, where histological analysis of the thyroid showed a significant enlargement of the thyroid follicles and an increase in the amount of extracellular matrix around them in response to an acute and single dose of excessive iodide treatment (29, 31). In the thyroid, two proteins play an important role in iodide transport and thyroid hormone synthesis, namely, the sodium–iodide symporter (NIS) and thyroid peroxidase (TPO). In a study by Arriagada and colleagues (28), immunohistochemical characterization of thyroid tissue indicated that the abundance and localization of these two proteins were unaffected 30 days after discontinuation of KI and these results are in agreement with Faggiano and colleagues (32). Finally, the results of histological analysis, proliferation assessment, and immunohistochemical characterization showed no negative effect of KI 1 mg/kg/day for 8 days on cytoarchitecture and thyroid function (33).

The absence of recognized harmful effects or clinical dysfunctions consecutive to repetitive iodide administration-based thyroid blocking does not mean that no subclinical dysfunction would occur. However, conventional toxicological approaches might lack the sensitivity needed to reveal physiological modifications in the subclinical range and occurring from subtle changes in thyroid function. Omics technologies, including transcriptomics and metabolomics, would bring further complementary information. They could reveal subclinical phenotypes or a ‘silent’ sensitization phase at the molecular level prior to the occurrence of phenotypic changes (34). It is well known that the Wolff–Chaikoff effect and its escape occur during exposure of the thyroid to supraphysiological concentrations of iodide (16). Leoni and colleagues analyzed the transcriptomic profile of a rat follicular cell line under normal and excess iodide conditions and found that 84 transcripts (specifically categorized as protein metabolism) were differentially expressed in response to excess iodide (35). In an *in vivo* study, the transcriptome profile of the rat thyroid was analyzed under treated and untreated conditions in a repetitive administration setting. No difference in the expression profile between treated and control groups was observed (20). Furthermore, even the expression of genes involved in iodide metabolism and thyroid hormone synthesis was similar between the treated and control groups 30 days after prophylaxis. This indicates that repetitive treatment with KI at a dose of 1 mg/kg/day does not affect important molecular and cellular processes.

We further conducted a metabolome characterization of the thyroid, plasma, and urine of adult male Wistar rats (aged 3 months) 30 days after completion of the ITB regimen (1 mg/kg/7 days of KI) (36), beyond acute thyroid blocking. The metabolomics analyses revealed many differences between the rats of the study group (control and KI treated), amongst which the thyroid still remained the most sensitive to ITB. This was exemplified by the highest number of associated biological functions that significantly diverged in treated vs control rats (60% of the total biological functions, vs 38% and 22% in both plasma and urine, respectively). This indicated a limited systemic impact of ITB compared to thyroid effects. In this organ, tyrosine and catecholamine metabolisms were among the top significant functions that were changed 30 days after the cessation of the treatment. In thyroid, tyrosine metabolism was also correlated with other metabolic functions (catecholamine metabolism, antioxidant status, vitamins metabolism, etc.), together with other metabolic outcomes measured in both plasma and urine (metabolic adjustment, amino-acid metabolism, antioxidant status). We showed that thyroid tyrosine metabolism modulated by ITB was more driven by the catecholamine pathways (dopamine) than the synthesis of thyroid hormones. Conversely, macroscopic evaluation did not reveal any differences between the treated and nontreated rats one month after the end of KI repetitive intake (body, liver, kidneys, thyroid masses, thyroid hormones). It was also elsewhere observed that the analysis of metabolic profiles of individuals (metabotypes) could better reveal subclinical outcomes to identify subjects at high risk for metabolic disruptions despite shifts in classical clinical parameters not yet being detectable (37, 38). Furthermore, the changes of a persistent metabolomics response after cessation of the KI trial would locate in the range of physiological variations, called ‘allostatic regulations’ (39), since they remained clinically asymptomatic. Therefore, it is unlikely that our metabolomics observations would project into the pathological metabolic space per se. Conversely, our findings highlighting allostatic regulation would indicate a shift toward a new but still healthy stage that prepares the physiological response for another challenge (40). However, if such allostatic conditions continue or are accompanied by other odd metabolic disruptions, then the cost could be pathological outcomes (40).

In the absence of clear clinical signs of dysfunction or toxicity, we concluded that the measured metabolomics response to the new ITB strategy is unlikely to reveal a pathological condition at the time of examination.

Thus, the results obtained in these preclinical studies showed that repetitive KI administration at a dose of 1 mg/kg/day for 8 days had no harmful effect on the health status, as well as the structure and function of the thyroid.

Molecular mechanisms associated with excess iodide

The mechanisms behind the effect of high dose iodide have been studied and are well documented in the literature (16). Indeed, the major consequence is that thyroid hormone synthesis is reduced when the thyrocyte intracellular iodide concentration is elevated (41), this mechanism being known as the Wolff–Chaikoff effect (42). This transient effect is associated with modulation of NIS and the enzyme TPO (26, 43). The mechanism that leads to escaping this blockade is the decrease of *Nis* expression and this is associated with the reduction of the NIS protein (16). More recently, posttranscriptional regulation of *Nis* at the level of mRNA stability has also been demonstrated (25). These mechanisms lead to a decrease in the intracellular iodide concentration, thus inducing inhibition of thyroid hormone synthesis.

During chronic KI administration, *Nis* expression is also downregulated (26, 29) and it has been shown that the thyroid hormones transport (*Mct8*), iodide organification (*Tpo*), and chloride iodide transporter (*Pds*) genes may also be differentially expressed, although other studies have found no difference (29, 31, 33). The mechanism behind the regulation of these genes upon repetitive administration of KI is currently unknown. However, we suggested that the Wolff–Chaikoff effect during chronic KI administration consists of a two-step mechanism: first, iodide rapidly inhibits *Nis* and *Mct8* expression upon ingestion, and the second step is a late Wolff–Chaikoff effect, which essentially involves inhibition of *Nis* gene expression by excess iodide (20) (Fig. 2).

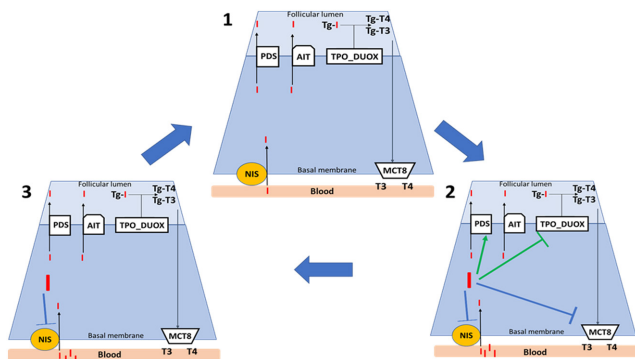


Figure 2

Hypothetical mechanism of the Wolff–Chaikoff effect in response to repetitive administration of potassium iodide (KI) on genes involved in iodide transport (sodium/iodide symporter (*Nis*), pendrin (*Pds*), and apical iodide transporter (*Ait*)), iodide organification (thyroid peroxidase (*Tpo*), thyroglobulin (*Tg*), dual oxidase (*Duox*)), and thyroid hormone transport (monocarboxylate transporter 8 (*Mct8*)). 1—thyrocyte basal state; 2—sequential Wolff–Chaikoff effect after repetitive administration of KI, in blue a rapid Wolff–Chaikoff effect, and in green a delayed Wolff–Chaikoff effect; 3—escape from the Wolff–Chaikoff effect after the end of the treatment (thyrocytes return to basal state).

Recently, through a systems biology approach, we proposed a new mechanism for the regulatory effect of repetitive prophylaxis of stable iodide on *Nis* expression (44). To understand the regulation of the Wolff–Chaikoff effect and its molecular constituents upon repetitive KI administration, a network of biochemical reactions was constructed as a ‘geographical’ map of the thyrocyte representing iodide metabolism and thyroid hormone synthesis. In this study, a putative mechanism of the Wolff–Chaikoff regulation was proposed, by which the sequential regulation of the highly organized thyroglobulin protein affects the level of both *Nis* and *Tpo* and regulates thyroid hormone synthesis step (*Duox2*), *Mct8*, and thyroglobulin itself. Of course, the ultimate validation would be experimental to test whether this hypothesis is correct. With this study, a putative mechanism was shown to regulate NIS and TPO without causing nontoxic adverse effects on repetitive administration of KI (42, 43, 44).

Toxicological assessment: good laboratory practice safety study of repetitive ITB

Generally speaking, KI is an antidote used in a context of an exceptional health emergency following a nuclear accident. Therefore, KI does not fall within the register of a conventional drug for therapeutic management. KI is indicated to prevent the accumulation of radioactive iodine in the thyroid in the case of possible contamination by radioactive iodine emitted during an incident/accident on a nuclear installation. As this is a special application (nuclear accident), in view of the classification of the product as an antidote, it is not conceivable to conduct conventional clinical studies for its use in humans.

The toxicological investigations reported below were conducted as part of the preclinical development phase of KI. The main studies were performed in accordance with the Organization for Economic Co-operation and Development (OECD) guidelines, guidelines concerning good laboratory practice (GLP), and other applications (45). Experiments were performed in accordance with well-established procedures in regulatory experimental toxicology and were deeply reviewed by the expert committee that provided a positive advice for a new marketing authorization of repeated KI administration (46). One rodent and one nonrodent species were selected as test systems, first looking for the maximum tolerated dose for 7 days and then the no observed adverse effect level (NOAEL) for a 28-day test. These data were provided for the modification of the marketing authorization of KI (65 mg, scored pills) for repetitive ITB in adults and children aged 12+, validated by the French National Agency for the Safety of Medicines and Health Products (ANSM).

Potential mutagenic activity of KI was assessed using Ames’ test in five *Salmonella typhimurium* strains

(TA1535, TA1537, etc.) tested both in the presence and in the absence of metabolic activation, in two independent assays according to OECD guideline 471 (47), using the maximum recommended dose, i.e. 5000 µg/plate. Under these experimental conditions, no mutagenic activity was revealed. Similarly, potential genotoxic activity of KI was assessed with the *in vitro* micronucleus test in human lymphocytes treated in the presence and absence of metabolic activation, both with short-term and long-term treatment, according to OECD guideline 487 and International Council for Harmonization of technical requirements for pharmaceuticals for human use (ICH) guideline S2(R1) (48). The highest concentration was chosen in accordance with the ICH recommendation. Under these experimental conditions, no genotoxic activity was observed in the presence and in the absence of metabolic activation.

In order to support an extension of the duration of treatment with KI from 1 or 2 days to 7 days in humans, two pivotal GLP toxicological studies were performed in rats and dogs for 28 days. These preclinical rodent and nonrodent models are commonly used as references in toxicology (49). Several parameters were studied, such as clinical signs, body temperature and weight, ophthalmological, hematological and biological parameters, thyroid hormones, organs macroscopic examination, histopathology, and weight. A toxicokinetics analysis was also conducted, as well as a safety pharmacology study for the cardiovascular and respiratory system (in the dog) and for the central nervous system (Irwin test in the rat (50)). From the aforementioned biological parameters examined, target organs in rats and dogs were determined as liver and kidneys, since hepatic and renal functions were modified at a higher dose of 500 mg/kg in the rat and from 40 mg/kg onward in the dog. In addition, KI administered during the 28 days at 500 mg/kg/day to rats did not induce any CNS disturbances (Irwin test). When KI was administered to dogs during the 28 days at 60 mg/kg/day, no changes were noted in respiratory or cardiovascular parameters recorded, compared with control groups (safety pharmacology studies).

Data obtained on the two species were extrapolated to humans in accordance with the ICH M3(R2) guideline (51) and the U.S. Food and Drug Administration recommendations (52). The GLP regulatory toxicology studies allowed to define a NOAEL of 100 mg/kg/day for 28 days in rats and 20 mg/kg/day for 28 days in dogs. Referring to the two abovementioned applications as well as to the article by Reagan-Shaw *et al.* (53), the NOAEL was calculated for extrapolation to humans, Human Equivalent Dose (HED), for each of the two species studied (toxicological data necessary to shift from the preclinical model to the clinical model). HEDs of 16.1 mg/kg and 11 mg/kg were obtained from the rat and dog models, respectively. Thus, the daily KI dosage of 130 mg (1.8 mg/kg) proposed in the application for the modification of the marketing authorization is much lower than the HED calculated. A safety factor >10 was

Table 1 Synopsis of KI posology as a function of age.

Age	Iodine (mg)	KI (mg)	Length of treatment
Adult and child above 12	100	130	Dose with possible repeat after 7 days
Pregnant/breastfeeding woman	100	130	Single dose ^a
Newborn (up to 1 month)	12.5	16	Single dose ^b
Infant/toddler (1 month to 3 years)	25	32	Single dose ^b
Child (3 to 12 years)	50	65	Single dose ^b

^aMarketed authorization evolution running; ^bMarketed authorization evolution planned.

noted for both rat and dog models. This safety factor >10 respects the recommendations put forward in the abovementioned reference documents.

Preclinical studies concluded a favorable benefit–risk balance for repetitive intake of KI up to 7 consecutive days. These data supported the extension of the new marketing authorization of KI (65 mg scored pills) for repetitive ITB (130 mg daily up to 7 days) in adults and children aged 12+. A first modification of the marketing authorization of KI for repetitive prophylaxis in adults (except pregnant or breastfeeding women) and children aged 12+ was thus obtained in France in March 2020 from the ANSM. A synopsis of the posology as a function of age is provided in Table 1.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This results of the PRIODAC consortium summarized in the manuscript were 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).

Author contributions statement

JCM, TP, GP, CC, MS, and MB were involved in conception, writing, review, and critical review. All authors contributed to the results produced by the laboratories of the PRIODAC consortium and commented on the manuscript.

Acknowledgements

The authors thank the ANR program manager Dr Antony Lebeau for his support and confidence and Dr Stéphane Flamant for grammatical correction and proofreading of the manuscript.

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