# Facing the Nuclear Threat: Thyroid Blocking Revisited

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**Context:** People being exposed to potentially harmful amounts of radioactive iodine need prophylaxis to prevent high radiation-absorbed doses to the thyroid.

**Objective:** Parameters determining the individual protective effect of a pharmacological intervention were investigated.

**Design and Participants:** Biokinetics of $^{123}$I was evaluated in 27 healthy volunteers (aged 22–46 yr, median 25 yr, in total 48 assessments) twice in a baseline measurement of the undisturbed kinetics and in an intervention assessment 48 h later.

**Interventions:** Seven regimens using single doses of potassium iodide (KI) or sodium perchlorate (SP) at different times relative to exposure were compared: 100 mg KI (−24, 2, 8, 24 h), 100 mg SP (2 h), or 1 g SP (2, 8 h).

**Main Outcome Measures:** Different drugs and dosages and the influence of individual parameters of iodine kinetics should be tested.

**Results:** Mean dose reductions for interventions at −24, 2, 8, and 24 h relative to the activity incorporation were 88.7, 59.7, 25.4, and 2.8%, respectively. One gram SP was equally effective as 100 mg KI; residual uptake was observed after 100 mg SP. The individual dose reduction decreased exponentially with the effective half-life of the activity in the blood. Kinetics in subjects older than 40 yr was as assumed in official guidelines for the prophylaxis after nuclear accidents but was faster in younger participants.

**Conclusions:** Data on the efficacy of thyroid blocking used in the guidelines are adequate for older people but not for young individuals with their typically faster kinetics. SP may be used for thyroid blocking as alternative for individuals with iodine hypersensitivity. **(*J Clin Endocrinol Metab* 96: 3511–3516, 2011)**

The history of nuclear technology is a history of incidents with occasional release of large amounts of radioactivity into the environment, currently mainly from nuclear power plant accidents. In the early phase of an accident, the responsible authorities have to decide timely about preventive measures (*e.g.* evacuation, sheltering, iodine blockade, or food ban). The primary route of incorporation after the Chernobyl accident was intake of contaminated food and drinking water. Adequate protective measures to prevent exposure by ingestion are food ban and specific guidance on foods and drinks that should not to be consumed. Iodine prophylaxis is of paramount importance for people being exposed to air contaminated with neutron-rich radioactive iodine isotopes, *e.g.* radioiodine ($^{131}$I), which are produced in nuclear fission of actinides. The thyroid concentrates these isotopes like stable iodine from the blood plasma and stores them in precursors of thyroid hormones. The associated radiation exposure induces a high risk of developing thyroid cancer, especially in children and adolescents (1). A strong dose-response relationship between radiation absorbed dose and thyroid cancer was observed in a case-control study in children from Belarus and the Russian Federation after the Chernobyl accident (2). The same study revealed that the risk was 3 times higher in children in iodine-deficient areas than in areas with moderate or high soil iodine concentrations.

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Abbreviations: $^{131}$I, Radioiodine; ICRP, International Commission on Radiological Protection; KI, potassium iodide; SP, sodium perchlorate.

The uptake of radioactive iodine into the thyroid can be prevented by administration of a sufficient amount of stable iodine, which competes with the radioactive isotopes for the transmembrane transport via the sodium iodide symporter and, at high intrathyroidal concentrations, inhibits organification, *i.e.* the formation of thyroid hormones inside the thyroid follicles (acute Wolff-Chaikoff effect) (3). Other monovalent anions with sizes similar to $I^-$ such as perchlorate, $ClO_4^-$, are also known to be transported by the sodium iodide symporter (4) but are not metabolized and diffuse through the cell membrane back into the blood.

The World Health Organization (5) and national authorities such as the U.S. National Research Council (6) recommend thyroid blocking with stable iodine, especially in children and young adults. The protective effect, *i.e.* the reduction of radiation absorbed dose to the thyroid, is stated to be 100% if adequate prophylaxis is initiated just before the exposure and 40% for blockage after 8 h (6).

Our experimental and theoretical study shows an alternative to the recommended blocking agent and gives strong indication that common assumptions on the time course of the inhibitory effect are too optimistic for young people; it also demonstrates why a reliable prediction of the effectiveness of delayed prophylaxis is not possible for a given individual.

## Subjects and Methods

### Subjects and ethical considerations

Twenty-seven healthy adult volunteers (13 males, 14 females; median age 25 yr, ranging from 22 to 46 yr) participated in a total of 48 assessments of $^{123}$I kinetics in the thyroid. To participate, subjects had to have functionally and morphologically normal thyroid glands and normal iodine supply before each experiment, as documented by physical and ultrasound examination and standard laboratory assays (free $T_3$, free levothyroxine, TSH, thyroperoxidase and thyroglobulin antibodies, urinary iodine concentration). Detailed information on the hormonal status of the study participants and the stable iodine uptake reflecting the dietary iodine supply is provided online in a Supplemental Data file, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. All female subjects had pregnancy ruled out by standard testing.

The study protocol was approved by an accredited ethics committee and the federal German radiation protection authorities, and each subject provided written informed consent to participate in the study. The study related cumulative thyroid radiation absorbed dose was less than 0.4 mGy for each individual.

### Study design

Kinetics was measured both with undisturbed metabolism and during blockage with single doses of potassium iodide (KI) or sodium perchlorate (SP) given at various time points before or after the administration of the radioactive tracer. $^{123}$I administration was used as a model of radioiodine exposure because of the isotope's low radiation dose to the volunteers, the well-detectable emission line at 160 keV, and the physical half-life of 13.27 h enabling uninfluenced measurement of baseline and intervention experiment at minimal time delay.

Each assessment started with the iv administration of 5 kBq $^{123}$I to measure the uninfluenced baseline iodine kinetics in the subjects and to deduce the individual transfer rate of renal elimination of the iodine from the blood plasma. After 48 h, when the remaining thyroidal activity was generally less than 0.2 kBq, a second iv injection of 25 kBq $^{123}$I was combined with the administration of a blocking agent and subsequent measurements to evaluate the transfer rate of thyroidal uptake and the reduction of the radiation absorbed dose to the thyroid by the respective countermeasures. Thyroid uptake was measured 2, 6, 24, and 48 h after each activity administration with additional facultative measurements if possible.

Seven different interventions were tested in subgroups of six or seven volunteers: 100 mg KI 24 h before or 2 h, 8 h, or 24 h after $^{123}$I exposure; 100 mg SP 2 h after exposure; or 1 g SP 2 h or 8 h after exposure. One hundred milligrams of KI is the dose recommended by the World Health Organization in the case of nuclear reactor emergencies (5). The SP doses were chosen in an attempt to determine a dose response for this agent.

### Uptake measurements

Thyroid uptake was measured by high-resolution $\gamma$-spectroscopy at a distance of 10 cm from the anterior neck in three counts of 100 sec each, using a collimated high-purity n-type germanium detector (model GR4520; Canberra Eurisys GmbH, Rüsselsheim, Germany) mounted in the shielded chamber of the whole-body counter of our department. To correct for photon attenuation and geometry, the mean thyroid depth was determined for each subject using ultrasound scans before the administration of radioactivity. Typical sensitivity for activity in the thyroid was 6 counts/sec/kBq, and the lower limit of detection was 5 Bq of $^{123}$I. Four percent of the blood pool activity was in the field of view during the thyroid measurement and was subtracted as background.

### Theoretical considerations

In healthy individuals, iodide transport into the thyroid is controlled, depending on iodide intake and renal elimination to provide adequate intrathyroidal iodine content and thus favorable conditions for a stable hormonal supply. Iodine deficiency is compensated for by an increase of fractional uptake by up-regulation of the transport capacity into the thyroid, *i.e.* expression of the sodium iodide symporter in the follicular cell membrane. The ratio of the transfer rates for thyroidal intake and renal clearance and the rate of physical decay mainly determine the uptake of radioactive iodine (*i.e.* the ratio of activity in the thyroid gland and the administered activity) and effective half-life, respectively, and thus the radiation absorbed dose to the thyroid.

The maximum thyroid uptake is reached when almost no radioactive iodide is left in the blood, and the rate of activity uptake equals the loss by physical decay and release of iodinated hormones. This maximum is reached earlier and the phase of thyroid uptake is shorter in individuals with a higher rate of elimination of the radioactive iodine from the blood, *i.e.* faster renal clearance and higher transfer rates into the thyroid. It must therefore be expected that the effectiveness of a delayed prophylaxis strongly depends on the individual iodine kinetics. Compartment model considerations indicate that the achievable protective effect falls exponentially with the rate of plasma iodine clearance and the time interval after exposure when the plasma levels of the blocking agent are sufficient to inhibit further thyroid uptake.

Details on the theory and the procedure of data evaluation are provided online in a Supplemental Data file.

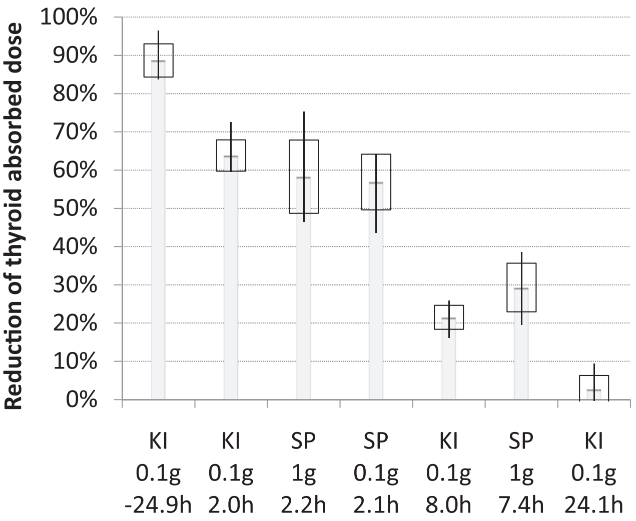

**FIG. 1.** Observed mean fractions (*box*, ± SD; *line*, range) of thyroid radiation absorbed dose after $^{123}$I incorporation averted by thyroid blocking with KI or SP in seven groups of volunteers.

### Statistical analyses

Data presented for the different groups are mean values ± SD, which were calculated after testing the null hypothesis of normal distribution with the Shapiro-Wilk test. The nonparametric Kruskal-Wallis test was used to test for significant differences between groups because variances often were not equal. The statistical significance was assumed for $P < 0.05$.

## Results

Stable iodine uptake into the thyroid was calculated for each subject from the transfer rates deduced in the baseline measurement of the undisturbed kinetics by neglecting the $^{123}$I decay constant. Mean fractional uptake was 24.8% (SD 7.8%; range 10.0–47.8%), indicating an adequate mean alimentary iodine intake in the study group. Further details are provided in the Supplemental Data file.

The mean observed reduction in thyroid-absorbed dose in the groups with different interventions is shown in Fig. 1 and listed in Table 1 together with measured iodine kinetics data. Expectedly, the time of the intervention relative to the activity incorporation has a marked effect on the efficacy. The highest mean reduction of thyroid absorbed dose, 88.7%, was observed in individuals blocked with 100 mg KI at 24 h before exposure. Mean efficacy in subjects blocked at nominally 2, 8, and 24 h after the injection of $^{123}$I is reduced to 59.7, 25.4, and 2.8%, respectively. The differences are highly significant ($P < 0.001$).

In three groups, subjects were blocked at nominal 2 h after the activity incorporation with medications of 100 mg KI, 100 mg SP, and 1 g SP. The observed differences in these groups in reduction of thyroid absorbed dose did not reach the level of statistical significance ($P = 0.08$). A significant difference was observed between the groups of subjects blocked with 1 g SP and 100 mg KI after 8 h ($P = 0.03$).

Measured further thyroid uptakes, *i.e.* the differences between the measured uptakes and the values expected after immediate and complete blockage are shown in Fig. 2 for the different interventions. Further uptake after the intervention is apparent in the group with only 100 mg SP (*filled circles* in Fig. 2A) and in the group with 100 mg KI 24 h before activity injection (*filled circles* in Fig. 2B). All but a few *filled circles* at early time points are clearly above the zero line in Fig. 2.

Further uptake values scatter around zero in the groups with 100 mg KI or 1 g SP after 2, 8, or 24 h (*open symbols* in Fig. 2), especially at late time points. Mean levels are slightly increased shortly after the intervention in the groups blocked at 2 h after the $^{123}$I injection due to thyroid uptake in the time interval $\Delta t$ between the administration of the agent and the onset of blocking. The elevation vanishes if the further uptake is recalculated under the assumption of complete blockage about 15 min after the intervention, indicating that this is the typical time interval for the drug to become effective. The observed time to onset of blockage is in good agreement with the delay of 10–15 min for oral administration quoted by the Medical Internal Radiation Dose Committee in their report no. 5 (7).

The measured individual reductions of thyroid absorbed doses are in good agreement with the values predicted by the theory that the protective effect decreases exponentially with

**TABLE 1.** Observed mean values ± SD in seven groups with thyroid blockage by KI or SP sorted by the mean time delay of intervention (INV)

| Intervention INV | | Thyroid dose reduction (DR) (%) | n | Transfer rate | | Thyroid residence time | | |
|---|---|---|---|---|---|---|---|---|
| Agent | Time (h) | | | Renal clearance ($k_r$) (1/h) | To thyroid without INV ($k_t$) (1/h) | Without INV ($RT_0$) (h) | From uptake after INV ($RT_{PI}$) (h) | With INV (RT) (h) |
| KI 0.1 g | −24.9 ± 1.4 | 88.7 ± 4.3 | 7 | 0.110 ± 0.029 | 0.032 ± 0.015 | 3.15 ± 1.12 | 0.37 ± 0.24 | 0.37 ± 0.24 |
| KI 0.1 g | 2.0 ± 0.2 | 63.8 ± 4.1 | 7 | 0.105 ± 0.038 | 0.045 ± 0.025 | 4.32 ± 1.68 | 0.07 ± 0.22 | 1.58 ± 0.70 |
| SP 0.1 g | 2.1 ± 0.2 | 56.9 ± 7.3 | 7 | 0.092 ± 0.034 | 0.034 ± 0.020 | 3.60 ± 1.81 | 0.36 ± 0.13 | 1.47 ± 0.57 |
| SP 1 g | 2.2 ± 0.1 | 58.3 ± 9.6 | 6 | 0.111 ± 0.036 | 0.052 ± 0.023 | 4.56 ± 1.43 | 0.10 ± 0.20 | 1.83 ± 0.54 |
| SP 1 g | 7.4 ± 0.4 | 29.3 ± 6.4 | 7 | 0.096 ± 0.027 | 0.034 ± 0.011 | 3.55 ± 0.63 | −0.10 ± 0.16 | 2.52 ± 0.55 |
| KI 0.1 g | 8.0 ± 0.7 | 21.5 ± 3.1 | 7 | 0.106 ± 0.022 | 0.038 ± 0.012 | 3.61 ± 0.71 | 0.00 ± 0.14 | 2.84 ± 0.64 |
| KI 0.1 g | 24.1 ± 0.4 | 2.8 ± 3.5 | 7 | 0.112 ± 0.049 | 0.035 ± 0.020 | 3.19 ± 1.00 | −0.02 ± 0.05 | 3.12 ± 1.05 |

n denotes the number of assessments in the group. A description of the procedure to deduce transfer rates and thyroid residence times by calculations based on a simple model with two compartments is provided online in a Supplemental Data file.

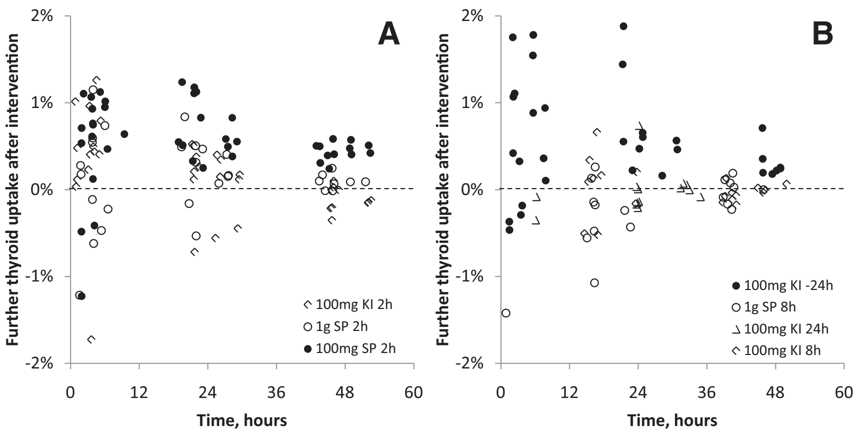

**FIG. 2.** Measured further thyroid uptakes in percent of administered activity after pharmacological interventions at 2 h after (A) and 24 h before and 2 or 8 h after (B) activity injection. The data represent the differences between the measured uptakes and the values expected after immediate and complete blockage by the intervention shown at the time after administration of both $^{123}$I activity and prophylaxis, *i.e.* the time after $^{123}$I incorporation in the group with 100 mg KI at 24 h before activity injection and the time after the intervention in all other groups.

the individual rate of plasma iodine clearance and the time to onset of the blockage after the exposure (Fig. 3). In Fig. 3, data from subjects in the groups with 100 mg SP at 2 h (*open rectangles*) and 100 mg KI at -24 h (*open circles*) are under the expected values (*line of unity*), indicating incomplete blockage. Data from assessments with 1 g SP (*filled rectangles*) and 100 mg KI administered after the activity incorporation (*filled circles*) scatter around the line of unity.

Based on the assumption that blockage is complete at 15 min after the intervention, as observed in the present study for $^{123}$I, the protective effect was calculated for $^{131}$I (physical half-life: 8.02 d) by replacement of the $^{123}$I decay constant (0.0522/h) by 0.0036/h (Fig. 4). The *thin solid line* in Fig. 4 is determined for a person with blood activity elimination according to the model published in International Commission on Radiological Protection (ICRP) 78 (8). Six hours after radioiodine incorporation, 48% of the radiation absorbed dose to the thyroid can be averted. The kinetics is representative for subjects exceeding 40 y of age in the present study (15 assessments). Kinetics of subjects in our study younger than 25 y of age (20 assessments) was significantly faster ($P = 0.02$). Mean dose reduction in this subgroup (*bold solid line* in Fig. 4) was calculated to be 50% after 4.0 h and 36% after 6 h. The time of intervention to achieve 50% dose reduction was 2.4 h for the subject with fastest kinetics (*lower dashed line* in Fig. 4; 20% dose reduction after 6 h) and 9.2 h for the individual with the slowest kinetics (*upper dashed line* in Fig. 4; 63% dose reduction after 6 h) observed in this study.

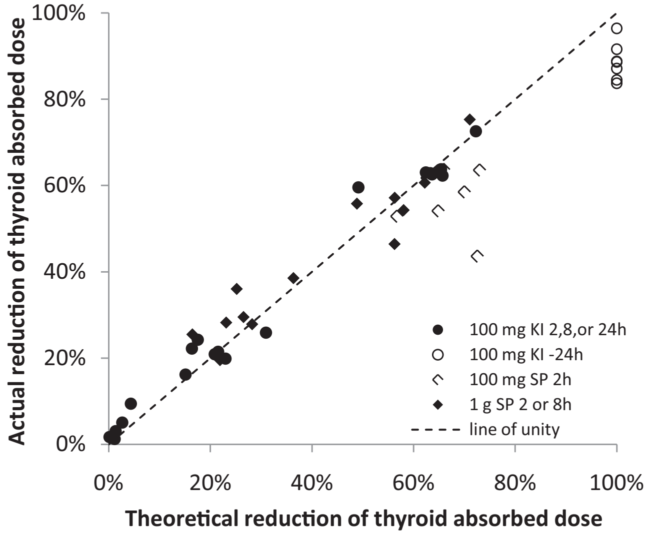

**FIG. 3.** Measured individual reduction of thyroid radiation-absorbed dose compared with values predicted by the theory that the protective effect decreases exponentially with the individual rate of plasma iodine clearance and the time to onset of the blockage after the exposure.

## Discussion

The radiation absorbed dose to the thyroid defines the risk associated with an intake of radioactive iodine after a nu-

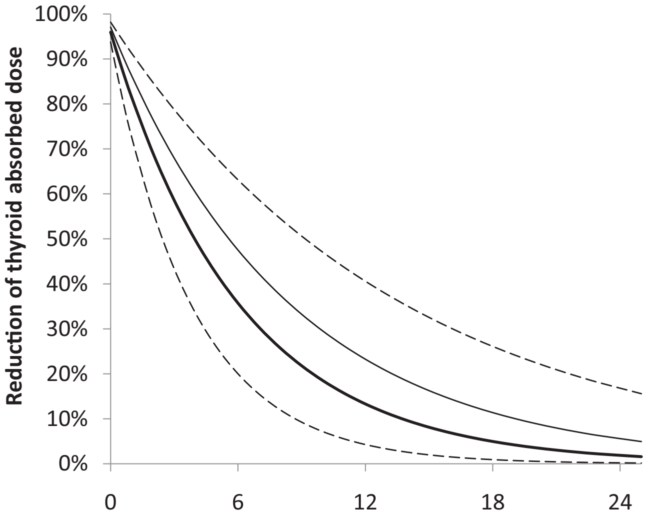

**FIG. 4.** Calculated dependence of the protective effect of thyroid blocking on the time of intervention and the rate of blood clearance for $^{131}$I. The *thin solid line* is determined with parameters for the iodine kinetics as published in ICRP78 (8) and is representative for subjects exceeding 40 yr of age in the present study. The *bold solid line* represents the theory based on mean data of the kinetics observed in subjects younger than 25 yr of age. The *lower* and *upper dashed lines* were deduced with the highest and lowest observed values, respectively.

clear accident. It depends on the iodine isotope; the activity incorporated; the fractional uptake into the thyroid being strongly correlated to the alimentary iodine supply; and the efficacy of protective measures like sheltering, iodine blockade, or food ban. Sheltering and iodine blockade are the methods of choice for short-term protection against passing radioactive clouds.

Two factors are decisive for the protective effect of thyroid blockage: the time of the intervention and the individual rate of plasma iodide clearance. The importance of both parameters becomes obvious in the differences of mean observed reduction in the thyroid-absorbed dose in the present investigation in the groups with 1 g SP and 100 mg KI after 8 h and the same interventions after 2 h, although the latter did not reach the level of significance. The lower efficacy in the SP group at nominal 2 h and in the KI group at nominal 8 h can both be explained by the concurrence of later mean time of intervention and higher blood clearance (Table 1).

The iodine isotope used in the present investigation, $^{123}$I, is neutron deficient. It is not produced in considerable amounts in nuclear fission and is irrelevant for radiation protection in nuclear accidents; $^{123}$I was chosen because it can be quantified precisely, has a short physical half-life of 13.27 h enabling baseline and intervention measurements at minimal time delay, and induces a low radiation dose to the volunteers. The risk of high radiation-absorbed doses to the thyroid comes from neutron-rich isotopes, especially $^{131}$I. A review of studies quantifying the protective effect of thyroid blockage with stable iodine after radioiodine incorporation can be found in a study by Kovari (9). The cited empirical data are decades old and show a wide and unexplained spread. More recent investigations are mainly computer simulations based on compartment model calculations. Zanzonico and Becker (10) found by such simulations that the protective effect of KI is less pronounced and decreases more rapidly with insufficient than with sufficient dietary iodine. This is confirmed by the present study. Data fit well to theory (Supplemental Data file, equation 4), indicating that the protective effect decreases exponentially with increasing transfer rate of thyroidal uptake. These findings, however, do not explain the high individual variations and the low observed dose reductions in regions with sufficient iodine supply (9).

A major cause of variations in the intervention efficacy, which has not been considered up to now, is the individual variability in the clearance of radioiodine from the blood plasma by physical decay, renal elimination, and transfer into the thyroid, which depends on both dietary intake of stable iodine and the rate of renal iodine clearance. The phase of thyroid uptake is shorter and the protective effect at a given time of intervention is less pronounced in people with fast iodine kinetics.

Because the renal filtration rate decreases physiologically with age, the reduction in the thyroid-absorbed dose is expected to be higher in older people compared with young adults. The mean rate of iodine clearance from the blood in subjects aged 40 yr or older in the present study was 0.123/h, which is slightly higher but in reasonable agreement with the value of 0.116/h used in ICRP78 (8). Clearance was significantly faster with 0.161/h in subjects younger than 25 yr of age and is most likely even faster in infants who have been reported to show both high rates of renal iodide clearance and fast iodide transfer into the thyroid, in small children even more pronounced than in adolescents (11, 12). Official guidelines for the prophylaxis after nuclear accidents (5, 6) recommend thyroid blocking almost exclusively for children and younger adults, but the assumptions on the time course of the inhibitory effect are mainly based on the data in ICRP78 and are too optimistic for this group of people.

The dependence of the thyroid dose reduction on iodine clearance from the plasma gives rise to a considerable variation in the expected efficacy of thyroid blocking that potentially can explain the wide range of published data for radioiodine reported by Kovari (9). A reliable prediction of the protective effect for the individual is not possible without definite knowledge of the actual blood iodine kinetics.

However, an individualized thyroid-blocking strategy is not feasible in case of an emergency. Instead, all reasonable measures should be taken in the vicinity of nuclear power plants to ensure the fastest possible distribution of blocking agent. Reasonable precautions are: 1) warranty of instantaneous notification of the authorities, *e.g.* by reinforced obligation on the operators to immediately notify faults, which may cause an release of radioactivity and by measuring networks for continuous monitoring of air-borne activity, 2) predistribution of tablets to households in close vicinity to the power plant (*e.g.* recommended in Germany up to a distance of 5 km) and to well-accessible central storage places in a larger area (*e.g.* in Germany up to 25 km), 3) active advice to the population and regularly repeated training of the local emergency services, and 4) improved means to alert the population. Another important measure to preventively reduce the adverse impact of incorporation of radioactive iodine after an accident in a nuclear power plant is to ensure good iodine supply of the population. This not only reduces the absorbed dose to the thyroid by reducing the maximum uptake and the rate of iodine elimination from the blood but also influences the sensitivity to the radiation. Cardis *et al.* (2) demonstrated in a case-control study in children from Belarus and the Russian Federation after the Chernobyl accident that the risk to develop thyroid cancer per radiation absorbed dose to the thyroid was 3 times higher in iodine-deficient areas than in areas with good supply.

The agent used for thyroid blocking turns out to be of minor importance. Both drugs KI and SP are associated with a minor risk of adverse reactions. The observed rate of side effects in a large field study in Poland on children and adults receiving iodine prophylaxis after the Chernobyl accident was low (13). Perchlorate, which has temporarily been used in the treatment of thyrotoxicosis and for prophylaxis against iodine excess derived from coronary angiography, was accused in the early 1960s of inducing aplastic anemia if administered in high doses over several months, but evidence is poor (4). One hundred milligrams of KI are sufficient to completely block thyroidal uptake. A higher dosage is unjustified because it will have no additional protective effect. One gram of SP also showed rapid and effective blockage and can therefore serve as alternative to stable iodine with equal efficacy, especially in individuals with known iodine hypersensitivity or elderly people at the risk of developing thyrotoxicosis. The lower dose of 0.1 g SP was slightly less effective.

### Conclusions

One thousand milligrams of SP is equally effective as 100 mg KI and may be used as an alternative for individuals with iodine hypersensitivity or older people at risk for thyrotoxicosis.

Official guidelines and recommendations for the prophylaxis after nuclear accidents most likely overestimate the efficacy of thyroid blocking for young adults and probably even more for children, being at higher risk of developing cancer after radiation exposure. Data used in the guidelines are representative for older adults. Because young people are at highest risk, the strategies of iodine distribution in the event of a nuclear accident should be adapted to ensure a significantly shorter intervention time.

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