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Pharmacological study of stable potassium iodide (KI) repeated prophylaxis in adult rats

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1 Introduction

Ingestion of stable iodine, mainly as potassium iodide (KI) tablets, is the only medical countermeasure available to prevent the binding of radioactive isotopes of iodine to the thyroid and to protect the gland from the occurrence of cancer. The international guidelines recommend the administration of a single dose of 130 mg KI in adults, corresponding to approximately 1.8 mg/kg, and envisage the possibility of a second dose in case of the impossibility to evacuate the populations. However, the nuclear reactors accidents at Fukushima in 2011 showed that the populations could be exposed to prolonged or repeated releases of radioisotopes of iodine for more than one week. In such situations, prolonged KI prophylaxis could be considered but no indication is currently available regarding the conditions for implementing repeated doses of stable iodine. The aim of this work was to study the protective effect of different KI doses in the rats in order to select an optimal KI dose which could be implemented in repeated prophylaxis. The pharmacokinetic parameters of stable iodine were then evaluated in the rats after oral ingestion of KI in order to model and assess a dose regimen for a repeated prophylaxis over 8 days.

2 Materials and methods

In a dose-response study, the effect of different oral single doses of KI (0.001; 0.01; 0.1; 1; 1.8; 5 mg/kg) was evaluated in the male Wistar rats (n=6 per dose) in terms of protection of the thyroid against the incorporation of radioactive iodine I-125 (1.11 MBq/kg) injected intravenously 1 hour after KI dosing. The thyroids were dissected 1 hour after exposure to I-125 and the total radioactivity of I-125 was determined by gamma counting (multidetector Packard).The plasma stable iodine concentration as a function of the time after oral single dose of 1 mg/kg KI was measured by inductively coupled plasma mass spectrometry (ICP-MS X Series II and iCAP Q, Thermo Electron) (n=6 per time point). The pharmacokinetic parameters of stable iodine were determined and the dose regimens were simulated using

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Phoenix WinNonlin v.6.3 software (Certara). The pharmacodynamic and pharmacokinetic modelling were performed using Phoenix WinNonlin v.6.3 and Prism v.5.0.1 (GraphPad) softwares. A dose regimen consisting of 1 mg/kg daily during 8 days was tested in rats (n=4 per time point) and verified through iodine plasma measurements at different times during the treatment (at 3; 5; 9 and 10 days).

3 Results and discussion

The protection of the thyroid in terms of avoided iodine I-125 activity compared with control rats as a function of KI dose is described by a saturation-type function (Figure 1). The results showed that avoided activities above 85% could be obtained for KI doses higher than 1 mg/kg. This dose could be hence selected as a minimum effective KI dose for repeated prophylaxis [1, 2].

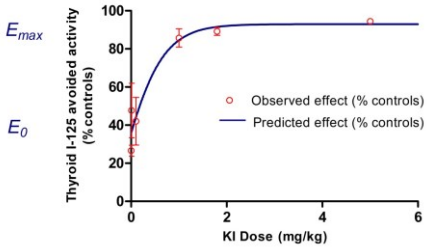

Fig.1. Stimulation model for iodine I-125 avoided activity in the thyroid as a function of stable KI dose (E_0: initial effect; E_{max}: maximum effect)

A correlation between plasma stable iodine I-127 and avoided I-125 activity in the thyroid was observed and showed that protection efficiencies from 63% to 88% could be achieved during 24h after oral administration of 1 mg/kg KI (data not shown). A dose regimen consisting of 1 mg/kg daily was modelled and tested in rats for 8 days. The plasma measurements at different times showed that stable iodine I-127 concentrations were consistent with the theoretical profile (Figure 2). This dose regimen should ensure high thyroid protection efficiencies throughout the treatment and could be proposed as an effective dose regimen for repeated KI prophylaxis [3].

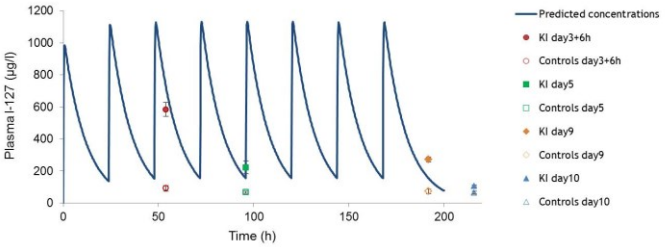

Fig.2. Plasma iodine concentrations measured at different times in rats treated by 1 mg/kg KI daily for eight days.

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