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QUALITY CONTROL OF ^{201}TlCl SOLUTION OBTAINED AT IPEN-CNEN/SP

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The radiopharmaceutical ^{201}TlCl (thallium-201 chloride) is used in nuclear medicine for myocardial visualization. The solution of ^{201}TlCl was prepared using ^{201}Tl obtained by irradiating a natural mercury target with protons from the CV-28 cyclotron installed at IPEN-CNEN/SP. This solution was subjected to different quality control processes required for its use in medicine. Some of these controls concerned the determination of the radionuclidic impurities: ^{200}Tl, ^{202}Tl and ^{203}Hg; the chemical identification of $^{201}Tl^{+}$; the hydrazine concentration, mercury contamination and the presence of phosphate. Furthermore, the biological distribution "in Wistar" rats and tests for sterility, pyrogenicity and toxicity were carried out. It was verified that the solution obtained was in the form of thallous chloride. This radiopharmaceutical gave good heart images in animals but due to the high levels of ^{200}Tl and ^{202}Tl its use in humans is not possible unless enriched ^{202}Hg is used as target in the irradiation.

The radioisotope ^{201}Tl is used in nuclear medicine to detect ischemia or infarction, because it has favorable decay properties that can be used to obtain myocardium images after intravenous injection.

A radioactive solution must be subjected to a severe quality control in order to be used for "in vivo" diagnostics. In this work the following controls of ^{201}TlCl solution were realized: radionuclidic, radiochemical, chemical, microbiological, biological and toxicity essay.

Experimental

Radionuclidic purity: The radionuclidic purity was performed by multichannel pulse-height analysis, using a Ge(Li) detector. The γ-spectrum of the ^{201}TlCl solution was also followed for approximately one week to confirm the half-lives of the product and the main impurities. Figure 1 shows the Ge(Li) spectrum of the ^{201}TlCl, the main peaks being the X-rays (70.8 keV and 80.2 keV) and photons (135 keV and 167 keV) of ^{201}Tl; photons (368 keV) of ^{200}Tl and photons (439 keV) of ^{202}Tl.

Radiochemical purity: The radiochemical purity of the ^{201}TlCl was checked by ascending paper chromatography to differentiate Tl^{+} and Tl^{3+}. Whatman 3MM paper and a solvent 1/10 ($Na_2HPO_4 \cdot 5H_2O$) and 9/10 (acetone) were used. Table 1 shows the

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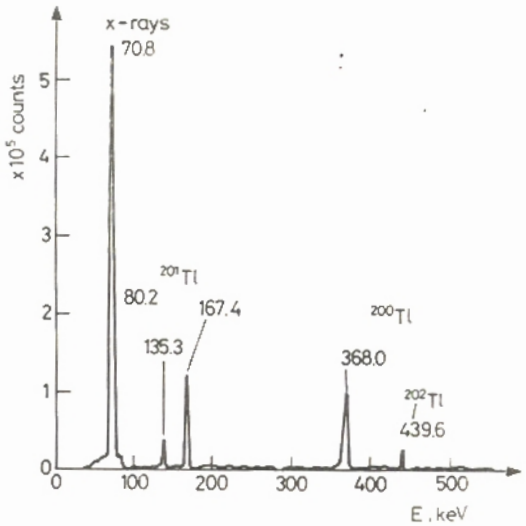

Fig. 1. Ge(Li) spectrum of ^{201}TlCl solution obtained at IPEN–CNEN/SP

Table 1

R_f values of Tl^+ and Tl^{3+}, and thallous ion percentage for ^{201}TlCl solutions of reference and obtained in this work. Whatman 3MM paper. Solvent: 1/10 $Na_2HPO_4 \cdot 5H_2O$ and 9/10 acetone, volume: 100 ml, run time: 30 minutes

No. of chromatography	R_f of ion Tl^+		R_f of ion Tl^{3+}		Ion Tl^+, %	
	Solution of reference	Solution of this work	Solution of reference	Solution of this work	Solution of reference	Solution of this work
1	0.00	0.00	0.90	0.89	99.9	99.0
2	0.00	0.00	0.91	0.88	99.9	98.5
3	0.00	0.00	0.90	0.90	99.9	99.5

resemblance of the Rf values obtained with this thallium solution and with the ^{201}TlCl solution of the Atomic Energy Commission of Canada, kindly given by the Nuclear Medicine Center of São Paulo's University, called here as solution reference.

Chemical purity: The hydrazine level in the ^{201}TlCl solution was determined by spectrophotometric adsorption analysis, using a calibration curve (Fig. 2) in accord with the method of NOVAK and HLATKY.[1] Table 2 presents the hydrazine concentration in the product when a 10% solution of hydrazine dihydrochloride/2N NaOH was used for thallium elution, in the Tl/Hg chemical separation process.

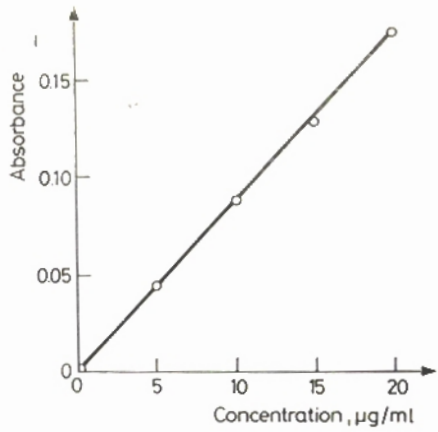

Fig. 2. Calibration curve for hydrazine determination in ^{201}TlCl solution (IPEN–CNEN/SP)

Table 2
Hydrazine concentration in the ^{201}TlCl product, when a 10% solution of hydrazine dihydrochloride/2N NaOH is used as thallium eluent

Absorbance	Hydrazine concentration, µg/ml
0.0601	6.9
0.0060	6.8
0.0062	7.0

The concentration of mercury impurity was checked via activation analysis using fast neutrons in the Radiochemistry Division of IPEN–CNEN/SP.

A ammonium molybdate spot test[2] was used to detect phosphate in the ^{201}TlCl solution, because tri-n-butyl phosphate was the stationary phase utilized in Tl/Hg separation by column extraction chromatography.

Microbiological control: The product was sterilized by filtration into a sterile multiinjection bottle through a 0.22 µm sterilized Millipore filter and by autoclaving at 120 °C for 1 hour. The sterility was controlled by inoculating the solution in three different culture media (simple broth, broth with thioglycolate and Sabouraud media). The pyrogenic test was done "in vitro" using the Limulus Test.

Biological control: For the biological distribution essays of ^{201}Tl, doses of 11.1 MBq (300 µCi/0.1 ml) of ^{201}TlCl solutions were used. The one obtained in this work and the

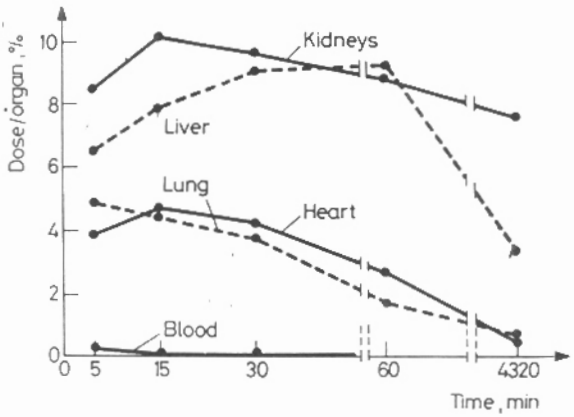

Fig. 3. Biological distribution of ^{201}TlCl (IPEN–CNEN/SP), at different times after administering dose to rats

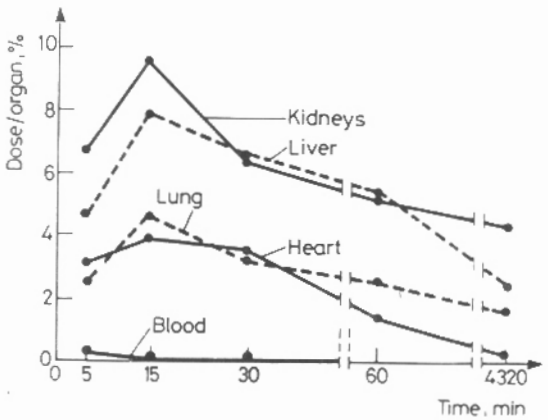

Fig. 4. Biological distribution of ^{201}TlCl solution (Reference), at different times after administering dose to rats

other given by the Nuclear Medicine Center were administered intravenously in adult male "Wistar" rats with an average weight of 250 g, anaesthetized with "urethane" solution (100 mg/100 g body weight).

The animals were sacrificed 5, 15, 30, 60 minutes and 72 hours after administration of the dose. Four animals were sacrificed at each time. Blood samples were collected and the following organs were taken out: heart, lung, kidney and liver. Each was individually washed and counted in a well–type scintillation counter (Automatic Counts "Nuclear Chicago") and compared with a standard aliquot of ^{201}Tl.

The percentage of dose uptake in each organ was estimated by the following expression, where cpm is counts per minute

$$\% \text{ dose} = \frac{\text{cpm in each organ}}{\text{cpm of standard } (^{201}\text{Tl-chloride})}$$

The data were expressed as percentage of administered dose per organ at the different times studied (Figs 3 and 4).

Toxicity testing: The toxicity, essays of ^{201}TlCl solution were made according to the United States Pharmacopoeia specification.[3] Doses of 11.1 MBq or 300 μCi/0.3 ml were administered intravenously in five rats weighing 250–300 g which were kept for 72 hours in a cage for observation.

Results and discussion

Figure 1 does not indicate the presence of ^{203}Hg in the ^{201}TlCl solution at the end of chemical process (about 36 h after target irradiation), but it shows contamination with ^{200}Tl and ^{202}Tl. This contamination comes from the fact that the target used for irradiation was of natural mercury with an isotopic composition (^{204}Hg: 7%, ^{202}Hg: 30%, ^{201}Hg: 13%, ^{200}Hg: 23%, ^{199}Hg: 17% and ^{198}Hg: 10%) that leads to this radionuclidic impurity.

It was observed (Table 1) that the thallium chloride solution obtained at IPEN–CNEN/SP was 99% in the form of Tl^+.

The hydrazine concentration found in the final ^{201}TlCl solution (Table 2) was about 7 μg/ml. This value corresponds to a hydrazine concentration in rats of 2.8 μg/kg, less than the lethal value given in the "Merck Index" (LD_{50} in rabbits = 25 mg/kg).[4]

The mercury concentration found in ^{201}TlCl final solution was 10–30 ng/ml, therefore, 4–12 ng/kg in rats, less than the lethal value related in the "Merck Index" for mercury (LD_{50} oral way in rats = 37 mg/kg).[5]

The ammonium molybdate spot test performed with the ^{201}TlCl final solution was negative, since the blue color characteristic of P_2O_5 was not observed. This negative spot test assures that less than 1.25 μg of phosphate is present in the product.

The ^{201}TlCl solution was apyrogenic when subjected to the Limulus Test and was sterile when sowed in the culture media described above.

The myocardial uptake rate presented in Figs 3 and 4 was similar. Figure 3 shows a myocardial uptake of ^{201}TlCl solution (IPEN–CNEN/SP) of 4.7% at 15 minutes after injection in the animals, which decreases to 0.5% 72 hours after injection, and a rapid

blood clearance at 5 minutes. The radioactivity concentration in the lung from $^{201}TlCl$ after 15 minutes stayed lower than that of the myocardium. While in Figure 4 the myocardial uptake of $^{201}TlCl$ solution (Reference) at 15 min. was 3.9%, which decreased to 0.3% 72 hours after injection and the blood clearance at 5 min was rapid too. The radioactivity concentration in the lung from $^{201}TlCl$ solution (Reference) was lower than that of the myocardium only at 30 minutes.

None of the animals utilized in the toxicity essays of $^{201}TlCl$ solution (IPEN–CNEN/SP) presented abnormality symptoms after 72 hours of observation.

Conclusion

By the quality control tests performed with the $^{201}TlCl$ solution obtained at IPEN–CNEN/SP, it is possible to conclude that this $^{201}TlCl$ solution is in the form of thallous chloride, is apyrogenic, sterile and not toxic. This radiopharmaceutical can give a good heart image in animals between 15 to 30 min after dose injection with low lung interference. Its use in humans is not possible unless enriched ^{202}Hg is used as target.[6]

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