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The Excretion of Thallium (I)-Ions Into the Gastrointestinal Tract in situ of Rats* **

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Abstract. 1. The excretion of Tl^+-ions from blood into the lumen was investigated on the stomach and an segments of jejunum, ileum, colon ascendens, and colon descendens in situ of anesthetized rats using the pendular perfusion technique. The kidneys of the rats were tied-off. Tl^+-ions were administered i.v. at the beginning of the experiments as ^{204}Tl-(Tl_2SO_4). The amount of ^{204}Tl-labeled Tl^+-ions in the perfusion fluid of the gastrointestinal sections was calculated from the ^{204}Tl concentration and the fluid volume.

2. Excretory activity for Tl^+-ions is highest in the the jejunum; it is followed by the colon ascendens. The ileum and the colon descendens show nearly equal excretory activity which is just half of that measured in the jejunum. The amount of Tl^+-ions excreted into the stomach is negligible.

3. At the end of the experiment in the perfusion fluid of all segments of the intestine the concentration of ^{204}Tl is statistically significently higher than that in plasma.

4. In jejunal and colonic (descendens) segments the amount of Tl^+-ions excreted increases with increasing i.v. doses tested from 2×10^{-8} up to 2×10^{-6} moles/kg body weight.

Introduction

The recommandation of ferrihexacyanoferrat (II) in cases of thallium intoxications dates back to Nigrovic (1963) and Nigrovic and Catsch (1965) who extrapolated the experiences of the removal of radiocesium by Prussian blue to

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the removal of ions of a comparable size of their ionic diameters. Further investigations in the group of A. Catsch made it probable that not only thallium (I) ions ingested are prevented from being absorbed but also thallium (I) ions excreted into the gastrointestinal canal were prevented from being reabsorbed (Heydlauf 1969). However, it is still unknown where in the gastrointestinal tract thallium (I) ions are excreted, e.g., by the liver with bile, or across the mucosal epithelial cells of the gastrointestinal tract.

On the excretion of thallium (I) ions in bile was reported already by Schäfer and Forth (1980). In the following paper the results of experiments will be published in which the excretory function for thallium (I) ions of the stomach and different segments of the intestinal canal, i.e., jejunum, ileum, colon ascendens, and colon descendens was investigated. The results were already presented during the spring meetings of the DPhG 1978 and 1979 (Henning and Forth 1978; Forth and Henning 1979).

Materials and Methods

Animals. Male Wistar rats (240–300 g body weight) were obtained from W. Gassner, Sulzfeld, FRG. The animals were fed with Höveler standard diet. Twenty hours before the experiment food was withdrawn; the rats had always free access to drinking water.

Substances. ^{204}Tl-(Tl_2SO_4) radioactively labeled ^{204}Tl was obtained from Buchler-Amersham Braunschweig, FRG; specific activity: 2.19 mCi/μM. Carrier: Tl_2SO_4, MG 504.8 Dalton, Merck AG Darmstadt, FRG; art. Nr. 8135, p.a. grade.
Polyethylenglycol-4,000, MG 4,000 Dalton, Merck AG Darmstadt, FRG; art. Nr. 9727.
^{14}C-polythylenglycol was obtained from Buchler-Amersham, Braunschweig, FRG; specific activity: 11.4 mCi/g, i.e., 45.6 mCi/mM.
^{3}H-polyethylenglycol 4,000 was obtained from New England Nuclear, Boston, USA; specific activity: 0.7 mCi/g, i.e., 2.8 mCi/mM.
Ferrihexacyanoferrate (II) (Prussian blue) was obtained as Antidotum Thallii Heyl from Heyl, Berlin.

Experiments on Rats

Determination of the Half-Life of ^{204}Tl-Radioactivity in Plasma of Rats. Anesthesia with urethane (1.25 g/kg); into the vena jugularis and the arteria carotis PVC tubes (1 mm ∅) were inserted. In one group of animals the blood supply of the kidneys was tied-off. Tl^+-ions were injected into the vena jugularis in a dose of 1.85×10^{-5} moles/kg as ^{204}Tl-(Tl_2SO_4) and in a volume of 3.7 ml/kg isotonic saline. After 1, 5, 10, 20, 40, 60, and 120 min 0.2 ml blood were withdrawn from the arteria carotis. The blood was centrifuged for 10 min at 300,000 rpm. The radioactivity in 0.05 ml plasma was determined. Blood clotting was inhibited by filling the arterial tube with heparin solution (0.1%). The body temperature of the rats was controlled and kept at 37° C.

Determination of the Secretion of $^{204}Tl^+$-Radioactivity Into the Gastrointestinal Tract. Anesthesia with urethane (1.25 g/kg). Atropinsulfate, 0.05 mg/kg was injected s.c. before the anesthesia. PVV-tubes were inserted into the vena jugularis and into the arteria carotis. The abdomen was opened, the blood supply of the kidneys was tied-off. Jejunal, ileal, and colonic segments were prepared and connected by silicon tubes with fluid reservoirs. Jejunal segments: starting with the flexura duodenojejunalis to 7 cm distally. Ileal segments: starting with the valvula ileocaecalis to 7 cm

proximally. The colon was divided into two parts, an upper one, the colon ascendens, and a lower one, the colon descendens (length of the colon segments: 7 cm). The stomach was opened at the pylorus; the esophagus was tied-off immediately before entering the stomach. All gastrointestinal segments were washed out with isotonic saline (20 ml) solution of body temperature. The rats were fixed on a heated plate (37° C) to which a battery of three reservoir vessels has been attached. The heated plate was moved up and down against the second battery of reservoir vessels (maximum distance in height: 12 cm). Each gastrointestinal segment was connected with two reservoir vessels. By moving the rat against the mobile reservoir vessels, the gut segments were perfused and the stomach was filled and emptied with a frequence of five pendular movements per min. The determination of the perfusion volume was possible by the simultaneous measurements of the radioactivity of ^{3}H (β_0^- 0.018 MeV) of ^{3}H-polyethyleneglycol and ^{204}Tl (β_0^- 0.765 MeV). The total amount of the ^{204}Tl-radioactivity excreted into the different sections of the gastrointestinal tract were calculated by multiplying the concentration of the ^{204}Tl-radioactivity with the perfusion volume.

In order to ensure a narrow range of the molecular weight of the radio actively labeled polyethyleneglycols only rechromatographed material was used (Sephadex LH 20, 0.3% NaCl). When having added cold polyethyleneglycol-4,000 to the radioactively labeled material up to a concentration of 0.1% in all gastrointestinal segments investigated here within 1 h 98% ± 3 ($s_{\bar{x}}$; $n = 40$) of the ^{14}C- or ^{3}H-radioactivity administered was recovered.

The frequency of removing samples from the perfusion fluid is limited by that time which is needed for the complete mixing by the movements of the storage vessels up and down. This time was determined by filling the gastrointestinal segments with 4 ml of isotonic saline containing 0.2 ml ^{14}C-polyethyleneglycol-4,000 solution (0.1%). During the following minutes the ^{14}C-radioactivity in the perfusion solution was determined. Homogenous mixture was achieved in the stomach 2 min later and inthe lumen of the intestinal segments 3 min later. The experiments were carried out with five rats. Thus, the intervalls of taking samples was fixed to no less than 5 min.

Movement of Fluid in the Gastrointestinal Segments. The movement of fluid in the gastrointestinal segments was measured in the stomach, filled with 3 ml isotonic saline containing 0.1% ^{14}C-Polyethyleneglycol-4,000, and in the jejunum and colon descendens filled with 5 ml of the same fluid. By the change of the ^{14}C-radioactivity in the perfusion fluid the movement of fluid across the mucosal epithelial layer can be calculated.

In the stomach a linear increase of the fluid volume within the experimental time of 60 min was observed. At the end of the experiment nearly 0.3 ml fluid was secreted ($\bar{x} = 0.28$; $s_{\bar{x}} = 0.04$; $n = 6$). In the jejunum and the colon the volume of the perfusion fluid decreased linearly within the experimental time. Calculated per cm intestinal length the absorption of fluid amounts to 0.05 ml in the jejunum ($s_{\bar{x}} = 0.006$; $n = 8$) and to 0.047 in the colon per cm and hour (SEM = 0.005; $n = 6$).

Since there remained residual fluid inthe gastrointestinal segments from the washing procedure which could not be removed by carefully blotting the segments in situ, the experiments were started after an equilibration period of 5 min for homogenous mixture of the gastrointestinal contents. In other words, the sample at the time 0 for the measurement of the ^{3}H-polyethyleneglycol-radioactivity by which the volume of the perfusion fluid was determined was taken after this equilibration period.

Measurement of the Radioactivity. ^{204}Tl emmits β^-- (98%) and K-rays (2%). In the following experiments, the β-radioactivity was measured in a liquid scintillation counter (β-Scint 5,000 Berthold-Friesecke, Wildbad, FRG). The fluids containing ^{204}Tl-, ^{14}C-, or ^{3}H-radioactivity were pipetted to 9 ml scintillation fluid mixed according to Bray (1960). Where necessary, a correction for quenching of the probes was carried out using an internal standard.

Statistics. The results were calculated as means ($\bar{x}$) of experiments ± the standard error of the mean ($s_{\bar{x}}$). The significance of the differences between the mean values of different groups was determined using students'*t*-test (cf. Weber 1972) prerequisit the *s*-test indicated that the handling of the results by the *t*-test was allowed. In cases of doubt in order to determine the probability of the error the U-distribution according to Wilcoxon, Mann, and Whitney was used (cf. Weber 1972).

Results

The Time Course of the Concentrations of ^{204}Tl in Plasma of Anesthetized Rats with Tied-Off Blood Supply of the Kidneys

Since it is well known that Tl^+-ions are excreted across the kidneys (Frey and Schlechter 1939), the time course of the ^{204}Tl-radioactivity in plasma was followed in rats with intact blood supply of the kidneys and animals whose blood supply of the kidneys was tied-off. The ^{204}Tl-radioactivity in the plasma was measured 1, 5, 10, 20, 40, 60, and 120 min after the administration of 1.85×10^{-8} moles ^{204}Tl-(Tl^2SO^4) per kg body weight i.v. corresponding to 7.4×10^7 cpm/kg. Two phases of the elimination of the ^{204}Tl-radioactivity could be discerned in rats with intact blood supply of the kidneys: $y_1 = 10.37 - 0.1803\,x$ (rapid phase) and $y_2 = 8.99 - 0.0099\,x$ (slow phase). Apparently there is no difference in the time course of the elimination of the ^{204}Tl-radioactivity from plasma when the blood supply of the kidneys is tied-off: $y_{1a} = 10.02 - 0.159\,x$ and $y_{2a} = 9.03 - 0.0093\,x$. The equations were calculated from means of 5–15 experiments. There is no statistically significant difference between the equations y_1 and y_{1a} as well as y_2 and y_{2a}.

The Time Course of the Concentration of ^{204}Tl in the Plasma After a Bolus Injection and Infusion of ^{204}Tl-(Tl_2SO_4)

The concentration of ^{204}Tl in plasma of rats was measured after a bolus injection of ^{204}Tl-(Tl_2SO_4) i.v. (dose 1.85×10^{-8} moles/kg corresponding to 7.4×10^7 cpm/kg) and, in addition to the bolus injection, during an infusion of ^{204}Tl-radioactivity starting 12 min after the bolus injection. Infusion velocity: 0.05 ml per h; concentration: 5×10^{-6} M ^{204}Tl-(Tl_2SO_4). After a rapid fall of the concentration of ^{204}Tl in plasma within 20 min the concentration of ^{204}Tl remained unchanged up to 60 min after the bolus injection. During infusion of ^{204}Tl-radioactivity between 20 and 60 min the concentration of ^{204}Tl in plasma is roughly doubled but not more stable than after the bolus injection of the ^{204}Tl-radioactivity only. Since in these experiments no difference in the excretion of ^{204}Tl-radioactivity into the stomach, the jejunum, and the colon could be observed, the following experiments were carried out without an additional infusion of ^{204}Tl-radioactivity after the bolus injection of the ^{204}Tl-(Tl_2SO_4) dose.

The Time Course of the Excretion of ^{204}Tl Into the Gastrointestinal Tract

The excretion of ^{204}Tl calculated as percent of the dose administered into the stomach, the jejunum, and the colon descendens was measured after a bolus injection of 1.85×10^{-6} moles ^{204}Tl-(Tl_2SO_4)/kg i.v. The results of these experiments are summarized in Fig. 1. Apparently the excretory function of the

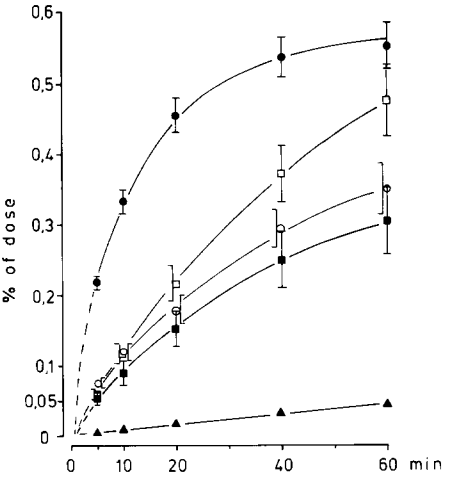

Fig. 1. Excretion of ^{204}Tl-radioactivity in the stomach and intestinal segments of jejunum, ileum, colon ascendens, and colon descendens in anesthetized rats in situ. At the beginning of the experiment ^{204}Tl-(Tl_2SO_4) was injected i.v. in a dose of 1.85×10^{-6} moles/kg; *ordinate:* amount of excreted ^{204}Tl-radioactivity, percent of the dose. *Abscissa:* time in minutes. $\bar{x}$ of 7–9 experiments $\pm$ $s_{\bar{x}}$. jejunum (●); ileum (○); colon ascendens (□); colon descendens (■); stomach (▲)

stomach for Tl^+-ions is negligible. In the jejunum, there is a rapid increase of the amount of the excreted ^{204}Tl-radioactivity within the first 20 min. The excretion of Tl^+-ions in the following 40 min is much slower. At the end of the experiment the amount of ^{204}Tl-radioactivity excreted across the epithelium of a jejunal segment of roughly 7 cm length amounts to somewhat more than 0.5% of the dose administered. In the colon descendens the amount of ^{204}Tl-radioactivity excreted increases with time steadily. At the end of the experiment little less than 0.3% of the dose are excreted across the epithelium of the colonic segment of about 7 cm length. There is apparently no major difference between the excretory function of the colon ascendens and the colon descendens segment for Tl^+-ions as can be taken from Fig. 1.

The Concentration of ^{204}Tl-Radioactivity in Plasma and in the Perfusion Fluid of the Intestinal Segments

The time course of the concentrations of the ^{204}Tl-radioactivity in plasma and in the perfusion fluid of the jejunum, the colon ascendens segments, and the ileum is summarized in Fig. 2. For the sake of simplicity the concentrations of ^{204}Tl in the plasma of all experiments are combined, and the standard error of the mean of these values is indicated by the hatched area. At the end of the experiment the concentration of the ^{204}Tl-radioactivity in the perfusion fluid of all intestinal segments is statistically significantly higher than that in the plasma of the rats. In the jejunal lumen, i.e., the segment with the highest excretory activity for Tl^+-ions, the concentration of ^{204}Tl-radioactivity in the lumen is already 20 min after the beginning of the experiment statistically significantly higher than that in the plasma. For the other segments, i.e., colon ascendens and ileum, the concentration of the ^{204}Tl-radioactivity exceeds that of the plasma statistically significantly 20 min later, i.e., 40 min after the i.v. dose.

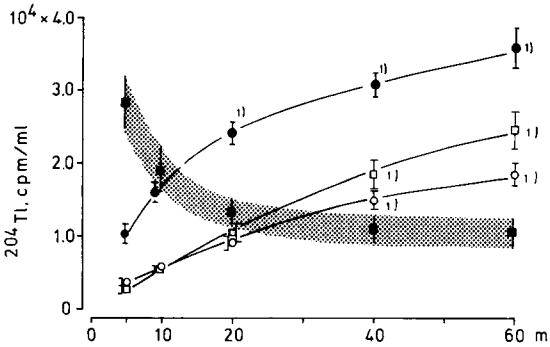

Fig. 2. Concentration of ^{204}Tl-radioactivity in plasma and the perfusion fluid of jejunum, ioleum, and colon ascendens of anesthetized rats in situ. At the beginning of the experiments ^{204}Tl-(Tl_2SO_4) was injected i.v. in a dose of 1.85×10^{-6} moles/kg corresponding to 7.4×10^7 cpm/kg. *Ordinate:* ^{204}Tl-radioactivity, cpm/ml. *Abscissa:* time in minutes. x of 4–9 experiments $\pm s_{\bar{x}}$. All values of the ^{204}Tl-radioactivity in plasma were combined ($n = 20-36$). The standard error of the plasma values is symbolized by the hatched area. jejunum (●); colon ascendens (□); ileum (○); plasma (■) (hatched area). [1]) indicates a statistically significant different concentration of ^{204}Tl-radioactivity as compared with that in plasma

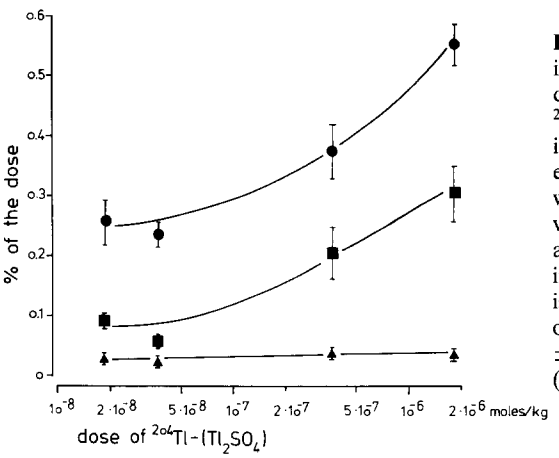

Fig. 3. Excretion of ^{204}Tl-radioactivity into stomach, jejunum, and colon descendens with increasing doses of ^{204}Tl-(Tl_2SO_4) in anesthetized rats in situ. At the beginning of the experiment a ^{204}Tl-(Tl_2SO_4) dose was injected i.v. according to the values indicated in the *abscissa.* The amount of ^{204}Tl–radioactivity excreted into the gastrointestinal segments is indicated on the *ordinate,* percent of the dose. $\bar{x}$ of 6–10 experiments $\pm s_{\bar{x}}$. jejunum (●); colon descendens (■); stomach (▲)

The Excretion of ^{204}Tl Into Gastrointestinal Segments with Increasing Doses

The dose of the bolus injection of ^{204}Tl-(Tl_2SO_4) were increased from 1.85×10^{-8} moles/kg up to 1.85×10^{-6} moles/kg. The experiments were carried out on the stomach, jejunal segments and segments of the colon descendens (Fig. 3).

In the stomach there is apparently no change of the amount excreted over the entire dose range. In the jejunum as well as in the colon descendens with increasing doses of ^{204}Tl-(Tl_2SO_4) the amount of ^{204}Tl-radioactivity increases. When comparing the results obtained with the highest and the lowest dose of

^{204}Tl-radioactivity administered, in the jejunum and in the colon descendens the amount of ^{204}Tl-radioactivity excreted is doubled or even more than doubled.

Discussion

The method of the pendular perfusion was used in our laboratory for the first time. This method by which three segments of the gastrointestinal tract were perfused simultaneously has the advantage of the smallest volume possible for the perfusion, i.e., of the stomach by 3 ml and the intestinal segments of 4–5 ml isotonic saline. It appears possible to develope storage vessels which allow even smaller perfusion volumes. Furthermore, the pendular perfusion using the gravity as driving force guarantees an especially gentle perfusion with a minimum of mechanical torquation of the intestinal segments. The physiological function of the intestinal segments as well as of the stomach can be derived simply from the absorption and/or secretion of fluid across the mucosal epithelium. For a more veliable evaluation of the secretory function of the stomach, e.g., its capacity to excrete protons, is concerned further experiments are necessary.

The absorption of fluid measured with the pendular perfusion method is less than that measured in tied-off segments in vivo of rats (Forth et al. 1968a, b): jejunum 0.1–0.13 ml per cm and h; colon 0.09–0.12 ml per cm and h. This may be due to the heavier operation procedures as compared to that of the simple tied-off segments. Furthermore, it should be added that in contrast to the experiments on tied-off segments the rats here were anesthetized during the entire experimental time; this may be the cause of a diminished pouring of blood across the intestinal vessels.

Tl^+-ions were excreted into the intestinal tract mainly in the jejunum. According to the capacity of excretion it is followed by the colonic segments of which the ascendent segment is superior to the descendent part by the epithelium of which at the end of the experiment just half of that amount of Tl^+-ions were excreted as by that of the jejunum. The amount of Tl^+-ions excreted by the ileal segments is in the same order of magnitude as that of the colon descendens.

Surprisingly, into the stomach Tl^+-ions are excreted only in negligible amounts. If Tl^+-ions interfere also in the gastrointestinal tract with the transport process for potassium ions as it was shown for erythrocytes (Gehring and Hammond 1964), for muscle tissue (Ling 1977; Mullins and Moore 1960), for the kidneys (Frey and Schlechter 1939; Lameijer and van Zwieten 1977; Lund 1956; Rauws 1974), and the jejunum as well as the colon of rats (Henning 1979; Henning and Forth 1977), then it was to be expected that according to the capacity of the gastric epithelium to excrete K^+-ions (Nordgren 1963) that also Tl^+-ions would have been excreted into the stomach lumen. It may be that the

concentration of Tl^+-ions in that compartment of the gastric mucosal epithelial cells from which excretion occurs was to low as there was any chance for a competition of Tl^+-ions with K^+-ions for the binding sites of the transport mechanism. It is worthwile to remember that the intracellular K^+ content being roughly $120-150 \times 10^{-3}$ M. Unfortunately, no higher doses of Tl^+-ions that $1.85 \times {}^{-6}$ moles/kg were administered because of the danger of intravascular hemolysis after Tl^+ doses above of 5×10^{-6} moles/kg in 3.7 ml isotonic saline/kg. Assuming an intracellular compartment of 40% of the body weight (200 g) and an equal distribution of Tl^+-ions in this compartment (kidneys were tied-off!) following to a total uptake of Tl^+-ions into the intracellular compartment the highest concentration of Tl^+-ions could have reached about 1.5×10^{-5} M. This is roughly 10^4 times less than the intracellular K^+ concentration mentioned above.

Tl^+-ions are transported against a concentration gradient. This holds true for all intestinal segments tested. Again the jejunum is the segment with the highest excretory activity. It may be that the excretion of Tl^+-ions is a secretory process, i.e., a transport of Tl^+-ions from S → M under clamped potential conditions has been proven (Schäfer et al. 1981).

For the first glance it may appear surprising that in the intestinal segments the amount of Tl^+-ions excreted increases with increasing doses. This indicates that the transport sites are not saturated with Tl^+-ions not even after the administration of the highest dose. Unfortunately, the capacity of the intestinal tract to excrete Tl^+-ions could not be titrated since the administration of higher doses caused an intravascular hemolysis.

The effectivity of the gastrointestinal canal to excrete Tl^+-ions can be calculated for the highest dose administered, i.e., 1.85×10^{-6} moles/kg. We assume the total length of the ileum of 40 cm. The entire length of the colon of rats of 220–250 g body weight amounts to 18 cm (unpublished results, Henning 1979). When summing up the percent fraction of the amounts excreted across the intestinal epithelium per h one may obtain roughly 7.7% of the dose administered. In the same time 0.07% of the dose of Tl^+-ions were excreted by bile into the gastrointestinal tract (Schäfer and Forth 1980). In other words, the excretion of Tl^+-ions into the gastrointestinal tract amounts to nearly 8% of the dose administered. This is just half of that amount excreted by the kidneys within 1 h (Lameijer and van Zwieten 1977). In these experiments the Tl^+-dose was about 5×10^{-5} moles. It must be admitted that these authors did not report an intravascular hemolysis after the i.v. injection. However, there may be a difference in the concentration of the fluid containing Tl^+-ions. In the experiments presented in this paper the concentration of the Tl^+-ions was 5 mM, i.e., about 1 mg per ml. Furthermore, in contrast of the experiments of Lameijer and van Zwieten (1977) in our experiments the blood supply of the kidneys was tied-off.

The results of the presented investigations show clearly that Tl^+-ions are excreted in the entire length of the intestinal canal. This offers the possibility to trapp excreted Tl^+-ions in the gastrointestinal tract by ferrihexacyanoferrat (II) (cf. Heydlauf 1979; Kamerbeck et al. 1971; Stevens et al. 1974; van Kesteren et al. 1980).

This antidote must be dosed around the clock in order to prevent any concentration of free Tl^+-ions which are absorbed from the gastrointestinal tract rapidly and nearly completely (Leopold et al. 1969).

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