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MODIFICATION OF RADIATION HAZARDS TO THE ADULT AND ITS FETUS FROM NUCLEAR MEDICINE PROCEDURES*

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Abstract

The effects of perchlorate on the quantitative distribution patterns of ^{99m}Tc intravenously administered as pertechnetate in the adult and its fetus have been studied in a variety of situations and are summarized. Perchlorate, when administered shortly before ^{99m}Tc, suppresses concentration in the adult thyroid gland, stomach, and urine; but tends to increase intestinal localization; and prolongs disappearance from the blood. It also inhibits concentration in the placenta and fetus. The greatest reductions in fetal concentrations occur in the femur, spleen, stomach, and thyroid, The estimated radiation absorbed doses to the human fetus are about 80 mrad/mCi for ^{99m}Tc-pertechnetate alone, and around 30 mrad/mCi if pretreatment with perchlorate is used. Previously localized ^{99m}Tc may be released by perchlorate from the thyroid gland and stomach; but, not from the placenta and fetus.

Introduction

Evaluation of radiation hazards from radiopharmaceuticals is generally based on the theoretical calculation of absorbed energy and compared with radiation doses from diagnostic x-ray procedures on similar anatomical areas. Deficiencies in this approach are due to nonuniformity in the radiation field caused by biologic distribution and to differences in the qualtiy of radiations from radionuclides. Energy released by electron capture and internal conversion may result in radiation damage greater than that produced from other decay modes, because highly excited atoms are formed and result in the disintegration of biomolecules into which they are incorporated. Decay by internal conversion occurs about 11% of the time in ^{99m}Tc ($t_{1/2}$ 6 h; γ 140 keV) which, in the form of pertechnetate, is possibly the most widely used radiopharmaceutical, an estimated 1 to 5% of the world population being examined with it yearly. Technetium-99m appears to be incorporated into biomolecules in some fetal tissues as well as in adult tissues. Another isotope of technetium, ^{99}Tc ($t_{1/2}$ 2.1 × 10^5 y; β^- 0.29 MeV), also concerns radiation protectionists because it is produced

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in substantial amounts [1] in the generation of electricity by nuclear reaction. Radiation absorbed doses resulting from the biologic distribution of these isotopes when they are administered as pertechnetate may be changed if the deposition can be altered.

Pertechnetate ion is concentrated by mammals very much like iodide, presumably because of similar anionic size, shape, and charge, [2] i.e., in the thyroid and salivary glands, urine, stomach, intestine, choroid plexus, and fetus. The quantitative distribution pattern of pertechnetate is influenced in the presence of iodide through competition for binding sites. This is to say that distribution is altered by iodide concentrated previously, administered simultaneously, or given subsequently to the pertechnetate. Analogous effects are produced with other anions of similar configuration and charge, such as perchlorated, fluoroborate, thiocyanate, and nitrate. These agents are effective only so long as the iodide or pertechnetate remains anionic, and not after organification has occurred. Perchlorate is used generally in nuclear medicine when ^{99m}Tc-pertechnetate is employed to produce images of the head. The use of perchlorate reduces the accumulation of radioactivity in the choroid plexus and salivary glands which may obscure abnormalities, but does not interfere with tests of iodine metabolism that may be made subsequently. The accumulation of radioactivity in other areas is changed by perchlorate, of course, and this in turn alters the radiation absorbed doses.

The investigations presented here were designed to determine the quantitative distribution pattern of pertechnetate and its modification with perchlorate.

Investigations and Results

Gastrointestinal Concentration

Technetium-99m, administered intravenously as pertechnetate, concentrates in the gastric mucosa and intestinal wall, and is excreted in the feces. Quantitative determinations of ^{99m}Tc localized in the stomach and intestine was made by first obtaining the count rate over, and an image of, the stomach after oral administration of an accurately assayed preparation of ^{99m}Tc-sulfur colloid, free of pertechnetate. This radiopharmaceutical is not absorbed from the gastrointestinal tract and may be recovered quantitatively in the feces. When the ^{99m}Tc had disappeared through fecal excretion and decay (in about three days), an accurately assayed solution of Na^{99m}TcO$_4$ was administered intravenously. The resulting count rate over the stomach, corrected for background and decay,

was related to the count rate per μCi obtained for the colloid, so that the percent of injected ^{99m}Tc from pertechnetate in the stomach could be calculated for any observation time. Similar observations were repeated over the intestine as the ^{99m}Tc moved through. Data were acquired by continous recording during the first thirty minutes after injection, the subject remaining immobile. Curves constructed with these data (Fig. 1) show an increasing localization to about 12% of the injected ^{99m}Tc, mostly in the fundus; some of the ^{99m}Tc appears to be removed by peristaltic action from time to time. Continuation of the study during 24 h by repeated single measurements provided data from which the upper curve in Fig. 2 was drawn and showed a maximum uptake of about 20% of the injected ^{99m}Tc. The lower curve in this figure represents results obtained on repetition of the study with oral administration of 0.5 g $NaClO_4$ 15 min before the ^{99m}Tc-pertechnetate was given intravenously. In this case only about 1% of the ^{99m}Tc could be detected in the stomach. Intake of food was noted to stimulate accumulation of ^{99m}Tc in the stomach in either situation.

The dependence of gastric secretion of ^{99m}Tc on the quantity of perchlorate administered was studied in a dog in which a Heidenhan pouch† had been produced. Perchlorate was administered intravenously 10 min before ^{99m}Tc-pertechnetate was given, also intravenously. The results, represented graphically in Fig. 3, show little effect from 0.32 mg/kg body weight of $NaClO_4$ on the amount of ^{99m}Tc present in the gastric secretions; about a tenfold reduction with 3.2 mg/kg; and a maximum reduction of about 100 times with 32 mg/kg, without further inhibition when 48 mg/kg were given.

A similar suppression of gastric secretion of ^{99m}Tc with perchlorate in humans was found with use of the quantitative techniques described. A comparison of the effect from 0 and 2 g of perchlorate shows (Fig. 4) respective gastric uptake values of 6.4% and 0% at 2 h, and 7% and 0% at 17 h. Corresponding values for the colon were 2.7% and 6.9%, and 20% and 39%, showing a reversal of the perchlorate effect for the two regions.

Urinary Excretion

Quantitative recovery of urine from about 20 subjects, after an intravenous injection of pertechnetate, showed wide variations in ^{99m}Tc excreton between individuals. The competition which seems to occur between

†A small closed off portion of the stomach constructed with an opening through the abdominal wall to obtain gastric juice.

fecal and urinary excretion of ^{99m}Tc is influenced by perchlorate. This is illustrated by studies for two subjects (Fig. 5), where the cumulative recoveries after two days varied by a factor of about two, with slightly over 30% being recovered in one case and almost 70% in the second. In each situation, administration of 2 g $NaClO_4$ resulted in reduction of ^{99m}Tc in the urine by about 10% of the injected amount.

Concentration by the Thyroid and Salivary Glands

Uptake in the thyroid and salivary glands of ^{99m}Tc from pertechnetate has been well studied in humans [3]. The 1 or 2% localization in the thyroid gland of euthyroid and up to 20% uptake by hyperthyroid individuals are virtually abolished when perchlorate is administered orally about 15 min before intravenous ^{99m}Tc-pertechnetate. Localized ^{99m}Tc may be released by administration of perchlorate. An example for a hyperthyroid subject is shown in Fig. 6, where approximately 80% of the neck radioactivity disappears. The residual radioactivity largely represents blood background, for which no correction was made. Uptake of ^{99m}Tc in the salivary glands is not more than 1 or 2%, but the tissue/blood ratio is about 50, [ ] 30 min after intravenous injection. This localization is also inhibited and released by administration of perchlorate.

Disappearance from the Blood

Technetium-99m injected intravenously as pertechnetate in the human is cleared very rapidly from the blood, [3] about 50 to 60% leaving with a half-time between 1 and 2 min; for about 15%, $t_{\frac{1}{2}}$ is 5 to 20 min; and for 20 to 30%, $t_{\frac{1}{2}}$ is 100 to 200 min. The effect of 1 g $NaClO_4$ given orally 15 min before intravenous ^{99m}Tc-pertechnetate is to prolong the disappearance times of the second and third components to about 20-40 min and 400-600 min, respectively. The effect of perchlorate in extending half-times was erratic. Repetition of the two studies in the same individual sometimes resulted in a higher content per ml of ^{99m}Tc and other times in a lower amount, even though an attempt had been made to maintain the subject under identical conditions.

Concentration by the Fetus and Placenta

Technetium-99m collected by the feto-placental unit of the mouse from pertechnetate injected intravenously in the mother is influenced by pre- and post-administration of perchlorate. [3] This has important implications

since recently published ovservations [5] from this laboratory indicate that the fetus may be affected by relatively low levels of ^{99m}Tc radiation received in utero, and since the nursing neonate also responds to ^{99m}Tc incorporated into milk by the mother. Two groups of pregnant mice, 200 in each, were divided into 5 equal subgroups and injected daily throughout gestation with 0, 5, 50, or 500 μCi of Na^{99m}TcO$_4$. After delivery, the mothers of Group B continued to receive daily injections for 1 mo; Group A mothers were not injected. Randomly selected first generation litter mates were paired to produce the second generation. All offspring were weighed at birth, and at 1 and 2 mos of age. Comparisons of weights made between groups are summarized in Table 1. The radiation absorbed dose to a mouse fetus in the 5 μCi group is estimated to be about 1 rad accumulated through gestation. Because of differences in absorbed fractions a similar amount of ^{99m}Tc/g gives a different radiation dose to the human fetus (~100 mrad per 0.2 μCi/g, or 1 rad/10 mCi single administration).

Perchlorate reduces the concentration of ^{99m}Tc in the feto-placental unit which in the untreated mother decreases from about 5%/g at the beginning of gestation to around 2%/g at term. This reduction increases with gestatory age (Fig. 7) to as much as 50% just before delivery. At this stage most of the ^{99m}Tc in the feto-placental unit is in the fetus (Fig. 8) and cannot be released by perchlorate, indicating incorporation into organic molecules. [5] Pretreatment with perchlorate inhibits localization in all three tissues. The placenta/blood ratios for ^{99m}Tc, listed in Table 2, indicate that the placental concentration is reversed by perchlorate and exclusion occurs.

The ratios between ^{99m}Tc concentration with and without perchlorate, given in Table 3, show greater suppression in the fetus than in the placenta. The increase in values with time suggests that inhibition from a single dose diminishes during the course of the experiment.

We have previously shown [5] that fetal thyroid concentration of ^{99m}Tc is about 1/10 of the maternal during the first hour and remains significantly reduced for at least 2 h. Gastric localizations are similar for fetus and mother. Significantly higher levels of ^{99m}Tc were found in the fetal spleen, liver, and femur than in the corresponding maternal organs. At 15 min, the concentration in the fetal spleen is equivalent

to the gastric value. The uptake found in the fetal femur is more than 10 times the maternal at 15 min. In both organs, the ^{99m}Tc levels decrease noticeably with time. Fetal liver concentration remained about 10 times the maternal throughout the two hours of study. The fetal blood level was several times the naternal, the fetal intestinal concentration was approximately 10 times the maternal, and the kidney uptake was about four times as high. The kidney localization, if considered as the tissue/blood ratio, was comparable to the maternal uptake. Other fetal organs accumulate substantially higher amounts of ^{99m}Tc from the blood than do the maternal organs. These findings suggest that ^{99m}Tc may be carried to the fetus in some form other than pertechnetate, then released and distributed as pertechnetate.

The effect of perchlorate ion on the concentration of ^{99m}Tc in some fetal organs is shown in Fig. 9. Not shown are the femur, spleen, and thyroid, in which no ^{99m}Tc could be detected at any time after pretreatment with perchlorate. Perchlorate, therefore, exerts its greatest inhibitory effect on the concentration of ^{99m}Tc in the femur, spleen, stomach, and thyroid of the fetus.

Conclusions

The biologic distribution pattern of ^{99m}Tc resulting from the intravenous injection of sodium pertechnetate can be altered quantitatively if preceded by 15 min with an oral administration of perchlorate. In the adult human 1 to 2 g of sodium perchlorate produces virtually complete suppression of ^{99m}Tc localization in the thyroid and salivary gland, and stomach. These are the regions where the highest concentrations occur normally. Perchlorate increases the quantity of ^{99m}Tc in the intestine, prolongs the residence time in the blood, and diminishes the urinary excretion at 48 h. Perchlorate releases much ^{99m}Tc previously localized in the thyroid and salivary gland, and in the stomach. Its action on ^{99m}Tc already contained in the intestine, on the blood level, and on excretion has not been determined.

Technetium-99m pertechnetate administered intravenously to mice during gestation and lactation significantly alters the weight gain in some first and second generation progeny. This effect could conceivably be mitigated with perchlorate which reduces and changes localization of

^{99m}Tc in the mouse fetus. The estimated radiation absorbed dose to the human fetus from ^{99m}Tc-pertechnetate is about 80 mrad/mCi, or about 30 mrad/mCi with perchlorate, if uniform distribution is assumed. Although the biologic distribution pattern of ^{99m}Tc in the fetus has been studied, data are meager at this time, and no absorbed dose calculations for the individual organs have been made.

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Table 1. Confidence Levels of Comparative Weight Differences Observed Between Various Groups of Progeny from Mothers Given $Na^{99m}TcO_4$ During Gestation (A) or Gestation and Lactation (B)

Groups Compared	5 μCi		50 μCi		500 μCi	
	1 mo	2 mo	1 mo	2 mo	1 mo	2 mo
A-1CM/A-1M**	*	*	P < 0.001	*	P < 0.001	P < 0.001
A-1CF/A-1F	*	*	P < 0.001	P > 0.01	P < 0.001	P < 0.001
A-1M/A-1F	*	*	*	*	*	*
A-2CM/A-2M	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
A-2CF/A-2F	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001	P < 0.001
A-2M/A-2F	*	*	*	*	*	*
A-1M/A-2M	P > 0.001	P < 0.001	P > 0.001	P < 0.001	*	P > 0.001
A-1F/A-2F	P > 0.001	P > 0.001	*	P > 0.001	*	*
B-1CM/B-1M	*	*	P > 0.01	*	P < 0.001	*
B-1CF/B-1F	*	P > 0.001	P > 0.01	*	P < 0.001	*
B-1M/B-1F	*	P > 0.01	*	*	*	*
B-2CM/B-2M	P > 0.001	P > 0.01	P > 0.01	*	P > 0.001	P < 0.001
B-2CF/B-2F	*	P > 0.01	*	P > 0.001	P > 0.001	P > 0.01
B-2M/B-2F	*	*	*	*	*	P > 0.01
B-1M/B-2M	P > 0.01	P > 0.01	*	*	P < 0.001	P > 0.01
B-1F/B-2F	*	P < 0.001	*	*	P < 0.001	P < 0.001
A-1M/B-1M	*	*	P > 0.001	*	*	P < 0.001
A-1F/B-1F	*	P > 0.01	*	*	*	P < 0.001
A-2M/B-2M	*	P > 0.001	*	P < 0.001	P > 0.01	P < 0.001
A-2F/B-2F	*	*	P > 0.01	P > 0.001	P > 0.01	*

*Not significantly different.

**M = male; F = female; C = Control; 1 = 1st generation (irradiated in utero); 2 = 2nd generation (not irradiated).

Table 2. Effect of $NaClO_4$ on Placenta/Blood Ratio

Minutes	RATIO: $\frac{^{99m}Tc/g\ placenta}{^{99m}Tc/ml\ blood}$	
	No $NaClO_4$	with $NaClO_4$
15	1.7	0.20
30	1.7	0.24
60	2.5	0.49
90	2.1	0.59

Table 3. Effect of $NaClO_4$ on Uptake of ^{99m} Tc-Pertechnetate

Minutes	RATIO: $\frac{^{99m}Tc\ with\ NaClO_4}{^{99m}Tc\ without\ NaClO_4}$	
	Placenta	Fetus
15	0.48	0.21
90	0.34	0.32
180	1.18	0.88

Fig. 1. Accumulation of ^{99m}Tc in stomach, determined by continuous recording.

Fig. 2. Action of perchlorate on ^{99m}Tc localization in the stomach. Both studies were made in the same individual.

Fig. 3. Effect of perchlorate on gastric secretion.

Fig. 4. Effect of perchlorate on localization of ^{99m}Tc in stomach and intestine of a human.
(A) 2 h after i.v. pertechnetate;
(B) 17 h. The upper images are of the upper abdomen; the lower, mid abdomen. The images on the left are without perchlorate, those on the right with 2 g, 15 min before pertechnetate.

Fig. 5. Variation between normal individuals in urinary excretion of ^{99m}Tc and the effect from oral administration of perchlorate, 15 min before intravenous pertechnetate.

Fig. 6. Release of ^{99m}Tc concentrated in the thyroid and salivary glands of a hyperthyroid subject, by oral administration of 2 g $NaClO_4$, 15 min after pertechnetate had been given intravenously.

Fig. 7. Reduction in ^{99m}Tc localization in the feto-placental unit of the mouse produced with $NaClO_4$, 15 min before pertechnetate (both i.v.), versus day of gestation. Concentration of ^{99m}Tc alone ranges from about 5%/g on day 1 to about 2%/g at delivery.

Fig. 8. Partition between tissues for ^{99m}Tc concentrated in the feto-placental unit of the mouse, at intervals after pertechnetate (i.v.).

Fig. 9. Influence of pretreatment with $NaClO_4$ on uptake of ^{99m}Tc by some fetal tissues.