

The placental binding and transfer of radiopharmaceuticals II: Tc-99m Sestamibi, Tc-99m Tetrofosmin and Tl-201 Thallous Chloride

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Abstract

It has been shown that some radiopharmaceuticals can cross the placental barrier and enter into fetal circulation. The objective of this study was to investigate placental transfer of cardiac perfusion imaging radiopharmaceuticals (Tc-99m sestamibi, Tc-99m tetrofosmin and Tl-201 thallous chloride (Tl⁺-201)) in pregnant guinea pigs and in-vitro mechanism of the transfer using human placental lobule. Pregnant guinea pigs in the first, second and third trimesters were used. Following intravenous injection of Tc-99m sestamibi, Tc-99m tetrofosmin or Tl⁺-201 the guinea pig was imaged using a gamma camera; killed and the fetuses removed. Each fetus was then imaged separately using a low energy general-purpose collimator. The placentas, ovary, and fetal hearts, lungs, liver, kidneys and blood were then removed and the radio-activity in each organ along with a 1.0 ml standard solution was counted separately in a dose calibrator. For the in-vitro experiment, the effect of ouabain on the transfer of Tl⁺-201 and tritiated water (as internal reference marker) in the maternal-fetal direction was studied in human placentas (collected postpartum) from normal uncomplicated pregnancies and suitable lobules perfused with either normal or ouabain-treated perfusate. The differential transport rate of Tl⁺-201 in the maternal-fetal direction was measured as time taken in minutes for 50% fraction of Tl⁺-201 (TR₅₀) to be transported across the fetal vein and expressed as the ratio of the TR₅₀ of Tl⁺-201 to tritiated water (TR₅₀ index). The following pharmacokinetic parameters were also measured: the area under the curve, clearance and absorption rate indices. Neither Tc-99m sestamibi nor Tc-99m tetrofosmin was transferred across the placental barrier while 1.7 ± 0.5% of the injected

activity (0.027 ± 0.005 % per gram) of Tl⁺-201 radioactivity during the third trimester was transferred across the placenta into fetal circulation. Most of the radioactivity from Tl⁺-201 in the fetus was in the liver, followed by the heart. For the in-vitro experiment, TR₅₀ index of Tl⁺-201 averaged 0.98 ± 0.05 for normal perfusion and corresponding index for ouabain-treated was 1.17 ± 0.03; the difference was statistically significant (p < 0.05) thereby implying a significantly reduced rate of Tl⁺-201 transport in the ouabain-treated lobules. The area under the curve (AUC), clearance and absorption rate indices of control perfusion were 4.12 ± 0.52, 0.62 ± 0.06 and 2.75 ± 0.12, respectively and the corresponding indices for ouabain-treated perfusion were 1.89 ± 0.28, 1.65 ± 0.12 and 1.64 ± 0.18, respectively and the differences were statistically significant (p < 0.05) also implying that ouabain treatment reduced transport of Tl⁺-201 in the human placental tissue in the maternal-fetal direction. The results indicate that while Tl⁺-201 is transferred across the placental barrier into fetal circulation, both Tc-99m sestamibi and Tc-99m tetrofosmin were not transferred. Furthermore, from the findings of the in-vitro experiments, the transfer of Tl⁺-201 across the placental barrier is by active transport probably through the Na⁺-K⁺ ATPase transport system.

Keywords: Cardiac Radiopharmaceuticals, Placental Transfer, Guinea Pig, placental lobule Tritiated Water.

World J Nucl Med 2005;4:120-126

Introduction

Radiopharmaceuticals are administered for diagnostic and therapeutic purposes. They could be given inadvertently during an unknown pregnancy or as has occurred in rare occasions, deliberately to save either the fetal or mother's life, as has been reported for Tc-99m HMPAO, Tc-99m MDP and Ga-67 citrate (1-6) and also for placental localization (7-9). In any of these situations, there is a need to have as much as possible an accurate estimate of the radiation absorbed dose to the fetus. Such a dosimetric calculation would be based on the amount of radioactivity transferred to the fetus across the placenta and/or irradiation from adjacent organs such as urinary bladder and the placenta. For obvious ethical reasons there are very

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limited human studies on the placental binding and transfer of radiopharmaceuticals. Even in experimental animals, few studies have been reported on transfer of radiopharmaceuticals across the placenta to the fetus (10 - 12). However, there are many reports on the placental transfer of radionuclides produced by U-236 fission (13-16)

In this report the transfer of myocardial radiopharmaceuticals across guinea pig placenta and their distribution in the fetuses are described. The radiopharmaceuticals used, are technetium-99m labeled hexakis-2-methoxy-2-isobutylisonitrite (Tc-99m sestamibi), technetium-99m 1,2-bis [bis(2-ethoxyethyl)phosphino] ethane (Tc-99m tetrofosmin) and thallium-201 thallos chloride (Tl^{+} -201). These tracers are used routinely in clinical nuclear medicine for myocardial perfusion imaging. They are increasingly being used in breast and thyroid cancer imaging (17-19) and in detection of multi-drug resistance (20). There may be women of childbearing age in whom it could be necessary to image breasts or thyroid with these radiopharmaceuticals. In such a situation, a thorough knowledge of whether or not the tracer is bound to the placenta and/or can be transferred across the placental barrier into fetal circulation becomes invaluable to the physician.

In a review on placental transfer of radiopharmaceuticals and dosimetry in pregnancy Russell et al (21), reported that although Wegst et al (22) showed that Tl^{+} -201 is transferred across the placenta into the fetus during the last stage of the gestation there was no quantitative data on the amount of radioactivity that localized in the placenta or fetal tissues. Therefore absorbed dose estimates to the fetus included only maternal contributions. Equally important is that for both Tc-99m sestamibi and Tc-99m tetrofosmin there is no report on the placental transfer of these tracers. Lack of human placental transfer data is the main limitation to estimating fetal doses (23).

Hence, the objective of this study was to investigate the placental transfer of Tc-99m sestamibi, Tc-99m tetrofosmin and Tl^{+} -201 in pregnant guinea pigs and *in-vitro* mechanism of the transfer using human placental lobule.

Materials and Methods

In-vivo studies

The pregnant guinea pigs were divided into 3 groups corresponding to the three radiopharmaceuticals: Tc-99m sestamibi, Tc-99m tetrofosmin and Tl^{+} -201. For each radiopharmaceutical, the guinea pigs were further divided into 3 subgroups: 1st, 2nd and 3rd trimesters. The 3rd trimester subgroups were studied first, to determine whether or not the radiopharmaceutical crossed the placental barrier into the fetal circulation since a previous study using Tc-99m HMPAO (11) had shown that the amount of the tracer that crossed the placental barrier into the fetus was dependent on the gestation period and that most of the radioactivity was transferred during the 3rd trimester.

Five pregnant guinea pigs were used for each subgroup. The guinea pigs were mated over a 24 hr period during estrous.

Mating was determined by the presence of sperm in the vaginal smear and the day of mating was designated as day zero of gestation. Each pregnant guinea pig was anaesthetized by intraperitoneal injection of 30 mg/kg (body weight) of sodium pentobarbital (SaggitalR). Approximately, 30 minutes later, a 22 GA-I cannula was inserted into the jugular or femoral vein. An activity of 74 MBq (2 mCi) Tc-99m sestamibi, Tc-99m tetrofosmin or Tl^{+} -201 was injected through the cannula.

A GE gamma camera (AT -400) linked to computer was used to take static images of the pregnant guinea pig 15-30 minutes after injection of the radiopharmaceutical. The guinea pig was then killed and the fetuses removed. Each fetus was separately weighed and imaged using a low energy general purpose collimator and a zoom factor of 1.5. The total activity in each fetus was assayed in a dose calibrator. The placentas, ovary, and the fetal heart, lungs, kidneys, livers and blood were removed and the radioactivity in each organ/tissue and a 1 ml standard solution was assayed separately in a dose calibrator. The standard solution of each radiopharmaceutical was prepared using similar amount of the injected activity diluted to 100 ml. The percent activity in each organ was calculated relative to the injected activity while that of the fetal organs was calculated relative to the total activity in the fetus.

Based on this preliminary experiment, only Tl^{+} -201 crossed the placental barrier into the fetal circulation during the 3rd trimester, and was therefore further studied during the second and first trimesters in the same manner as described above. The average radioactivity transferred to the fetus for each trimester was computed and compared.

In-vitro Studies

The effect of ouabain on the transport of Tl^{+} -201 was studied in perfused human placental lobule. Human placentas from normal, uncomplicated pregnancies were collected postpartum and perfusion of suitable placental lobules performed as previously described (24-26). Briefly, National Culture and Tissue Collection (NCTC135) medium (Sigma Chem.co., USA) diluted with buffered Earle's salt solution was used as the perfusate. Circulation of the perfusate through the maternal and fetal circuits was done using a Harvard digital pump. The advantages and suitability of using NCTC medium as the perfusate have been detailed elsewhere (27). Perfusion flow rates were measured in the maternal and fetal circuits by BROOKS R215 flow meters and mercury manometers monitored the perfusion pressure.

After an initial washout period of 10 minutes, 1.85kBq (50 μ Ci) of Tl^{+} -201 along with tritiated water (specific activity: 5 mCi/mmol) as a reference marker (Amersham, UK), were injected into the maternal arterial circulation as a 200 μ l bolus at a site close to the insertion of the microcannulas in the basal plate. After a period of 1 minute, serial perfusate samples were collected from the fetal venous outflow every 30 seconds over a period of 5 minutes. The lag time of one minute before the start of sample collection was based on our preliminary study (27).

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The study period of 5 minutes was based on the time required for 90% of injected substance in the bolus to appear in the combined fetal and maternal venous efflux in control experiments performed previously (28).

In experiments with ouabain, the placental lobules were perfused with the metabolic poison (ouabain concentration: 1 mmol/l) for a period of 7 minutes immediately after the wash-out phase and then the same bolus mixture of Tl^{+} -201 and tritiated water was injected into the maternal circulation and serial sample collection done as earlier. Viability of placental perfusions was assessed by verifying absence of perfusion flow rate mismatch between fetal arterial and venous flows and by the determination of oxygen consumption of perfused tissue during the period of study.

The radioactivity of tritium in various perfusates was determined by scintillation spectrometry (LKB Wallac Model, Copenhagen, Denmark) while that of Tl^{+} -201 was measured in a gamma counter (Packard Instrument Company, Meriden, CT, USA)

Transport Parameters

The differential transport rate (TR_{50}), the area under the curve (AUC), absorption and clearance rates were calculated as described below. The TR_{50} of Tl^{+} -201 and tritiated water was determined as time in minutes for 50% of the efflux fraction of the tracers to be transported across to the fetal vein as previously described (26, 28). A ratio of Tl^{+} -201 over that of tritiated water was calculated and expressed as TR_{50} index for both control and ouabain studies in order to account for any variations in the experimental parameters: flow rates, surface area and weight of the lobules of the placenta. Thus, the higher the value of TR_{50} indexes the slower the rate of transfer of the tracer in the maternal-fetal direction. The area under the curve (AUC) was computed using trapezoid integration.

The absorption and clearance rates were determined using the IMSL software package (Visual Numerics, San Ramon, CA, U.S.A.).

Data Analysis

One-way ANOVA (Analysis of Variance) and paired Student's t test was performed using the SPSS Version 10 software package for the transport parameters. P-values less than 0.05 were considered statistically significant.

Results

In-vivo studies

Anterior images of the pregnant guinea pig injected with Tl^{+} -201 showed accumulation of radioactivity in the heart, liver, kidney and fetuses (Figure 1) during the third trimester. The number of sites identifiable as fetuses on the image corresponds to the actual count of the fetuses, particularly in the third trimester. The number of fetuses per mother varied from as little as two to a maximum of 6 (Table 1). The mean \pm standard deviation of the amount of radioactivity that accumulated in the placenta, as a percentage of the injected activity, varied according to the gestational age from 0.3 ± 0.2 in the first trimester to $0.7 \pm 0.3\%$ in the third trimester (Table 2). The average amount of the injected activity transferred to the fetus also varied from $0.06 \pm 0.04\%$ (first trimester) to $1.7 \pm 0.5\%$ (third trimester) as in Table 2. Relatively, small amounts of radioactivity accumulated in the ovary during the second and third trimesters. The amount of radioactivity in the fetal organs relative to the total activity transferred to each fetus is given in Table 3 for second and third trimester fetuses. For the fetuses in the first trimester, the fetal organs were too small to dissect and as such the radioactivity in them was not assayed. It is worth mentioning that a very small amount of radioactivity ($0.06 \pm 0.04\%$) of the total injected amount

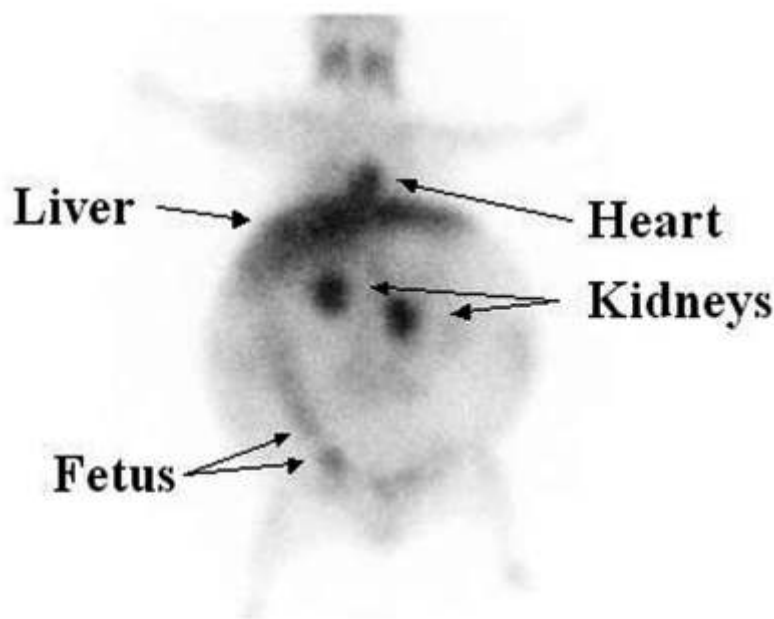


Figure 1 Image of a pregnant guinea pig injected with Tl -201 during the third trimester

Trimester	Total Number of Fetuses	Average Weight of Fetus (Gm)
First	14	2.89
Second	13	36.2
Third	22	62.0

Table 1. Total number of Fetuses and Average weight according to Trimester for Tl-201 Experiments

Trimester	Percent uptake of Injected Activity			Percent uptake of Injected Activity/ Gram		
	Ovary	Placenta	Fetus	Ovary	Placenta	Fetus
First		0.3 ± 0.2	0.06 ± 0.04		0.26 ± 0.17	0.02 ± 0.01
Second	0.07	0.9 ± 0.2	0.9 ± 0.4	0.53	0.24 ± 0.08	0.025 ± 0.003
Third	0.07	0.7 ± 0.3	1.7 ± 0.5	0.22	0.15 ± 0.05	0.027 ± 0.005

Table 2 Guinea pig percent uptake of injected activity of Tl-201 in Ovary, Placenta and Oetuses according to Trimesters

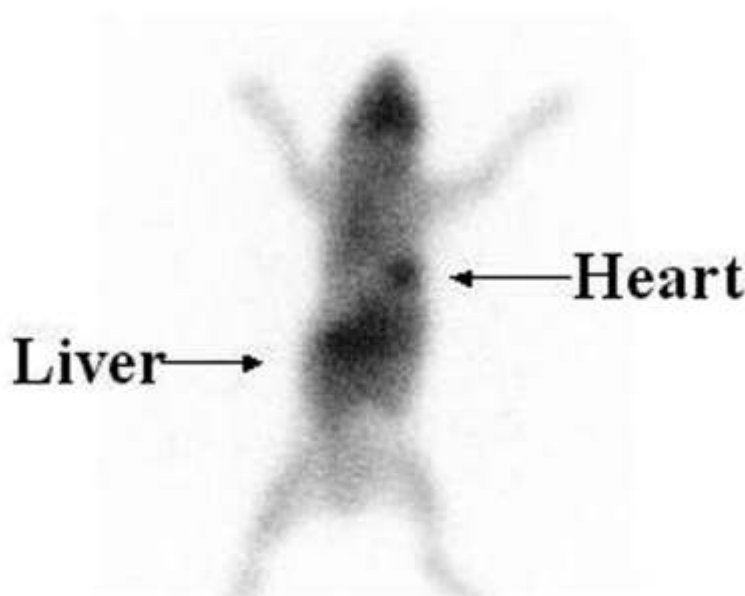


Figure 2 Image of a third trimester fetus showing accumulations of Tl-201 in the heart and liver

was transferred to each fetus during the first trimester (Table 2). For both second and third trimester fetuses, of the radioactivity transferred to the fetus, the order of accumulation in the fetal organs was liver>>heart> blood > kidney > lung. Tl⁺-201 accumulation in the heart, as a percentage of the injected activity was not significantly different during the second (1.81 ± 0.3%) and third (3.0 ± 1.4%) trimesters, despite a decrease of circulating radioactivity in the blood. There was a decrease in the amount of the uptake of Tl⁺-201 in the liver from 33.0 ± 8.7% in second trimester to 18.0 ± 8.0% in the third trimester (Table 3). Images of the third-trimester fetus showed uptake of radioactivity in the heart of the fetus

(Figure 2). Radioactivity was not seen in the fetuses of the guinea pig injected with Tc-99m sestamibi or Tc-99m tetrofosmin during the third trimester. The fetus to mother organ uptake ratios for Tl⁺-201 accumulation, normalized by the weight of the organs, for the second and third trimester are shown in Figure 3. The figure shows that as the fetal organs develop in the 3rd trimester the radioactivity concentrates in them rather than circulating in the blood. Assuming an uptake of 2% of the injected activity of Tl⁺-201 into the fetus with no biological removal would result in an internal radiation dose of 0.16 mGy/MBq being delivered to a 1kg fetus from electrons and X-rays emitted during the decay.

Organ	Percent uptake of Injected Activity		Percent uptake of Injected Activity/ Gram	
	Second	Third	Second	Third
Heart	1.8 ± 0.3	3.0 ± 1.4	0.1 ± 0.05	0.2 ± 0.1
Liver	33.0 ± 8.7	18.0 ± 8.0	0.34 ± 0.1	0.25 ± 0.1
Kidney	1.7 ± 0.6	1.8 ± 0.9	0.03 ± 0.01	0.03 ± 0.01
Lungs	1.8 ± 1.0	1.8 ± 1.0	0.06 ± 0.03	0.1 ± 0.09
Blood (1 ml)	1.5 ± 0.8	0.8 ± 0.7	3.0 ± 0.4	0.5 ± 0.5

Table 3 Guinea pig uptake of Tl-201 in fetal organs relative to the total activity in the fetus

In-vitro studies

The fetal perfusion flow rate of the human placenta in control and ouabain experiments averaged 6.1 ± 0.4 and 5.2 ± 0.6 ml/min in 6 successful perfusions while maternal flow rate averaged 11.2 ± 1.2 and 8.9 ± 0.8 ml/min, respectively. Fetal-maternal flow rate ratio averaged 0.54 ± 0.07 and 0.6 ± 0.1 in control and ouabain perfusion series, respectively. The maternal and fetal perfusion flow rates were adjusted such that the maternal-fetal rate ratios were within the physiological range. The control and experimental flow rates did not differ statistically ($p > 0.5$). The TR_{50} index of Tl^{+201} in control to ouabain perfusions were 0.98 ± 0.05 and 1.17 ± 0.03 , respectively times that of corresponding tritiated water values in 5 control perfusions. The difference was statistically significant ($p < 0.05$) implying reduced rate of Tl^{+201} transport in ouabain-treated placental lobules.

The AUC, clearance and absorption rate indices of Tl^{+201} compared to corresponding reference marker values averaged 4.12 ± 0.52 , 0.62 ± 0.06 and 2.75 ± 0.12 in the 5 control perfusions while the corresponding AUC, clearance and absorption rate indices for ouabain perfusions ($n=5$),

averaged 1.89 ± 0.28 , 1.65 ± 0.12 , and 1.64 ± 0.18 , respectively. The Student's t-test showed that all the three pharmacokinetic indices differed significantly ($p < 0.05$) between control and ouabain series implying that ouabain treatment significantly reduced transport of Tl^{+201} in the perfused human placental tissue in the maternal-fetal direction.

Discussion

The experimental animal used in this study was guinea pig because of several reasons: a) its small size; b) its placenta closely resembles that of human. Both are hemochorial placentas but the guinea pig has labyrinthine vascular bed while that of human is villous and c) at full gestation period or birth, the fetal guinea pig is developmentally as mature as human fetus. The three radiopharmaceuticals (Tc-99m sestamibi, Tc-99m tetrofosmin and Tl^{+201}) studied are routine cardiac perfusion imaging tracers. The Tc-99m sestamibi and Tc-99m tetrofosmin are both positively charged and lipophilic tracers that diffuse passively into the

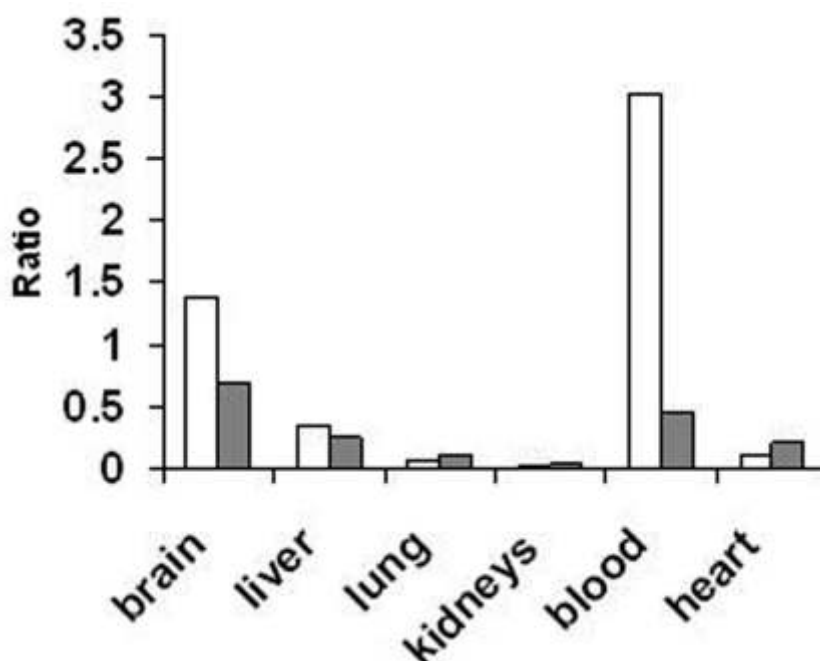


Figure 3 Histogram of the fetal to mother organ Tl-201 activity for the second (open bars) and third trimester (shaded bars)

myocardial cell and bind to the negatively charged mitochondrial membranes (29). The Tl^{+} -201 on the other hand is actively transported into the myocardium through the Na^{+} - K^{+} ATPase transport system (30). The energy required is derived from the break down of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) by the activation of membrane-bound enzyme, Na^{+} - K^{+} ATPase and Tl^{+} -201 being a biologic analog of K^{+} is transferred into the myocardial cell.

In the *in-vivo* experiment both Tc-99m sestamibi and Tc-99m tetrofosmin were not transferred across the placental barrier. It has been reported that drugs, which are both ionized and lipophilic, are not transferred across the placenta (31). This explanation could be the reason for non-transfer of both Tc-99m sestamibi and Tc-99m tetrofosmin across the guinea pig placenta. However, a measurable amount of radioactivity was observed in the fetuses of pregnant guinea pig injected with Tl^{+} -201 (Tables 1 and 2). This internal radioactivity resulted in an estimated radiation dose of 0.16 mGy/MBq per kg mass to the fetus which is higher than the estimate of the radiation dose of 0.05 mGy/MBq per kg mass the fetus would receive from the external radioactivity in the mother's organs (32). This higher internal radiation dose underscores the need for determining whether or not a given radiopharmaceutical could be transferred across the placental barrier and be distributed in the fetus. It is noteworthy to point out that the amount of radioactivity transferred increased with gestation consistent with higher maternal-fetal transfer of drugs due to thinning of placental membrane towards late gestation (31). It could also be due to increased placental exchange area necessitated by increased vascularity to meet fetal nutrient needs (31).

In the *in-vitro* experiment Tl^{+} -201 was shown to be transported actively across the placental membrane as indicated by the higher differential transport rate and the lower AUC, reduced absorption and higher clearance rates of the radiopharmaceutical in lobules pre-treated with ouabain compared to the control experiment. It may be recalled that the higher the differential transfer rates the slower would be the transfer of the substance in the maternal-fetal direction. Hence the higher differential transport rate of Tl^{+} -201 in ouabain perfusions indicates reduced transfer Tl^{+} -201 compared to the control. Equally the lower AUC, the reduced absorption and higher clearance rates of the Tl^{+} -201 in the ouabain-treated placental lobules compared to controls, all indicate reduced transfer of Tl^{+} -201 across the placental membrane into the fetal circulation. The use of an internal reference marker (tritiated water) in the experiments showed that the results on reduced transport of thallium in ouabain-treated placental lobules was not due to experimental artifacts as variations in perfusate flow rates, membrane surface area or weight of cotyledon. It has been generally established that the majority of drugs are transferred across the human placental membrane by passive diffusion along a concentration gradient (31). However, the results of this study point to the fact that placental membrane can participate actively in transporting select agents or

chemicals, to the fetal circulation in humans as in the case of some amino acids and certain vitamins (27,31)

The relative significance of this study is that since Tc-99m sestamibi and Tc-99m tetrofosmin are used routinely for myocardial perfusion, breast and thyroid tumor imaging, and the results indicate that these two radiopharmaceuticals do not cross the placenta, if they are inadvertently administered into a pregnant woman, fetal radiation absorbed dose will be due mostly to irradiation from adjacent maternal organs. However for Tl^{+} -201, there will be a contribution from the fetus itself. This knowledge is invaluable when advising a woman of child bearing age who is about to undergo myocardial, breast or thyroid tumor imaging using any of these radiopharmaceuticals.

CONCLUSION

Thallium-201 thallos chloride was transferred across the placental barrier into fetal circulation but Tc-99m sestamibi and Tc-99m tetrofosmin were not transferred. Furthermore, the transfer of Tl^{+} -201 across the placental membrane was by active transport as shown by the reduced transport of Tl^{+} -201 across ouabain-treated placental

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