Sumatriptan (Imitrex$_R$) Transport by the Human Placenta (43941)

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Abstract. **Sumatriptan (Imitrex$_R$), a selective 5-hydroxytryptamine receptor agonist, has been found to be of therapeutic benefit in the acute management of migraine. There is no information on the transfer of this agent across the human placenta. Accordingly, the current study assessed the transport of this drug across the normal term human placenta, using the isolated perfused single cotyledon technique.**

We found that only about 15% of a single dose of the agent placed in the maternal reservoir crossed into the fetal compartment over 4 hr. Given the average elimination half-life of 2 hr for sumatriptan, it is evident that only very small amounts of the agent will cross from mother to fetus after single doses of Imitrex$_R$. Only the parent drug entered the fetal compartment. Metabolites were not detected in the perfusates, but there was evidence of some metabolism of sumatriptan in the placenta. The nature of the metabolites has not been determined. The mechanism of transfer of the drug across the placenta is passive (i.e., the clearance is similar to L-glucose which is passively transported), the rate of transfer is equal in both directions (maternal to fetal and in the reverse), and the drug does not cross into the fetus against a concentration gradient. This passive transport of sumatriptan across the placenta is consistent with its molecular weight, its water solubility, and its slow penetration across the blood-brain barrier in experimental animals. [P.S.E.B.M. 1995, Vol 210]

Sumatriptan (Imitrex$_R$) is a selective 5-hydroxytryptamine receptor agonist which has been found to be a valuable therapeutic agent for migraine (1, 2). Migraine is predominantly a disorder of young women in the childbearing years, and sumatriptan is not presently recommended for patients over the age of 65 and under 18 (3). Sumatriptan is classified in category C regarding its usage in pregnancy (i.e., the benefits of its use have to justify possible risks). Data on embryo lethality and teratogenicity of sumatriptan in experimental animals have varied with the species and manner of drug administration (4). No data are available in pregnant women.

Moreover, there appears to be no information on human transplacental transfer of this agent (3). Theoretically, a drug like sumatriptan (3-[2-(dimethylamine)ethyl]-N-methyl-1H-indole-5-methanesulfonamide butane-1,4-dioate[1:1]), with a molecular weight of 413.5 and significant water solubility, may cross the placenta only slowly, unless it is transferred by a carrier system. By comparison, glipizide, an oral antidiabetic agent with similar molecular weight, crossed the human term placenta at about 30% of the antipyrine rate in our recent studies (5). Indeed, sumatriptan crosses the normal blood-brain barrier very slowly despite only modest drug binding to plasma proteins (6, 7), presumably because this is a lipid barrier. Our aim in this study was to determine the rate and mechanism(s) of sumatriptan transfer by the normal term human placenta.

Materials and Methods

All placentas were obtained from women with a normal term delivery, via spontaneous vaginal delivery or by Cesarian section. The study had the approval of the Institutional Review Board for the protection of human subjects. We employed the single cotyledon perfusion model described earlier by others (8) and

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utilized by us extensively (9–15). In essence, a freshly obtained human placenta was perfused immediately with heparinized Krebs-Ringer buffer and was then mounted in a chamber with the maternal surface pointing up. The fetal vessels supplying a single cotyledon were cannulated with polyethylene catheters and the maternal surface was perfused by two or three needles placed in the intervillous space. The perfusate consisted of Krebs-Ringer buffer, at pH 7.4, with human albumin at a concentration of 2 g/l. Addition of erythrocytes was found not to improve active transport of test substances in preliminary studies. The pressure in the system was kept at 40–60 mm Hg, and the temperature at 37°C. The system was oxygenated with 21% O_2/5% CO_2 on both sides of the placenta. The fetal flow was 2–4 ml/mm, depending on the size of the perfused cotyledon and the maternal flow was 20 ml/min. Viability of the system was previously established by absence of leakage of reservoir fluid to the opposite compartment during the study implying no tissue tears, predictable transfer rates of passively diffusible and actively transported reference markers, L-glucose or antipyrine and cycloleucine or thiamine, respectively, and in some instances, measurement of lactate production, glucose consumption, and oxygenation. In this series of studies, absence of tissue tears, selected studies of lactate production and glucose consumption, and transport rate of four markers were employed as an index of tissue viability.

Three types of perfusions were used. The first was a recirculating, closed system wherein both the maternal (250 ml) and fetal (100 ml) reservoirs are recirculated for 4 hr. By placing sumatriptan initially in either the maternal or fetal compartments and assessing its transfer into the opposite reservoir, the rate of transfer of slowly transported substances versus known markers as well as the formation of any metabolites can be determined. This protocol resembles the normal maternal/fetal relationship. The second system was an open one. Both reservoirs were open, permitting steady state infusion of the sumatriptan and frequent measurements of clearances across the placenta versus known markers.

The first system permitted the calculation of a transfer ratio or percent of initial dose transferred, as described by us earlier (9, 10). Sumatriptan transfer was compared at the same time intervals to reference markers, in this case L-glucose, a substance transported slowly by passive diffusion.

The second system permitted the use of clearance calculations, with nine 10-min clearances averaged for each perfusion and the data expressed as the ratio of clearance of sumatriptan versus two known reference markers, antipyrine and L-glucose. Antipyrine was used in a concentration of 100 μg/ml and L-glucose as 7 ng/ml. Antipyrine, in contrast to L-glucose, is a rapidly equilibrated and transferred substance (12). Clearance was calculated as follows:

a. Maternal/fetal clearance =

$$\frac{\text{Fetal outflow (ng/ml)} \cdot \text{Fetal flow rate (ml/min)}}{\text{Maternal concentration (60 ng/ml)}} \cdot 60 \text{ min}$$

b. Fetal/maternal clearance =

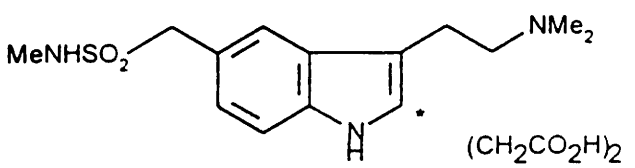
$$\frac{\text{Maternal outflow (ng/ml)} \cdot \text{Maternal flow rate (ml/min)}}{\text{Fetal concentration (60 ng/ml)}} \cdot 60 \text{ min}$$

Each value is divided by placental lobule weight, in grams, for greater uniformity. More detail on these measurements is given elsewhere (5).

The third system assessed drug transfer against a concentration gradient. In this approach, the maternal side was perfused by a constant concentration of the drug and the same concentration was placed in the recirculating fetal compartment. Accumulation of drug in the fetal compartment against such a concentration gradient (i.e., a ratio greater than 1.0) is consistent with active transport. Data for each placenta were compared with a known reference marker which was transferred against a concentration gradient.

In this perfusion system, a well-demarcated cotyledon was used and verified by blanching or staining. As the size of the cotyledon and pressure/flow characteristics vary somewhat and there may be some differences in the matching of the two perfused compartments (maternal and fetal), it is customary to decrease this variability by the use of a freely permeable marker (i.e., antipyrine) as a reference (16). This is the procedure followed here.

For transport studies we utilized ^{14}C-sumatriptan succinate, kindly supplied by Dr. Michael H. Tarbit, at Glaxo Research and Development (United Kingdom). The label was in position two of the heterocyclic indole (Figure 1) and the drug was pure (single peak) as determined by a modification of a high-performance liquid chromatography (HPLC) procedure described earlier (16). Briefly, our HPLC analysis was carried out by using a 250 mm by 4.6 mm 5 μ Supelcosil LC-18S stainless steel column purchased from Supelco Chromatography Products. Detection was by UV with



* = ^{14}C label

Figure 1. Structure of sumatriptan and position of ^{14}C label.

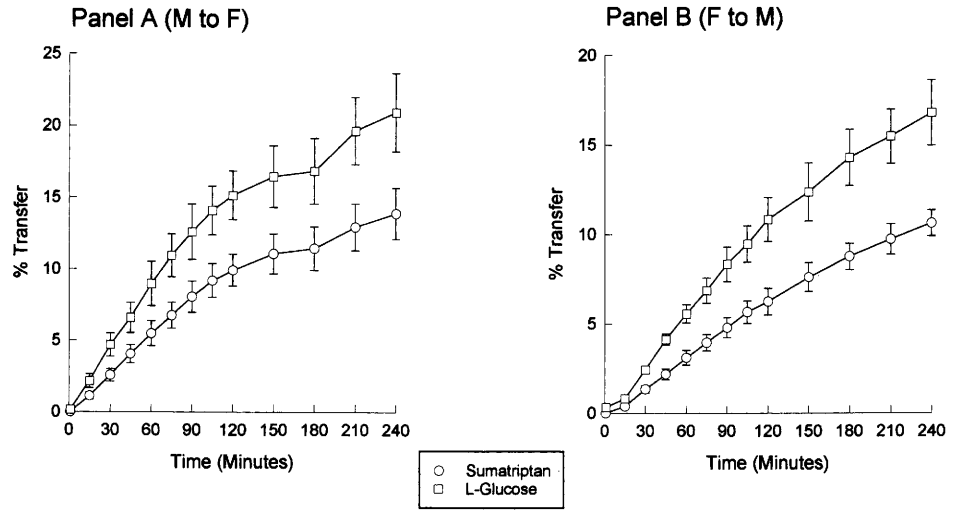


Figure 2. Transfer of sumatriptan from (A) maternal to fetal (M to F) and (B) fetal to maternal (F to M) compartments compared with L-glucose. This is a 4-hr recirculating system. $n = 4$ for each set of studies. This mean ± SEM for each time point is shown. Details of the procedure and statistics are in the text.

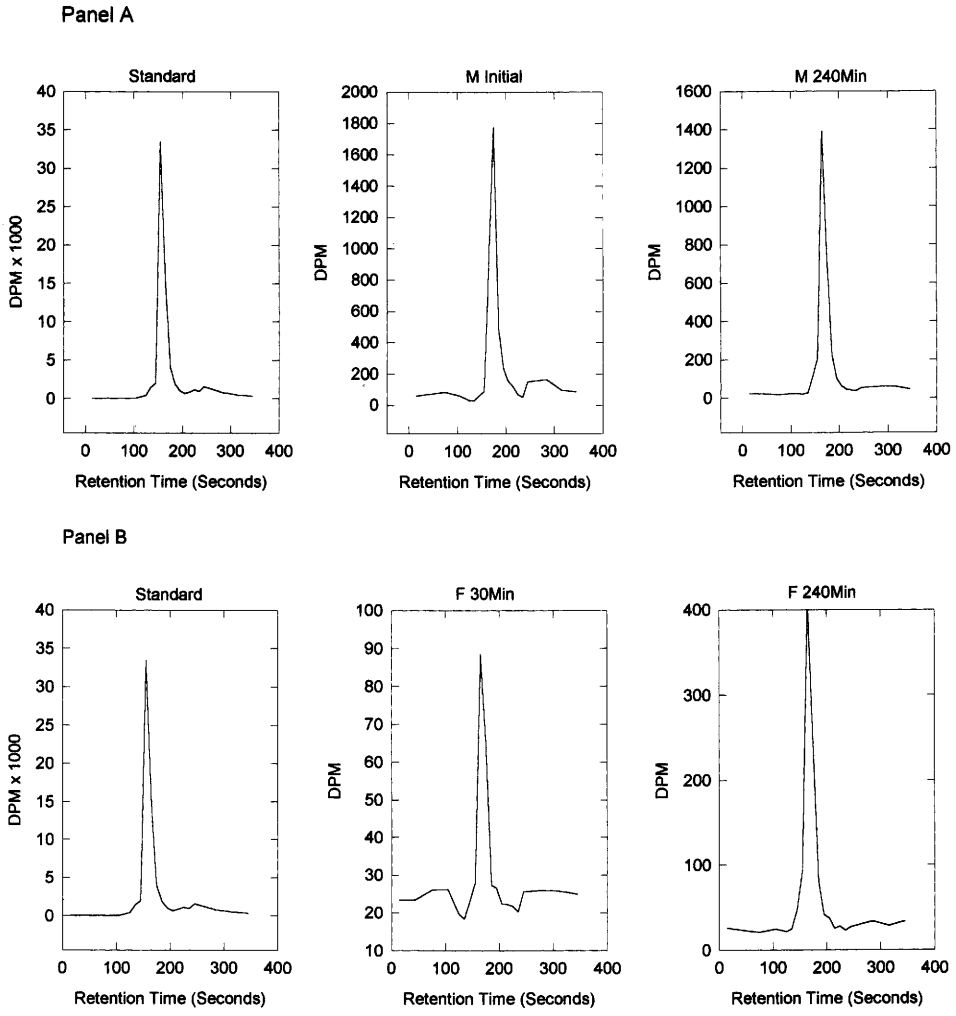


Figure 3. Analyses of maternal and fetal recirculating perfusates for the presence of sumatriptan metabolites. At various time point of the perfusion (given in the plots), radioassay of ^{14}C-sumatriptan was compared with assay of sumatriptan by HPLC (18) as determined initially for sumatriptan standard. Coincidence of label and HPLC in a single sharp peak implies lack of significant metabolism. This was shown for both maternal perfusate (A) and fetal perfusates (B). Representative sequential peaks during perfusion are shown.

a LDC Spectromonitor 1000 detector set at a wavelength of 253 nm. The mobile phase consisted of four parts phosphate buffer (4.19 g of disodium hydrogen orthophosphate and 2.79 g of potassium dihydrogen orthophosphate dissolved in 1.0 liter of water) pH 7.0 to six parts methanol. The flow rate was at 1 ml/min. The ^{14}C-sumatriptan had a specific activity of 137 μCi/mg. For transport studies we utilized a sumatriptan concentration of 60 ng/ml, approximately the maximum level seen on injection of 6 mg of the drug to a 70 kg patient (1, 3). Sumatriptan in the two compartments and the placenta was measured by scintillation spectrometry. To ascertain that the isotope measurements reflected only the parent compound (and not any metabolites also), sequential perfusion and placental samples were studied by both scintillation spectrometry and HPLC to determine the correspondence (identity) of these peaks.

Because some perfused placental samples showed more than one isotopic peak, *in vitro* studies with human placental homogenate were carried out. In these studies ^{14}C-sumatriptan was incubated with term human placental homogenate. Briefly, two 10-g portions of fresh placenta were minced and homogenized each in 10 ml of PBS, pH 7.4, with a Brinkman homogenizer. One homogenate was heated to a boil for 20 min to inactivate the enzymes, and served as a control. To each beaker with homogenate was added 0.0458 ml of 70% Dextrose (final concentration 1.6 mg/ml) and 16.5 μl of ^{14}C sumatriptan succinate which had been diluted 100-fold from a stock solution with a specific activity of 137 μCi/mg. The homogenates were incubated at 37°C for 2 hr. Samples from each were taken in 1-ml aliquots at 0, 10, 20, 30, 45, 60, 90, and 120 min. The reaction was stopped by chilling the sample on ice. Two centrifugations were conducted at 4°C in a microcentrifuge at maximum speed for 10 min, the final supernatants were decanted into microfuge tubes and stored at −20°C for HPLC analysis and radioassay. The active and boiled homogenates were compared.

^{14}C-sumatriptan and ^{3}H-L-glucose transport was measured by scintillation spectrometry. Antipyrine was assayed by HPLC (17). Sumatriptan was also assayed by HPLC, essentially as was described earlier (18).

Statistical analysis involved the nonparametric Mann-Whitney *U* test, suitable for small numbers as it does not assume a normal distribution. Statistical significance was defined as $P < 0.05$ (two-tailed).

Results

In the studies reported here, there was no leakage of reservoir fluid from one compartment to another, the reference markers were transferred at a rate consistent with their transport characteristics and prior

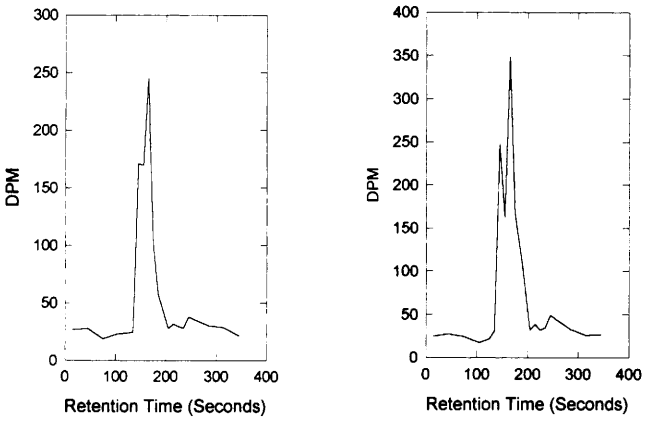


Figure 4. Analyses of perfused placental lobules for sumatriptan metabolites. At the end of various perfusions, the individual perfused lobules were analyzed for radioactivity and by HPLC for sumatriptan, as described in Figure 3 for the placental perfusate. The presence of a shoulder on the peak implies the presence of metabolites, in addition to the parent compound. Analyses of two representative lobules are given.

data (9) and lactate production was 0.58 ± 0.16 μmoles/g/min and glucose consumption 0.51 ± 0.10 μmoles/g/min, similar to data reported by others (16).

As is shown in Figure 2A, sumatriptan was transferred slowly from the maternal to fetal compartments over 4 hr of perfusion in a recirculating system. The percent transfer (see Materials and Methods) was slower than for the passively transported L-glucose, it was essentially linear for both substances over the first 100 min and then tended to equilibrate (became curvilinear) between the two compartments. Calculation of the sumatriptan/L-glucose transfer ratio at 45 and 60 min (in the middle of the linear phase of transport) yielded values of 0.616 ± 0.01 (mean ± SEM) and 0.618 ± 0.02, respectively, for four studies. Thus, sumatriptan transfer was about 62% that of L-glucose. As is shown in Figure 2B, similar findings for the relative rates of transfer of these two substances were seen when fetal to maternal sumatriptan transfer over 4 hr was examined. The sumatriptan/L-glucose transfer ratios at 45 and 60 min (linear transfer plot) were 0.538 ± 0.08 and 0.568 ± 0.08, respectively, for four studies. Thus, sumatriptan transfer in this study was about 56% that of L-glucose. While the transfer ratio from maternal to fetal compartments appears to be a little more rapid than in the opposite direction, the differences lack statistical significance ($P > 0.05$). Most importantly, thus measured, only about 10%–14% of a single dose of sumatriptan crosses the placenta into the opposite compartment in 4 hr. Very similar data (not shown) were obtained when the transfer was calculated in terms of initial drug dose (10). This means that little isotope was retained in the placenta at the end of the study. Indeed, excellent recovery of the initial isotope used was obtained from the composite of maternal and fetal perfusates. The recovery, thus

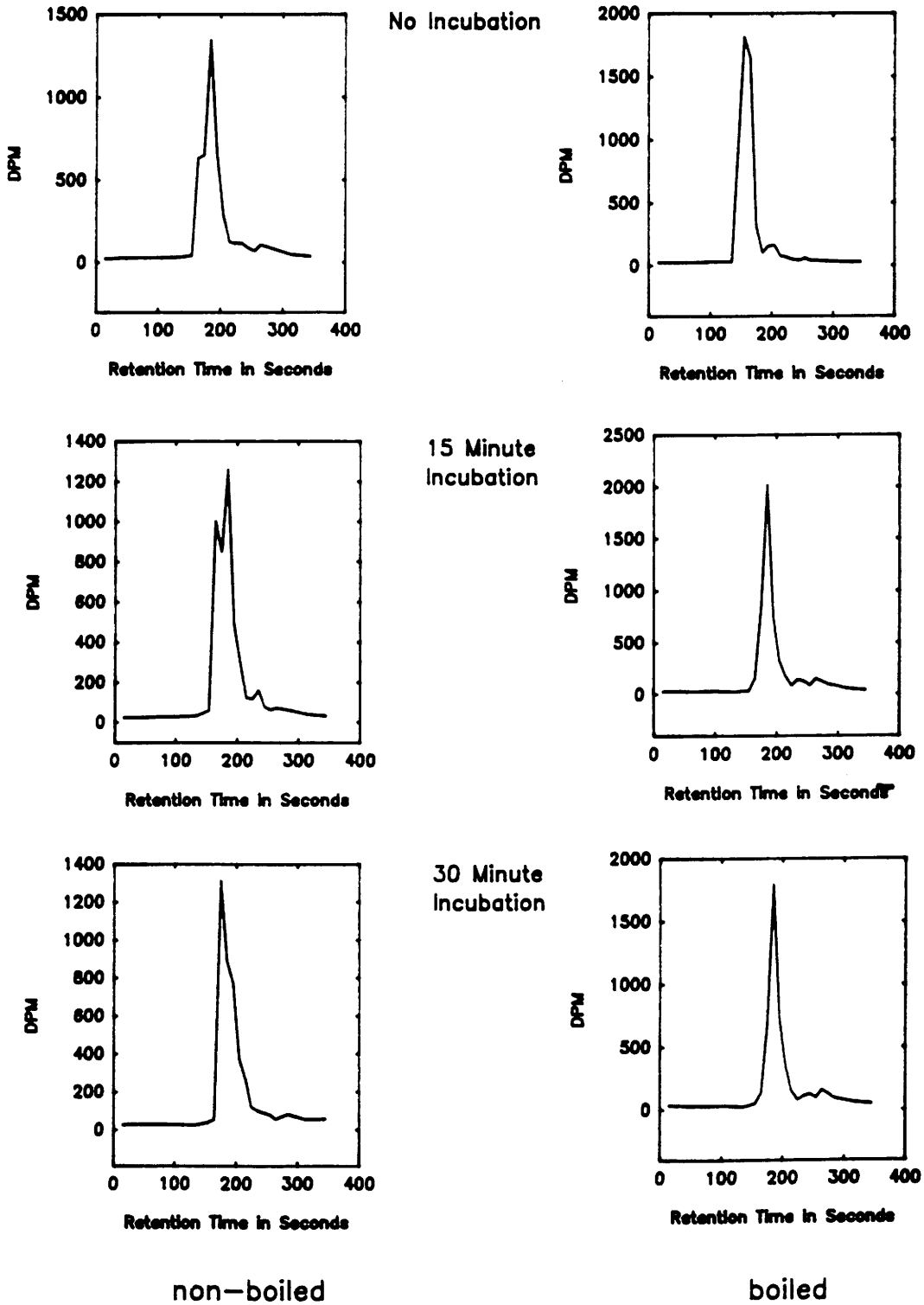


Figure 5. Analyses of placental homogenates incubated with sumatriptan for sumatriptan metabolites. ^{14}C-sumatriptan was incubated with term human placental homogenates, as described in Materials and Methods. Label (measured by scintillation spectrometry) was compared to HPLC analyses, as for sumatriptan standard. Any discordance (shoulder) on the peak obtained, implies the presence of metabolites. Boiled (inactivated) and active homogenate is compared. The presence of a small peak in the 0 time (nonincubated) specimen, likely represented a rapid metabolic reaction as chilling took about 15 sec.

calculated, in three maternal to fetal closed studies was 93.6%, 98.5%, and 103.3%.

As is shown in Figure 3, A and B, early and late analyses of perfusate in the fetal compartment in maternal to fetal sumatriptan studies (Fig. 3A), as well as of maternal compartment perfusate in fetal to maternal studies (Fig. 3B) showed only one isotope peak which coincided with the sumatriptan standard on HPLC. Thus, there appeared to be no metabolite(s) of sumatriptan in either perfusate. This validates the use of label as an index of the parent drug in the perfusates. The sensitivity of this approach is attested by full recovery of labelled sumatriptan originally placed on the column from the single perfusate peak, which coincided with the standard. By contrast, in the perfused placental lobules, obtained at the end of various perfusions, a shoulder (second peak) was apparent in some studies (Fig. 4). This suggests the presence of a metabolite. The nature of this is unknown, but placental sumatriptan concentration *per se* clearly cannot be safely defined from isotopic quantitation only. As indicated above, however, little isotope was retained in the placenta at the end of 4 hr. Moreover, as shown in Figure 5, in some (but not all) studies utilizing placental homogenates, several peaks, likewise, were noted during the incubation, again suggesting the presence of sumatriptan metabolites retained in the tissue. This was not usually evident with prior boiling of the homogenate and presumed inactivation of the relevant enzymes.

As is shown in Table I, the sumatriptan/L-glucose clearance ratio ($n = 4$) from maternal to fetal compartments was 1.023 ± 0.012 (mean ± SEM) (i.e., essentially the same for both substances). The clearance ratio in the fetal to maternal compartments ($n = 3$) was 0.914 ± 0.026, again basically the same. Thus, the clearance of passively transferred L-glucose and sumatriptan did not differ. The clearance ratio from the maternal to fetal direction seems to be a little higher, but this does not quite reach statistical significance for this number of studies ($P = 0.056$). By contrast, the sumatriptan/antipyrine clearance ratio ($n = 4$) was only 0.205 ± 0.042 in the maternal to fetal direction and 0.170 ± 0.069 from the fetal to maternal compartments ($n = 3$). This means that sumatriptan crosses the placenta at only a 17%–20% rate of the rapidly diffusible marker, antipyrine. The clearances of sumatriptan/antipyrine were similar in both directions ($P > 0.05$). The individual clearance rates (ml/min/g) of sumatriptan, L-glucose and antipyrine from maternal to fetal compartments were 0.958 ± 0.509, 0.959 ± 0.515, and 3.710 ± 0.927, respectively. The clearance rates of these substances in the opposite direction were 1.461 ± 0.535, 1.584 ± 0.574, and 7.576 ± 1.561, respectively.

Table I. Clearances of Sumatriptan across the Human Placenta

	Maternal to fetal clearance ratio ($n = 4$)	Fetal to maternal clearance ratio ($n = 3$)
Sumatriptan/ L-glucose	1.023 ± 0.012[a]	0.914 ± 0.026[b]
Sumatriptan/ antipyrine	0.205 ± 0.042	0.170 ± 0.069[c]

[a] Mean ± SEM.
[b] $P = 0.056$ versus maternal to fetal clearance ratio.
[c] $P = 0.400$ versus maternal to fetal clearance ratio.

Figure 6, A and B, depicts the transfer of sumatriptan from maternal to fetal compartments against a concentration gradient. In Figure 6A, leucine, which is known to be transported actively (12), is used as a positive control. In Figure 6B, thiamine, likewise known to exhibit active transport (13), is used as a positive control. While both leucine and thiamine (to a lesser and more variable extent) accumulated as expected in the fetal compartment with a fetal/maternal ratio exceeding unity, sumatriptan was not concentrated and its values were at about unity. Thus, with this experimental technique there was no evidence of active transport of sumatriptan.

Discussion

Sumatriptan (Imitrex$_R$) is a new effective agent for the therapy of migraine. This disorder is common in women of child-bearing age. As there is no information on either transplacental transfer of this drug in such patients or any possible mutagenic effect, caution is presently advised about the use of this drug in pregnancy.

This study defines the rate and nature of sumatriptan transport by the term human placenta. First, our data show that in this system after a single dose of the agent only very small amounts of the drug cross the placenta to the fetus, about 15% of the administered dose over 4 hr. Considering that the average terminal elimination half-life of the drug in adults is only about 2 hr (with a correspondingly high clearance), the fetus should be exposed to only a minor quantity of the drug (3), especially when administered as single doses. At steady state, to be sure, greater transfer of the drug will occur, but at present a single dose of the drug in a 24-hr period is usually recommended (4). The small transfer of sumatriptan across the placenta is consistent with its high molecular weight of 413.5 and its water solubility, as well as its slow transfer across the blood-brain barrier in animal models (10). Similar findings regarding human placental transfer have been reported by us with single doses of oral hypoglycemic agents of comparable molecular weight (5). Moreover, only small quantities of sumatriptan have been found to cross the rat or rabbit placenta (19).

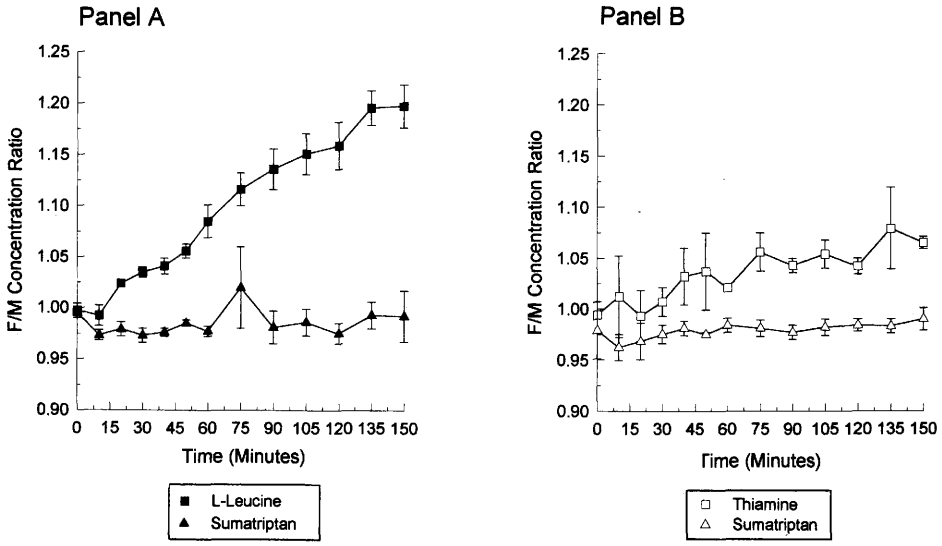


Figure 6. Maternal to fetal transport of sumatriptan in an open/closed system. Transfer of sumatriptan versus leucine (A) and sumatriptan versus thiamine (B) is compared. Each drug is given by constant infusion in the maternal circuit and the same concentration of the drug is placed in the fetal compartment. Accumulation of the drug in the fetal compartment with time (fetal/maternal concentration greater than one) implies a concentrative (active) transport process. Concentration of leucine (A) and of thiamine (B) as positive controls and no concentration of sumatriptan are shown. The data are shown as the mean ± SEM of three studies in each panel. The concentration of sumatriptan was 60 ng/ml, of leucine 100 μM, and of thiamine 50 nM.

Second, we show here that no metabolites of sumatriptan can be identified over 4 hr of recirculation in the placental perfusate. Thus, apparently only the parent drug reaches the fetus. By contrast, a metabolite of sumatriptan, albeit in small quantities, seems to be retained in the placenta. This is shown both in the perfusion studies and in placental homogenate. The nature of this metabolite is uncertain. In adults, however, sumatriptan is metabolized in the liver by a monoamine oxidase (20) to an indole acetic acid analog which is then excreted in the urine both free and as an ester glucuronide (3). It is known that human term placenta contains high levels of monoamine oxidase (21), hence similar metabolites may be generated. Further studies are needed, however, to identify the metabolite(s) of sumatriptan in the placenta.

Finally, the mechanisms of sumatriptan transfer across the placenta has been defined as passive transport. The evidence for this is as follows: (i) Clearance of the drug approximated passively transferred L-glucose in both directions, but was only about 17%–20% of rapidly equilibrated antipyrine. (ii) Calculated as percent transfer, sumatriptan transport was only about 60% that of L-glucose. The lower relative transfer of sumatriptan in this system than with clearance is probably accounted for by the different conditions in these two types of perfusion. Clearance calculations are for a short-term (10-min) transfer and the concentration of the drug given is constant. In the recirculating system the concentration of the drug in the initial compartment is falling. Still, in both systems transfer is very slow and similar. (iii) Transport of sumatriptan is essentially equal in both directions, maternal to fetal and the opposite, implying lack of selective directional carrier. (iv) Transport of the drug does not occur against a concentration gradient. In contrast, leucine and thiamine as positive controls in the same perfusion system are actively transported. It should be emphasized that this perfusion system tests transfer across placental membranes and not any effect of placental blood flow. However, in view of the very slow placental transfer of sumatriptan, tissue transfer seems to be rate limiting and changes in flow are unlikely to play a quantitatively significant part. Moreover, binding of sumatriptan in plasma is very low (6), hence the perfusion system used without physiological protein concentration is reasonable. However, our data relate only to transport across the normal, term placenta, and do not necessarily define transfer rates in early or abnormal pregnancy.

In summary, sumatriptan crosses the human term placenta very slowly and by passive transfer. Only very small quantities of the agent are likely to make an impact on the fetus after single doses of the drug, and these are in the form of the parent drug. Small amounts of metabolites may be retained in the placenta, but their nature requires further study.

ADDENDUM: Since submission of this paper, sumatriptan has also become available in the U.S. as oral tablets. The recommended adult dose is a single 25 mg tablet and the maximum single dose recommended is 100 mg. The mean maximum plasma concentration after a single 100 mg oral dose is 51 ng/ml. This is actually a little lower than the 60 ng/ml concentration used in our studies and is based on an injection of 6 mg SC to a 70 kg patient (1.3). Thus, we

believe that our study applies also to oral sumatriptan use.

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