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Blood–Brain Barrier Penetration of Zolmitriptan—Modelling of Positron Emission Tomography Data

Mats Bergström,[1,2,3,*] Roger Yates,[4,5] Anders Wall,[1] Matts Kågedal,[6] Stina Syvänen[1,2] and Bengt Långström[1]

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Positron emission tomography (PET) with the drug radiolabelled allows a direct measurement of brain or other organ kinetics, information which can be essential in drug development. Usually, however, a PET-tracer is administered intravenously (i.v.), whereas the therapeutic drug is mostly given orally or by a different route to the PET-tracer. In such cases, a recalculation is needed to make the PET data representative for the alternative administration route. To investigate the blood–brain barrier penetration of a drug (zolmitriptan) using dynamic PET and by PK modelling quantify the brain concentration of the drug after the nasal administration of a therapeutic dose. [^{11}C]Zolmitriptan at tracer dose was administered as a short i.v. infusion and the brain tissue and venous blood kinetics of [^{11}C]zolmitriptan was measured by PET in 7 healthy volunteers. One PET study was performed before and one 30 min after the administration of 5 mg zolmitriptan as nasal spray. At each of the instances, the brain radioactivity concentration after subtraction of the vascular component was determined up to 90 min after administration and compared to venous plasma radioactivity concentration after correction for radiolabelled metabolites. Convolution methods were used to describe the relationship between arterial and venous tracer concentrations, respectively between brain and arterial tracer concentration. Finally, the impulse response functions derived from the PET studies were applied on plasma PK data to estimate the brain zolmitriptan concentration after a nasal administration of a therapeutic dose. The studies shows that the PET data on brain kinetics could well be described as the convolution of venous tracer kinetics with an impulse response including terms for arterial-to-venous plasma and arterial-to-brain impulse responses. Application of the PET derived impulse responses on the plasma PK from nasal administration demonstrated that brain PK of zolmitriptan increased with time, achieving about 0.5 mg/ml at 30 min and close to a maximum of 1.5 mg/ml after 2 hr. A significant

[1]Uppsala Imanet AB, University Hospital, SE-751 85, Uppsala, Sweden.
[2]Department of Pharmaceutical Biosciences, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden.
[3]Current Address: Novartis Pharma AG, WKL-135.1.73, CH-4002 Basel, Switzerland.
[4]AstraZeneca, Alderly Park, Macclesfield, UK.
[5]Current Address: RayCandoc Ltd., Macclesfield, UK.
[6]AstraZeneca, Södertälje, UK.
*To whom correspondence should be addressed. Tel: +41-61-696 2772; fax: +41-61-696 6992; e-mail: Mats.Bergstroem@Novartis.com

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brain concentration was observed already after 5 min. The data support the notation of a rapid brain availability of zolmitriptan after nasal administration.

KEY WORDS: positron emission tomography; zolmitriptan; modelling; convolution; brain; pharmacokinetics.

INTRODUCTION

Positron emission tomography (PET) is becoming more widely used and proven as an important tool in drug development (1–4). One reason for this is the development of new labelling methods that allow a multitude of candidate or existing drugs to be labelled with positron emitting radionuclides. In particular, a new option to use [^{11}C]CO as the synthon has enabled a range of chemical entities to be labelled and their *in vivo* kinetics probed (5).

PET studies for drug development has until now predominantly explored a drug's effect on a target system using a tracer specific for this target and evaluation of the reduction of the tracer binding, interpreted in terms of the drugs inhibition or occupancy of the target system (6). Although crucial in the early drug development (7,8) standard PK studies do not reveal organ distribution, and only sometimes can reasonable assessments be made in this respect, by combining human PK data with information from animal studies. This is a case where PET gives unique possibilities. Utilising a drug candidate labelled with a positron emitting radionuclide, PET allows direct recording of the labelled drug's distribution within the body (9–13). A high temporal and spatial resolution, plus tomographic imaging with excellent quantitative accuracy, are features which give PET an important role in drug distribution studies (14). The major technical drawbacks include limited follow up times, reduced to a few half-lives of the radionuclide. In studies with ^{11}C, the half-life of 20 min restricts the follow up times to about 1.5 hr. Another important aspect is that PET does not allow a discrimination between labelled entities and hence radioactive native compound is interpreted together with possible radiolabelled metabolites.

A PET study allows accurate determinations of radioactivity concentration, and with the limitations given above, this can be recalculated into drug concentrations when tracer and cold compound is co-administered. This is based on the fact that the relation between radiolabelled and non-labelled drug is maintained since they are chemically identical and hence have identical distribution and elimination. In this way the organ kinetics of a drug can be determined in a PET study in absolute terms.

However, PET studies are preferably performed with the tracer given as intravenously (i.v.) injection because through this route of administration the radioactivity is rapidly distributed in the body. With oral or other

administration routes the amount of radioactivity given must be reduced for radiation safety concerns. A very localized radioactivity such as in a small volume swallowed, could potentially give rise to a locally high radiation dose to an aspect of the gastro-intestinal tract. Oral administrations are therefore performed with about a 10–20 fold reduction in given radioactivity (1,15) and are therefore associated with an impaired image quality and impaired precision in the measurements. In order to overcome this dilemma, a possibility is to perform a PET study with i.v. administration of the tracer and observation of organ kinetics associated with this. Together with tracer kinetics in plasma a PK-model is generated to describe the rate of tracer exchange between plasma and organ (9). Thereafter this model is used for the calculation of organ "cold drug" kinetics, using PK after oral administration as input.

Zolmitriptan is widely used as an effective anti-migraine treatment. A new nasal spray formulation is associated with a more rapid appearance in plasma (from 2 min post dose) and a more rapid relief from the migraine pain (from 10 min post dose) (16–18). The mechanism of action is believed to be agonistic effects on $5HT_{1B/1D}$-receptors and it has been suggested that this action by zolmitriptan is exerted both at the vascular level and in the brain parenchyma. Since no data were available on the entry of zolmitriptan over the blood–brain barrier (BBB), a PET study was initiated for the determination of zolmitriptan kinetics in brain.

The purpose of the present communication is to illustrate this suggested concept of generating organ distribution data, utilising data from a study of the distribution of ^{11}C-labelled zolmitriptan into brain as assessed by PET after i.v. administration of the tracer, and combining it with cold zolmitriptan administered as a nasal spray. The clinical data are included in a separate communication (19).

MATERIALS AND METHODS

Eight healthy volunteers, 5 men and 3 women were recruited for the studies. Each volunteer underwent the same procedures, including one PET study with ^{15}O–CO for the determination of region blood volume in the brain and one ^{11}C-zolmitriptan brain distribution study. This was followed by a nasal spray administration of 5 mg unlabelled zolmitriptan. Thirty minutes later a new ^{11}C-zolmitriptan brain distribution study was performed. An additional PET study with ^{15}O-water and an MRI study was inserted for anatomical localisation. The ^{11}C-zolmitriptan PET-investigations included a 5 min i.v. infusion of about 600 MBq ^{11}C-zolmitriptan and dynamic imaging with 18 frames (5 frames of 60 s

each, $5 \times 180, 2 \times 300, 6 \times 600$ s) acquired during 90 min. The studies were made in three dimensional (3D) mode on a CTI HR + PET-camera with 64 tomographic images obtained simultaneously covering an axial field of view of 15 cm. The spatial resolution was approximately 5 mm using the supplied 3D filtered backprojection algorithm.

During each of the ^{11}C-zolmitriptan studies, 11 venous blood samples were taken for the determination of blood and plasma radioactivity concentration. Four additional blood samples were taken and used for the determination of intact ^{11}C-zolmitriptan and its prime metabolite ^{11}C-183C91. Further plasma samples were taken after nasal administration of zolmitriptan for the determination of PK of zolmitriptan and its prime metabolite 183C91.

Since blood sampling failed during the first 5 min in one individual, the data from that person was not used and only 7 studies are included in this report.

The studies were performed with informed consent from the volunteers and with permissions from the Local Ethics Committee, Radiation Ethics Committee and the Swedish Medical Products Agency.

Generation of Quantitative Data

The images were reconstructed with attenuation and scatter correction (Fig. 1). In the ^{11}C-zolmitriptan images regions of interest were outlined to represent different grey matter regions. For each of the regions, time-activity data were generated and recalculated as SUV values.

$$\text{SUV} = \text{local radioactivity concentration (Bq/g)/(injected radioactivity (kBq)/body weight(kg))}.$$

The radioactivity concentration in each region was corrected for vascular tracer contribution by subtracting the product of local blood volume (obtained from the ^{15}O–CO study) and whole blood radioactivity concentration for each time point (also represented in SUV).

The brain time-activity curves were averaged for all grey matter regions within each individual, after subtraction of vascular contribution (Fig. 2).

Utilising HPLC-separation, the radioactivity in plasma samples were analysed with respect to intact ^{11}C-zolmitriptan and ^{11}C-183C91. Since both these are pharmacologically active and brain penetrating, the combined fraction of total plasma radioactivity constituted by these two was determined for the four different time points. For each individual a bi-exponential function, conditioned to be 100% at time zero, was fitted to these data. Then

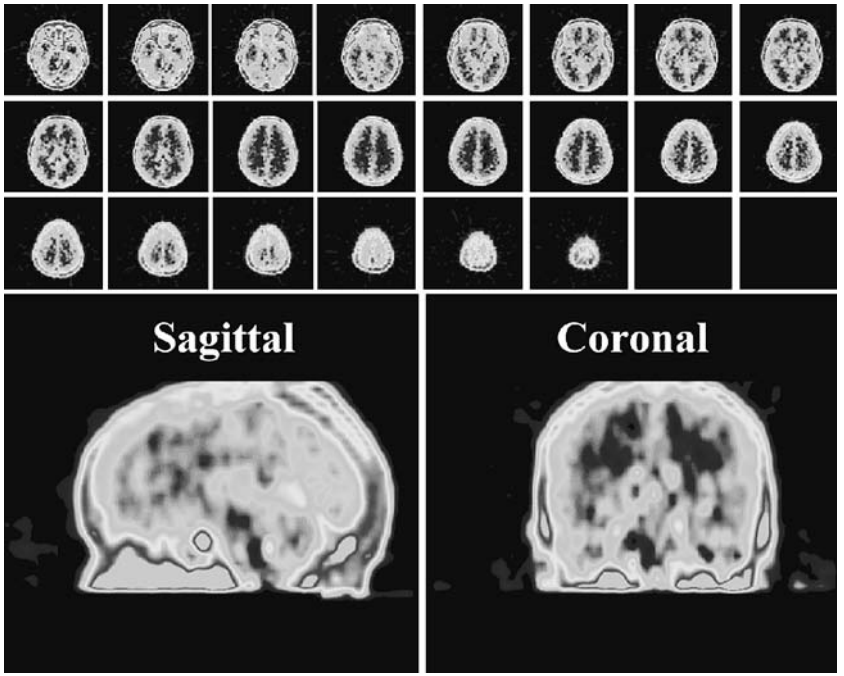

Fig. 1. PET images over a central part of the brain, obtained after administration of ^{11}C-zolmitriptan. Upper three rows show sequential caudal to cranial transaxial slices. Lower images show midline sagittal (left) and coronal (right) slices. The highest uptake is noted in extracranial structures, and a low uptake is seen in brain tissue.

the plasma radioactivity was multiplied by the data from this bi-exponential, to obtain plasma values corrected for other metabolites than 183C91. The plasma time-activity data were expressed in SUV (Fig. 2).

Deconvolution of Brain Time-Activity Data

With the assumption that the transfer of drug from capillaries to brain parenchyma is linear with respect to concentration and time independent, that is at each time point and for each concentration in plasma the rate constants for transport of drug across the BBB are the same, a so-called convolution method could be applied. This can be understood as that the time course of plasma concentration in the capillaries is divided into small portions, e.g. every second, and the fate of drug during each of these time periods is handled separately. Hence, the exposure from one such period will lead to a certain uptake in brain, followed by a washout since no further exposure is given. This is what we define as the impulse

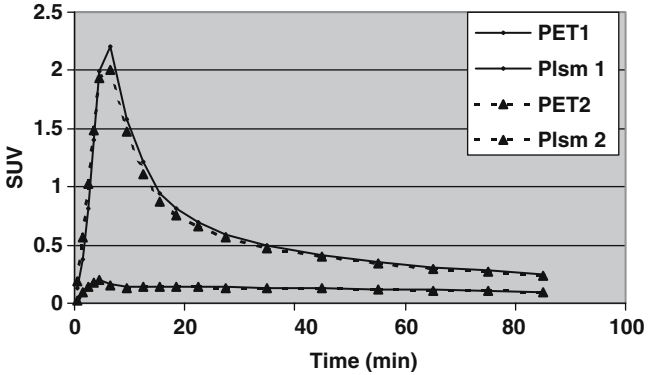

Fig. 2. Time activity curves of brain tissue (PET1 and PET2) and venous plasma, expressed in SUV. Higher curves show plasma and lower curves brain concentrations from the two different studies, before (full lines, PET1 and plsm1) and after nasal administration of zolmitriptan (broken lines, triangles, PET2 and plsm2). The highest values are seen in plasma, with peak SUV of 2.2 whereas brain concentration reaches a maximum of about 0.2. The data from the two occasions are very similar. Averages of all individuals with plasma corrected for metabolites and brain values corrected for vascular contribution.

response if we normalize for the plasma concentration of the period. The overall resulting brain kinetics will be the summation of each small contribution which in turn will be the impulse response multiplied by the momentary plasma concentration.

The brain PET data is represented by the impulse response, convolving the full capillary plasma time-activity data (20,21):

$$B(t) = I(t) \otimes A(t), \tag{1}$$

where $B(t)$ represents brain time-activity data, $A(t)$ represents capillary plasma time-activity data, $I(t)$ represents impulse response from capillary to brain and $\otimes$ denotes convolution.

Since venous blood samples were used for the determination of plasma time-activity data, a correction must be made for the fact that arterial and capillary time-activity data are different from venous time-activity data (22). This correction was based on the assumption that the passage of tracer from arterial plasma via the tissue to venous plasma could be described as composed of two components: one component representing plasma from which no extraction to tissue occurs and one component where a certain fraction E is extracted. The extracted radioactivity is then assumed to have a first order elimination kinetics from tissue to plasma. With this assumption, an impulse response can be defined to represent the relation between arterial plasma and venous plasma:

$$V(t) = g(t) \otimes A(t) \tag{2}$$

$$\begin{aligned} g(t) &= (1 - E) * \Delta t \quad \text{for } t < \Delta t \\ g(t) &= k * E * \exp(-a * t) \quad \text{for } t > \Delta t, \end{aligned} \tag{3}$$

where $V(t)$ represents venous blood time-activity data, $A(t)$ represents arterial blood time-activity data, $g(t)$ represents impulse response from arterial to venous plasma, $\otimes$ denotes convolution, E = extraction during passage from artery to vein in the hand, Δt represents transit time from capillary to venoules, a represents an exponential for the washout from hand tissue and, the constant k is set so that the integral of $g(t) = 1$.

We define now a new function $g^{-1}(t)$ such that:

$$B(t) = [g^{-1}(t) \otimes I(t)] \otimes V(t). \tag{4}$$

In order to solve the relationship between venous plasma time-activity $V(t)$ and brain time-activity $B(t)$, a program was written in MATLAB which iteratively fitted Eq. (4) to PET data. Hence $I(t)$ was described as a tri-exponential function with 6 free parameters to allow sufficient degrees of freedom, and $g^{-1}(t)$ was described by three singular terms, hence 3 free parameters (see below). These free parameters were iteratively optimized so that the convolution according to Eq. (4) fitted the data of $B(t)$.

Convolution of PK Data

With the assumption that PET-data could supply an impulse response, describing the relation between brain time-activity data and venous plasma time-activity data, and with the assumption that the relationship between brain and plasma is time invariant and linear, brain PK data can be obtained as a convolution of plasma PK-data with this impulse response.

$$Bc(t) = [g^{-1}(t) \otimes I(t)] \otimes Vc(t), \tag{5}$$

where now $Bc(t)$ equals brain kinetics of cold zolmitriptan and $Vc(t)$ equals venous plasma PK of zolmitriptan, $g^{-1}(t)$ and $I(t)$ are the impulse responses obtained in the PET study.

There is always a risk that the transfer from plasma to brain is non-linear with respect to plasma concentration, that is proportionally less or more of drug enters the brain when plasma concentration of drug changes. This can happen e.g. if active transport systems or efflux systems become saturated as the drug concentration increases. Therefore the PET investigations with ^{11}C-zolmitriptan were performed under two different conditions:

at tracer alone doses and at a time when cold zolmitriptan had reached close to its maximum in plasma. In the first instance the plasma concentration is of the order of nM while in the second it is of the order of μM. A comparison of these two allows an assessment if brain penetration is dependent upon the plasma concentration of cold compound. In the present case the impulse response functions were similar at the two occasions and an average of the two, to reduce statistical variations, was used.

RESULTS

Convolution Arterial to Venous Plasma

Using an arterial to venous convolution function g(t) as defined above, and a simulated arterial function, a venous function was generated (Fig. 3). This venous function was then converted to the original arterial function by convolution with an "inverse" function specified by a 3–5 value function with an initial positive value and negative followers. The deconvolution of simulated venous curve to an arterial curve restored the original with a difference in area less than 1%.

Convolution Function Plasma to Brain

Fitting of a plasma-to-brain impulse response, described solely by the sum of three exponentials, to data utilising Eq. (1) resulted after reconvolution in values which clearly did not fit well to the original data (Fig. 4). Applied on the average data, the area under the curve difference was 10%. The errors were especially pronounced in the early time period where the peak was delayed as compared to the original data.

When an arterial-to-venous convolution function was included, the curve generated fitted much better to the data. If the average of all brain curves and the average of all plasma curves were generated for the whole group, and the method suggested was applied on these averages, the area under curve deviation was 2.2%. Applied in all individual studies, the area under curve deviation was on the average 4.2% (SD 2.1 and range 2.0–9.3).

The convolution function obtained by only utilising a three-exponential as impulse response had a rapidly reducing aspect initially followed by almost constant values (Fig. 5). The convolution function including arterial-to-venous convolution had one initial high value, followed by two negative values and thereafter a close to mono-exponential decrease described by $0.048^* \exp(-0.023^* t)$. This latter part corresponds to a half-life of 30 min.

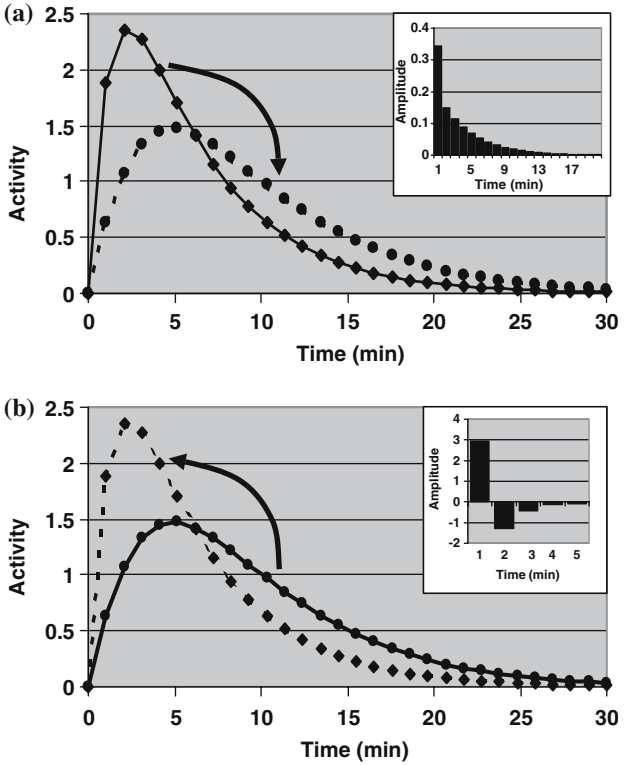

Fig. 3. (a) Illustration of a simulated arterial curve (full line) and its convolution (dotted line) with a function g(t) from Eq. (3) with E = 0.85 and $a = 0.25$. (b) The arterial curve of (a) has then been restored by convolution of the venous curve (full line) using the "inverse" of the function g(t). The recalculated arterial curve agrees with the original within less than 1%. Inserts show the respective impulse response functions.

Convolution to Obtain Brain PK

The impulse responses as obtained above from PET data were in turn used for each individual to obtain the time course of cold zolmitriptan in brain by convolving plasma PK data with these impulse responses. The results show that brain zolmitriptan increases with time, reaching 0.5 mg/ml after about 0.5 hr and coming close to a maximum of 1.5 mg/ml after 2 hrs (Fig. 6).

Data Variability

The data obtained in this study are based on a rather small group of individuals, but still allow for estimates on variability in the PK parameters.

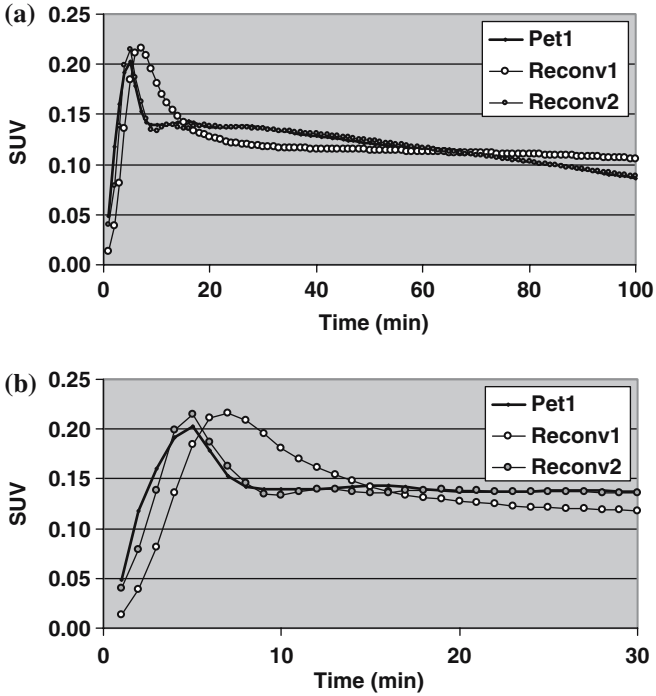

Fig. 4. Brain kinetic data (PET1, full line), averaged over all individual baseline studies. Reconv1 (large filled circles) represents data obtained by convolving plasma with an impulse response for plasma to brain transfer. This impulse response is described as a three-exponential with parameters obtained by fitting Eq. (1) to actual data. The deviation in AUC compared to the original brain data is 10%. Reconv2 (smaller circles) represents data obtained where the impulse response from plasma to brain, is described by a three-exponential combined with a three point description of the "inverse" of arterial-to-plasma impulse response. Then plasma was convolved with the combination of these two impulse responses. The deviation in area from the original brain data is 2.2%. (b) represents a magnification of (a) and shows that the inclusion of an additional arterial-to-venous convolution term improves the description.

The differences in values between baseline and after drug administration were determined. The ratio of the integral of the impulse response comparing post nasal spray to baseline study was on the average 1.11 with a CV of 14%, suggesting lack of difference between the two instances and an inter-occasion variability of the order of 14%. The integral of the impulse response at baseline was on the average 0.24 with a 14% CV when comparing the different individuals, suggesting that the inter-individual differences in brain penetration were smaller than or of the same order as the method variability. The AUC of the plasma radioactivity in the baseline studies was on average 60 SUV*min with a CV of 25%. The AUC of plasma PK was on

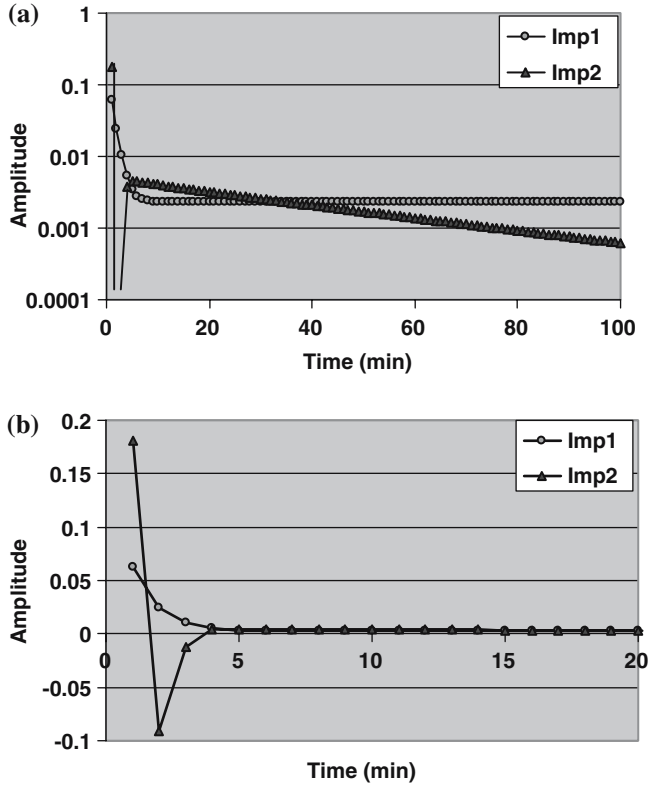

Fig. 5. Impulse responses determined with two concepts: Imp1 from a three-exponential fit, Imp2 from three-exponential combined with an arterial-to-venous "inverse" impulse response. in (a) logarithmic scale and (b) in linear scale.

average 669 ng/ml*min with a CV of 56%. However, one individual might be an outlier with low PK-values (7 ng*min) possibly related to an unfavourable nasal absorption. Excluding this individual the average increased to 768 ng/ml*min and the CV decreased to 38%. The AUC of brain kinetics of zolmitriptan showed an inter-individual variability of 42%.

Discussion

The present work presents a method whereby the brain kinetics of a drug is described as a convolution of venous plasma kinetics with an impulse response for exchange over the BBB. This impulse response is derived from a PET study where the labelled drug is given as a short i.v. infusion and plasma radioactivity is measured in venous blood samples

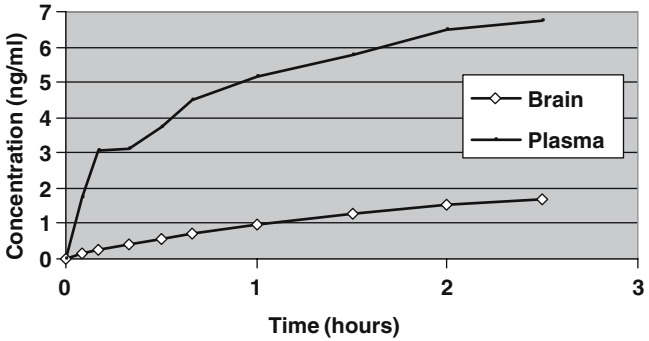

Fig. 6. Plasma PK of zolmitriptan (upper line) after intranasal administration and brain PK of zolmitriptan (lower line with diamonds) as obtained by convolution of plasma PK with the impulse response for transfer from plasma to brain obtained from the PET study. Method applied individually whereupon average determined over the group.

and brain radioactivity is measured with a PET camera. With the assumption that this impulse response is unchanged in relation to the administration route and the actual plasma kinetics, the brain kinetics from any administration route can be derived as the convolution of the actual PK with the impulse response.

In order to ensure one important condition for this concept, that the exchange over the BBB is concentration independent, the study was performed both at tracer concentration, that is before administration of therapeutic amounts, and at a time point after administration of drug, when close to maximum plasma concentration has been reached. The data in the present study do suggest that the exchange of zolmitriptan over the BBB is independent of drug concentration in plasma, since the impulse responses obtained at the two occasions were not statistically significantly different. The ratio of the integral of the impulse response after and before drug administration was 1.11 (SD: 0.16) and the shapes of the impulse responses were the same. The proposed methodology might give the opportunity to correct for non-linearities by including an impulse response function which change with plasma concentration. In such case the mathematical operation would not be denoted convolution but rather integral transformation. However, such operation would only be adequate if the full concentration dependence was known and considered. Biological factors which could give rise to lack of dose-linearity and time independence, and hence invalidate the suggested method, include: saturable transport and efflux over the BBB because of selective pump systems, saturable enzymes in the BBB, physiological effects on the capillaries by the drug, e.g. exerting effects on cerebral blood flow.

A more direct way of performing a pharmacokinetic study with PET is to have the tracer and drug mixed and co-administered. This mode is ideal for i.v. administrations and will then give the possibility to directly derive organ kinetics. The drug concentration is simply achieved by multiplication of the tracer SUV with administered drug in mg/kg. This concept is, however, not always possible to utilize. One situation could be when an i.v. administration formulation is not available or more difficult to apply. Another situation is when the preferred route of administration is other than i.v. Finally, instances when the drug has a very slow kinetics compared to the possible follow up time with PET could make it difficult to use a co-injection scheme.

In the PET field, the exchange of tracers over the BBB has predominantly been described by compartment modelling (23,24), although a spectral analysis method has been described by Cunningham and Jones (25). Similarly to the method described in the present communication, such concepts would allow a definition of exchange parameters, which through mathematical modelling could be applied on plasma PK to derive organ kinetics. We have, however, preferred to use the convolution concept since it conceptually suggest an exchange process rather than dividing the pharmacokinetic events into compartments, which can lead to oversimplifications in the descriptions of the biological complexity. However, the two modes may mathematically be equivalent if the parameters in the convolution is limited. Both methods have in common that they may need additional parameters to include non-linearity with dose and with time. The convolution concept is also used in other aspects of pharmacology, e.g. IVIVC (26) and in certain in silico-*in vivo* predictions (27). A special feature has been introduced here, and that is the utilisation of venous blood samples for description of plasma radioactivity kinetics. One motivation for this is the fact that traditional PK is derived from venous plasma samples and therefore a direct conversion from a PET tracer study to PK data should also involve radioactivity derived from venous plasma samples. Otherwise a separate determination of the venous-to-arterial conversion must be made.

Some studies have demonstrated erroneous PK parameters when based on venous concentrations (28). Hysterisis (i.e. a delay between brain concentration and effect, which has been shown when predicting brain concentration utilizing venous PK data) has been demonstrated to be an artifact related to a delay between arterial and venous PK data (29,30).

Traditional PET modelling includes the acquisition of arterial blood samples obtained with rapid sampling to supply the input function. In the proposed scheme with implicit correction for the arterial-to-venous blood impulse response, arterial sampling is avoided, which is of great advantage

for the practical performance of the study. The method allows this function to be estimated, but it should not be taken in strict biological sense as the arterial-to-venous conversion but only as part of a general impulse response describing the relation between venous plasma and brain tissue. The practical advantages of the proposed method includes the avoidance of the ethical aspects of arterial sampling, with a slight risk for extensive bleeding. Furthermore, there is a recommendation to limit arterial needles to maximum twice which may place limits in the planning of studies. The disadvantages could include that the true relation of venous to arterial plasma curves are not known and when mathematically derived could be slightly misleading. The method is less suited for a determination of a direct tissue influx parameter ki, but should adequately describe the overall tissue PK of the drug. Further work with a direct measurement of venous and arterial plasma kinetics of the tracer on an individual basis would allow a comparison between the true arterial-to-venous impulse response and the mathematically derived.

The present study shows that zolmitriptan, with some caution with respect to the inclusion of radiolabelled metabolites, does enter brain tissue and that at a level which approaches 25% of the plasma concentration. The rate of passage over the BBB is rapid enough to give a brain concentration of 0.5 mg/ml at 30 min after administration as a nasal spray. Already 5 min after nasal administration, a significant concentration of zolmitriptan is detected in the brain. These data give new insights into the brain distribution of zolmitriptan and can as such serve as a basis for the speculation whether the effect is exerted inside the brain or is restricted to effects on the brain capillary endothelium.

This study confirms that the major contribution to inter-individual variability in organ kinetics of a drug is related to variability in plasma kinetics which is in turn due to absorption, elimination and metabolism. The kinetic parameters describing exchange over the BBB shows a moderate variability between occasions in the same individual, of the order of 14%. This is a combination of the precision of the different measurements, including camera and plasma measurements, and individual physiological factors of the volunteer. Test–retest variability of other types of PET studies has been shown to be of the order of 5–15% depending on tracer and analysis method (31–33). The inter-individual variability of the impulse response describing passage over blood-brain-barrier was of the order of 14%, which would also include the method variability, indicating that in this volunteer material the BBB properties with respect to zolmitriptan are very similar.

The AUC of the plasma kinetics of the tracer showed a CV of about 25%, indicating the further introduction of inter-individual variability by

elimination and metabolism of the tracer. The highest variability of 38% was seen in the AUC of zolmitriptan plasma concentrations. This includes the different factors of elimination and metabolism but suggests that a dominant source of variability of drug kinetics in this case is the degree of absorption of zolmitriptan over the nasal mucosa. Combining this with the variability of the passage over the BBB, the brain concentration of zolmitriptan showed an inter-individual variability of 42%.

CONCLUSIONS

This work illustrates a situation in which a PET study with i.v. administration of the labelled drug [^{11}C]-zolmitriptan has been used to describe the exchange of drug between plasma and brain. This information has in turn been applied on "cold" plasma concentration after a therapeutic administration via nasal inhalation to describe the brain concentration kinetics of drug. The method utilizes a convolution modelling in which plasma kinetics from venous blood sampling is used as input, which simplifies the study as compared to most PET-modelling concepts which require arterial blood sampling.

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