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Hepatic plasma clearance of ^{99m}Tc-HEPIDA as a diagnostic tool: theoretical basis for a simplified determination

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Abstract

The determination of hepatic plasma clearance of ^{99m}Tc-HEPIDA is becoming a clinically attractive test. It is not necessary to perform always the determination using an extensive sampling of blood over the period of 0–90 min post injection of the radiopharmaceutical. For screening purposes a simplified method is adequate, even if less precise of the low values of the clearance. In this paper a theoretical basis has been presented for the development of such a simplified procedure, based on a single plasma sample for determination of the hepatic and urinary clearance of ^{99m}Tc-HEPIDA.

Key words: ^{99m}Tc-HEPIDA: total plasma clearance, ^{99m}Tc-HEPIDA hepatic and urinary clearance

Introduction

The methodology of specific hepatic plasma clearance of ^{99m}Tc-HEPIDA was presented in a previous paper from this series [1]. Apart from the method elaborated, a justification for the use of this test was presented. The main reason for the use of the test in elaborated form rests in the observation that total plasma clearance of the radiopharmaceutical is, in fact, the sum of hepatic and urinary clearance. The latter amounts to a very variable fraction of the total, both in absolute and relative terms. Therefore, the total plasma clearance seems a deficient tool for the specific assessment of the excretory functioning of the liver.

The performance of hepatic clearance determination, as outlined in previous studies [1–6], requires serial blood sampling over about 90 minutes post intravenous administration of ^{99m}Tc-HEPIDA. This test seems quite precise but at the same time laborious.

A simplified method for total plasma clearance has been proposed by Studniarek and Wojciechowski [7]. The method is quite simple, based on the sampling of a single blood sample, and its empirical basis rests on the very strong negative correlation between the concentration of ^{99m}Tc-HEPIDA (in relative terms, i.e. in per cent of injected activity per ml of plasma) at a given time post injection and the integral ($0 \rightarrow \infty$) of the time plasma activity concentration function, used for clearance calculation. From our previous studies on urinary clearance, such simplified methods are quite accurate and precise at normal and slightly impaired renal function, but lose these characteristics at very low values of the clearances [8–14]. For screening of patients, i.e. for discrimination between those with normal and substantially impaired excretory function, they are completely adequate.

To streamline the specific hepatic plasma ^{99m}Tc-HEPIDA clearance, a simplified method would obviously be desirable. One should try, however, to examine whether there are satisfactory theoretical grounds to develop a respective method taking into account that the hepatic clearance is in fact the difference between total plasma and urinary clearance of ^{99m}Tc-HEPIDA.

Theoretical considerations

Let us assume that at time τ after initial mixing, the radiopharmaceutical in plasma has become uniformly distributed and its concentration amounts to $c(\tau)$. Owing to the clearance of plasma by an organ (or organs), the radiopharmaceutical undergoes elimination from the organism (not necessarily by one route). As there

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is no indication that elimination could be a non-first order process, the amount dm of the substance, separated at the moment $d\tau$ from the plasma, should be proportional to the actual concentration $c(\tau)$ in the plasma. Then

$$dm = Cl_{Pl} \bullet c(\tau)d\tau \quad (1)$$

The proportionality coefficient Cl_{Pl}, in the above equation will be called plasma clearance.

Solving the above equation one can obtain another equation, describing the amount (mass, activity), $m\Big|_{t_1}^{t_2}$, separated from plasma in a discrete time interval from t_1 to t_2:

$$m\Big|_{t_1}^{t_2} = Cl_{Pl}\int_{t_1}^{t_2} c(\tau)d\tau \quad (2)$$

After transformation, a formula can be obtained which enables calculation of the clearance:

$$Cl_{Pl} = \frac{m\Big|_{t_1}^{t_2}}{\int_{t_1}^{t_2} c(\tau)d\tau} \quad (3)$$

When a respective radiopharmaceutical of the activity A_p has become injected (instantaneously) at $t = 0$, and the substance undergoes neither metabolic modification nor reabsorption into the blood or an organ, it will become completely eliminated from the system (by all possible routes) over an infinitely long period of time ($t_2 \to \infty$), and therefore:

$$m\Big|_{0}^{\infty} = A_p \quad (4)$$

The formula (3) assumes then a well-known form, used commonly for calculation of the plasma clearance:

$$Cl_{Pl} = \frac{A_p}{\int_0^{\infty} c(\tau)d\tau} \quad (5)$$

To determine the clearance Cl_{Pl}, one must know the injected activity of the radiopharmaceutical (A_p), and an area under the curve, representing the function $c(\tau)$ from the moment of injection ($t = 0$) until infinity. The injected activity can be directly measured; the area can be mathematically calculated if the analytical form of the function $c(\tau)$ is known.

One can further assume that elimination of the radiopharmaceutical from the organism occurs by a finite number (n) of organs and that each organ eliminates until infinity activity A_i, where $i = 1,2,...,n$. The total activity removed from the body must equal that injected and can be expressed as a sum of the activities eliminated by all the relevant organs:

$$A_p = \sum_{i=1}^{n} A_i \quad (6)$$

Substituting the right hand side of the equation (6) into formula (5) and transforming, one obtains:

$$Cl_{Pl} = \frac{\sum_{i=1}^{n} A_i}{\int_0^{\infty} c(\tau)d\tau} = \sum_{i=1}^{n} \frac{A_i}{\int_0^{\infty} c(\tau)d\tau} \quad (7)$$

and thus:

$$Cl_{pl} = \sum_{i=1}^{n} Cl_i \quad (8)$$

where Cl_i - the i-th organ clearance ($i = 1,2,...,n$).

This formula demonstrates that total plasma clearance is the sum of particular organ clearances. When a radiopharmaceutical is eliminated only by a single organ ($n = 1$), e.g. by the kidneys, then

$$Cl_{Pl} = Cl_{Ur}$$

where Cl_{Ur} denotes kidney clearance. In such a situation plasma clearance can be utilised as a measure of organ clearance.

When a radiopharmaceutical is eliminated by two organs, by the liver and the kidneys, then

$$Cl_{Pl} = Cl_{Hp} + Cl_{Ur} \quad (9)$$

and therefore hepatic plasma clearance

$$Cl_{Hp} = Cl_{Pl} - Cl_{Ur} \quad (10)$$

The kidney plasma clearance (Cl_{Ur}) can be determined when measurement of the activity eliminated with urine is possible and total plasma clearance Cl_{Pl} can be measured as explained above. Thus,

$$Cl_{Hp} = Cl_{Pl} - Cl_{Ur} = \frac{A_p}{\int_0^{\infty} c(\tau)d\tau} - \frac{A_{Ur}(Y)}{\int_0^{Y} c(\tau)d\tau} \quad (11)$$

In the formulas (11) $A_{ur}(Y)$ denotes the activity eliminated with urine until moment Y after injection of the radiopharmaceutical.

From formula (11) further conclusions can be drawn regarding a simplified (one blood sampling time) method for determination of the hepatic plasma clearance. Two procedures should be taken into account:

a) how to simplify the total clearance (Cl_{Pl}) measurement

b) how to simplify the determination of the urinary clearance Cl_{Ur}.

In this paper these questions relate to respective clearances of ^{99m}Tc-HEPIDA.

Theoretical basis for the simplification of total plasma clearance determination

After intravenous injection of activity A_p of a radiopharmaceutical, which serves for clearance measurement, its concentration $c(\tau)$ in plasma declines with time. For the purpose of this article, as the residual ($p(\tau)$) a quantity will be defined:

$$p(\tau) = 1000\,\frac{c(\tau)}{A_p} \tag{12}$$

It is easy to see that $p(\tau)$ denotes the fraction of the administered activity which remains in one litre of the circulating blood plasma at time τ.

If for convenience a simplifying assumption is made that one is dealing with a single compartment model of substance distribution, the clearance Cl_{Pl} must be proportional to the volume V of the dilution space:

$$Cl = k \bullet V \tag{13}$$

where k — is the proportionality coefficient denoting the elimination rate of the radiopharmaceutical from the compartment. At each moment in time τ the diluting volume equals the quotient of the activity $A(\tau)$, contained in the compartment by the concentration $c(\tau)$:

$$V = \frac{A(\tau)}{c(\tau)} \tag{14}$$

According to the assumption that we are dealing with a single diluting compartment, the total activity in the latter should decline exponentially:

$$A(\tau) = A_p e^{-k\tau} \tag{15}$$

After substituting the right hand side of equation (15) into the formula (14), one receives:

$$V = \frac{A_0 e^{-k\tau}}{c(\tau)} = \frac{e^{-k\tau}}{\frac{c(\tau)}{A_0}} \tag{16}$$

After substituting the right hand side of this last equation for V into the equation (13), an equation for clearance is obtained:

$$Cl = k\,\frac{e^{-k\tau}}{\frac{c(\tau)}{A_0}} = k'\,\frac{e^{-k\tau}}{p(\tau)} \tag{17}$$

If, further on, a constant blood sampling time $\tau = T$ is assumed, then e^{-KT} becomes a constant value and the clearance can be expressed as:

$$Cl = \frac{K\big|_T}{p(T)} \tag{18}$$

where $K|_T$ denotes a new constant, characteristic for this given time T.

From the presented reasoning it follows that the relationship between the clearance and the residual could be described by a hyperbole of the general form $Cl = K|_T/p$, or after substitution $x = 1/p$ the relationship between the clearance and inverse of the residual ($1/p$) should be linear, i.e. $Cl = K|_T \bullet x$ or in a more general form:

$$Cl_{Pl} = L\big|_T + K\big|_T \bullet x \tag{19}$$

The parameters $L\big|_T$ and $K\big|_T$ of the linear function, developed for the moment T of blood sampling, assume values appropriate only for a given moment. In other words, if blood were sampled at a moment different from T, the parameters would be different too; they must be treated as functions of blood sampling time: $L(T)$ and $K(T)$. If one wishes to obtain a more general formula for calculation of the clearance, then on an empirical basis the parameters L and K need to be varied, dependent on a range of $T \in < T_1, T_2 >$. The boundaries of the range and shape of the functions $L(T)$ and $K(T)$ must be derived from analysis of empirical data.

Theoretical basis for the simplification of renal Tc-HEPIDA clearance determination

On the basis of the argument presented above, one can assume that the blood sample is being withdrawn at time $\tau = T$ post-injection when the concentration of the radiopharmaceutical (i.e. ^{99m}Tc-HEPIDA) in plasma amounts to $c(T)$. Collection of urine takes place still at another time X; the patient voids urine therefore at the time $\tau = T + X = Y$ post administration of the compound. Its concentration in the plasma then equals $c(X)$ and the activity eliminated with the collected urine $A_{Ur}(Y)$ is easily determined. For calculation of the renal clearance of ^{99m}Tc-HEPIDA, one still has to derive the integral, which occurs in the denominator of the second term of the equation (11).

If an additional assumption is made, that the blood sampling time is late (T»0), i.e. when the first exponential term given by equation (1) is already insignificantly small ($A_1 e^{-b1\tau} \approx 0$), then only the second term, representing the slow phase of the declining ^{99m}Tc-HEPIDA concentration in plasma, depicts adequately the phenomenon, i.e. $c(\tau) = A_2 e^{-b2\tau}$. By analogy to the equation (13), the renal clearance Cl_{Ur} becomes proportional to the total volume V of the diluting space. In other words:

$$Cl_{Ur} = k_{Ur} V \tag{20}$$

where k_{Ur} - is proportionally constant for the elimination rate of ^{99m}Tc-HEPIDA by the kidneys (with urine).

Comparing the right hand side of the formula (20) with the second term of the equation (11) one obtains the following equality:

$$\frac{A_{Ur}(Y)}{\int_0^Y c(\tau)\,d\tau} = k_{Ur} V \tag{21}$$

The total diluting volume V equals the ratio of the activity present in by latter to the actual concentration in plasma:

$$V = \frac{A(T)}{c(T)}$$

By substituting this expression into the equation (21), one obtains

$$\frac{A_{Ur}(Y)}{\int_0^Y c(\tau)d\tau} = k_{Ur}\frac{A(T)}{c(T)} \qquad (22)$$

and by further transformations

$$\int_0^Y c(\tau)d\tau = H\big|_{TY}\, c(T)$$

where

$$H\big|_{TY} = \frac{1}{k_{Ur}} \bullet \frac{A_{Ur}(Y)}{A(T)}$$

or in more general form:

$$\int_0^Y c(\tau)d\tau = G\big|_{TY} + H\big|_{TY}\, c(T) \qquad (23)$$

The obtained equation (23) is a linear function for which $G|_{TY}$ is an intercept and $H|_{TY}$ a slope, whereas $c(T)$ is an independent variable. This equation shows that, for the times greater than the blood sampling time ($Y > T$), the integral from time zero until time Y of the function describing the blood concentration of ^{99m}Tc HEPIDA should be in a linear dependence on the plasma concentration at the time T. It remains an empirical task to check the validity of this derivation, and if it is found to be adequate, to derive experimentally the parameters of the equation (23).

One has to observe, however, that the numerical values of $G|_{TY}$ and $H|_{TY}$ should be specific for selected values of T and Y, i.e. for the blood sampling and urine voiding times, respectively. If these operations take place at other times than originally established (T,Y), the parameters will vary. They should be treated therefore as functions of two variables: $G(T,Y)$ and $H(T,Y)$. These functions must be derived empirically.

Having taken account of these transformations, the final formula for the real clearance of ^{99m}Tc-HEPIDA will assume the following form:

$$Cl_{Ur} = \frac{A_{Ur}(Y)}{G\big|_{TY} + H\big|_{TX}\, c(T)} = \frac{A_{Ur}(Y)}{G(T,Y) + H(T,Y)\, c(T)} \qquad (24)$$

This formula seems to indicate that, at least theoretically, it should be possible to elaborate a simplified method for the determination of renal ^{99m}Tc-HEPIDA clearance by determining the activity voided with urine at time Y post injection and by single concentration measurement of the radiopharmaceutical in plasma, sampled at time T ($T < Y$).

Discussion

The argument presented above seems to indicate unequivocally that there should be a possibility to elaborate a simplified method for the determination of specific hepatic clearance of ^{99m}Tc-HEPIDA, understood as the difference between respective total plasma and renal clearance. To achieve this goal, empirical studies are necessary. In particular, experiments should help in deriving the functions of Y and T given in the equations (19) and (24). Respective experiments have confirmed theoretical expectations and will be presented in the next publication — on the subject of specific hepatic ^{99m}Tc-HEPIDA plasma clearance.

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