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Original

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

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Abstract

Determination of the plasma (Cl_{Pl}) and specific hepatic clearance (Cl_{Hp}) of ^{99m}Tc-HEPIDA is gaining acceptance as one of the best tests for the assessment of liver parenchyma functional capacity. A standard method utilises numerous blood samples, collected after injection of the radiopharmaceutical, plus collection of the urine if specific hepatic clearance is required.

It is not always necessary to obtain values of the clearances by means of the laborious multi-sample procedure. In the paper there are presented formulas, based on experimental data, that form the basis of a simplified method for determination of Cl_{Pl} and Cl_{Hp} using single administration of ^{99m}Tc-HEPIDA. To arrive at the value of Cl_{Pl} it is sufficient to withdraw 1 blood sample in the time range of 60 to 83 min post administration of the radio-pharmaceutical. If Cl_{Hp} is required, additional collection of urine over the time from 0 to 88–100 min post injection is necessary.

The values of Cl_{Pl} and Cl_{Hp} obtained by the simplified procedure are in full accordance with those obtained by the reference method utilising a series of blood samples, collected from 5 to 90 min post injection. The simplified method is sufficient as a procedure for screening of patients for liver parenchymal damage.

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

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Introduction

Derivatives of iminodiacetic acid, labelled with ^{99m}Tc, are being used for the assessment of the patency of bile ducts. In addition, total plasma clearance of ^{99m}Tc-HEPIDA (Cl_{Pl}) is a non-invasive procedure used in the functional diagnostics of liver parenchyma damage [1–4]. the magnitude of the clearance reflects the intensity of uptake of the substance from the blood by the organ and its excretion with bile. There is a disadvantage of using ^{99m}Tc-HEPIDA for the latter purpose, namely the partial elimination of the substance via the urinary tract [4, 5]. The pronounced variability of the latter contribution, both in terms of absolute and relative values, when referred to the hepatobiliary excretion, may render the assessment of the specific hepatic clearance of Tc-HEPIDA uncertain. On the basis of the above reasoning a procedure was elaborated [5] for the determination of the specific hepatic clearance of ^{99m}Tc-HEPIDA (Cl_{Hp}), which is the difference between the total plasma clearance of the substance (Cl_{Pl}) and its kidney clearance (Cl_{Ur}). For these purposes multi-sample methods for determination of both latter clearances may be used. These methods may be characterised as accurate and precise and, therefore, the derived values of Cl_{Hp} of ipso should be of a similar quality. However, these procedures are laborious and from the clinical point of view it is not always necessary to aim at a very accurate and most reproducible clearance determination. For screening purposes a less precise and less time-consuming determination of Cl_{Hp} could be acceptable.

As demonstrated in a preceding paper [6], elaboration of a simplified method for determination of the hepatic plasma clearance of ^{99m}Tc-HEPIDA, based on a small number of blood plasma samples, produces a simplified determination of Cl_{Pl} and Cl_{Ur}. In particular the concept of such a determination depends on the feasibility of finding relationships between the plasma concentration of ^{99m}Tc-HEPIDA at a chosen time and: 1) values of Cl_{Pl}, and 2) the integral of plasma concentration over time between the moment of administration of the drug and the time at which the

collection of urine is completed. As shown in the previous paper [6], there are good reasons for assuming that such correlations should exist. The purpose of the present study was therefore the search after respective experimental formulas in which such correlations could be expressed, and to assess how good the fits are, once obtained. A final check of the quality of the elaborated simplified procedure would be the quality of the regression between the results obtained by means of the simplified procedure and those yielded by the reference multi-sample procedures.

Material and methods

For analysis and processing, the archive of the data was used, consisting of 165 determinations of ^{99m}Tc-HEPIDA clearance in patients referred to the Department of Nuclear Medicine in Łódź for diagnostic purposes. In all studied subjects, multi-sample methods were used for determination of the total plasma clearance (Cl_{Pl}), urinary clearance (Cl_{Ur}) and hepatic clearance (Cl_{Hp}), the latter being difference between the former two. The methods have been described in detail elsewhere [5]. The ^{99m}Tc-HEPIDA complex was obtained from a kit preparation supplied by ORiPI POLATOM. The range of Cl_{Pl} in the individuals studied was very wide and permitted a search of general relations between the directly and indirectly measured quantities Cl_{Pl}, Cl_{Ur}, Cl_{Hp}, C(t), and A_{Ur}. The above quantities and parameters were defined in the preceding paper [6]. An interested reader should consult that publication for details regarding definitions and descriptions of their meaning.

Preparation of data for analysis. The analytic form of the function describing concentration of the radiopharmaceutical v. time post-injection, i.e.

$$c(t) = A_1 e^{-b_1 \cdot t} + A_2 e^{-b_2 \cdot t}$$

has been known for each patient. The same applied to the activity of ^{99m}Tc-HEPIDA administered to each individual. Therefore the following quantities, defined in publication [6], were calculated:

— concentration of the radiopharmaceutical in the plasma c(T) and residual p(T) at various times T; it was assumed that T varied by 1 min from 44 to 100 min post injection;

— integral of the function c(t) from the moment of injection (t = = 0) until the moment of urine voiding: t = Y. It was further assumed that Y varied by 1 min from 70 min until 100 min post injection of ^{99m}Tc-HEPIDA.

Single sample determination of Cl_{Pl}. The search was made for a relationship between total plasma clearance of ^{99m}Tc-HEPIDA and reciprocal values of the residual p(T) (see [6]). Preliminary analysis demonstrated unambiguously that for a description of the relationship between $\frac{1}{p(T)}$ and Cl_{Pl} a straight line was adequate and fully satisfactory. Regression equations of the linear relationship:

$$Cl_{Pl} = L + K \times \frac{1}{p(T)}$$

were determined by using a least square fit. For each fit a determination coefficient R^2 was calculated, whose value is a measure of the quality of fit. The larger the value of the coefficient, the better the fit for a given regression line of blood sampling. *Eo ipso* the value of the clearance derived from a concentration of ^{99m}Tc HEPIDA in plasma at a given moment will be more precise, the higher the value of R^2 for a given time T. A range of T was selected in which the values of R^2 were higher than 0.986 (corresponding to r = = 0.975). In this range the determination of plasma clearance was assumed to be equally good for clinical purposes.

For each moment T of the above range, parameters of the regression line $L|_T$ and $K|_T$ [6] were derived, and consecutively their variation was analysed as a function of T. In this way analytical equations were obtained for L = L(T) and K = K(T), demonstrating changes in parameters of the regression line, as dependent on the blood sampling time T. This procedure enabled the obtaining of a complete equation relating the clearance with the residual p(T) over the range of T values:

$$Cl_{Pl} = L(T) + K(T) \times \frac{1}{p(T)} \quad (1)$$

Simplified method for determination of urinary clearance (Cl_{Ur}). In the previous paper from this series [6] it had been theoretically postulated that there should be a possibility of determining the urinary clearance (Cl_{Ur}) of the ^{99m}Tc-HEPIDA provided the activity of the compound is known in the urine voided at time Y [A_{Ur}(Y)] and the concentration of the radiopharmaceutical in plasma c(T), at some properly selected sampling time T. It was concluded that the success of the simplification is equivalent to the experimental finding of a significant and tight correlation between instantaneous concentration c(T) in the plasma and the integral of the function describing the decline of the concentration with time from injection (τ = 0) to the moment of urine voiding τ = Y. From consideration of the compartment model of ^{99m}Tc-HEPIDA behaviour in the body, it was also postulated that this correlation is likely to be a linear one, of the form:

$$\int_0^Y c(\tau)d\tau = G|_{TY} + H|_{TY}\, c(T) \quad (2)$$

where $G|_{TY}$ is intercept and $H|_{TY}$ — slope of the linear function, dependent both on T and Y.

The changes of G and H with selected values of T and Y must be searched from the experimental data. Analysis of the real data leads to a tentative conclusion that both G and H change linearly with changes in T. Therefore one should be able to express these dependencies by equations of the form G(T) = kT + l and H(T) = = mT + n.

To establish these parameters, analysis was made of the relationship between the earlier found values of the concentration c(T) for T between 60 and 100 min on the one hand and values of the integral for voiding times Y in the range 60 < Y < 100 min on the other. In the first step it was assumed that voiding took place at Y = 60 min post injection, whereas blood sampling time could take place at various moments of the range (T = 60 to 100 min). This led to the calculation of $G_{Y=60}(T)$ and $H_{Y=60}(T)$ for a series (41) of blood sampling times T = 60,61,62... and 100 min. From these two rows the functions could be inferred, describing changes in G and H as dependent on blood sampling time T: $G_{Y=60}(T) = k_{Y=60} \times \times T + l_{Y=60}$ and $H_{Y=60}(T) = m_{Y=60} \times T + n_{Y=60}$. In the next and further series an analogous procedure was repeated, assuming a con-

stant voiding time Y = 61,62,63... 100 min post injection and varying the T as above in the first series. For each value of Y in the selected range a separate set of $k|_Y$, $l|_Y$ as well as $m|_Y$ and $n|_Y$ was obtained. In this way four series of parameters $k|_Y$, $l|_Y$, $m|_Y$ and $n|_Y$ were obtained. In each series 41 discrete values were obtained for each coefficient, calculated for varying Y from 60 to 100 min. Using a least square procedure functions could be derived describing changes of the parameters with values of Y (voiding time). Thus equation (2) will assume the form:

$$\int_0^Y c(\tau)d\tau = (k(Y)T + l(Y)) + (m(Y)T + n(Y))c(T) \quad (3)$$

The function k(Y), l(Y), m(Y) and n(Y) may be non-linear, and therefore they were established using non-linear regressions. For a description of the variation of the parameters with Y polynomial functions were selected for which the coefficient of determination R^2 was close to unity.

Verification. To check the agreement between the results of Cl_{Pl} and Cl_{Hp}, as determined by means of the formulas derived above, with the reference values determined by means of multi-sample methods, an orthogonal correlation was applied using an appropriate computer program.

Results

The range of Cl_{Pl} values measured in the studied individuals (multi-sample determination) spanned values from 64 to 370 ml/ /min. The corresponding values of Cl_{Hp} were in the range from 16 to 302 ml/min. Such a range clearly permitted a search for the relationships studied.

A single sample method for determination of Cl_{Pl}. In Figure1 there are presented values of determination coefficients R^2, of the linear functions between plasma clearance Cl_{Pl} as determined by means of a multi-sample method and the reciprocity of the residual, at various moments of blood sampling (single sample). From inspection of the graph it follows that a most strict correlation was obtained for c(T) of 75 min post injection (the highest value of R^2). The respective equation for the line is the following:

$$Cl_{Pl} = \frac{K}{p(71)} + L = \frac{4.091}{p(71)} + 7.922$$

From Figure 1 it follows also that the criterion of $R^2 > 0.9513$ is fulfilled for the range of the sampling time between 63 and 88 min post injection (where the continuous line exceeds the dotted line). In Figure 2 regressions are presented between the plasma clearance (as determined by the multi-sample reference method) and reciprocity of the residual, calculated at 60, 71 and 80 min post injection of ^{99m}Tc-HEPIDA. The correlations are very strict (R^2 between 0.973 and 0.9768). The parameters of the regression lines vary with the time of blood sampling. Their dependence on the time of the sampling is presented in Figures 3 and 4 (for the slope and intercept, respectively). There are also equations given showing functional dependence of the parameters on the sampling time. These equations enable formulation of a single equation that relates clearance (Cl_{Pl}) to the residual, measured at various times (T) between 63 and 88 min post injection:

$$Cl_{Pl} = \frac{5.63 \times 10^{-4} T^2 - 0.1536T + 12.16}{p(T)} + 0.9989\mathrm{T} - 62.98 \quad (4)$$

A simplified method for determination of Cl_{Ur}. In Figure 5 there is a correlation shown between ^{99m}Tc-HEPIDA concentration in plasma at T = 75 min and the integral of the function describing radiopharmaceutical concentration in blood plasma, calculated for the time range from 0 min to Y = 100 min post-injection. From inspection of the figure it follows that the correlation is very tight (r = 0.98). Similarly tight correlations were obtained between the same quantities for other values of T and Y. Of these the tightest one was that for T = 60 and Y = 100 min (r = 0.99).

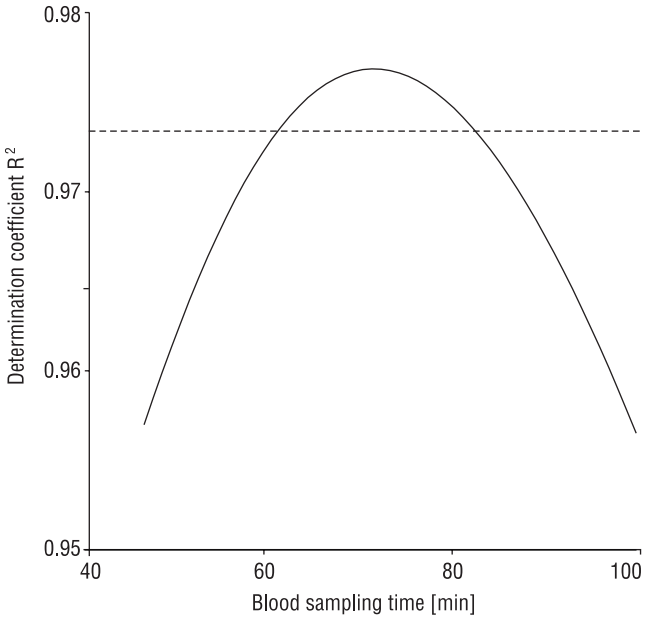

Figure 1. Determination coefficient R^2 for regression line linking Cl_{Pl} with the reciprocal of radiopharmaceutical residue as dependent upon blood sampling time.

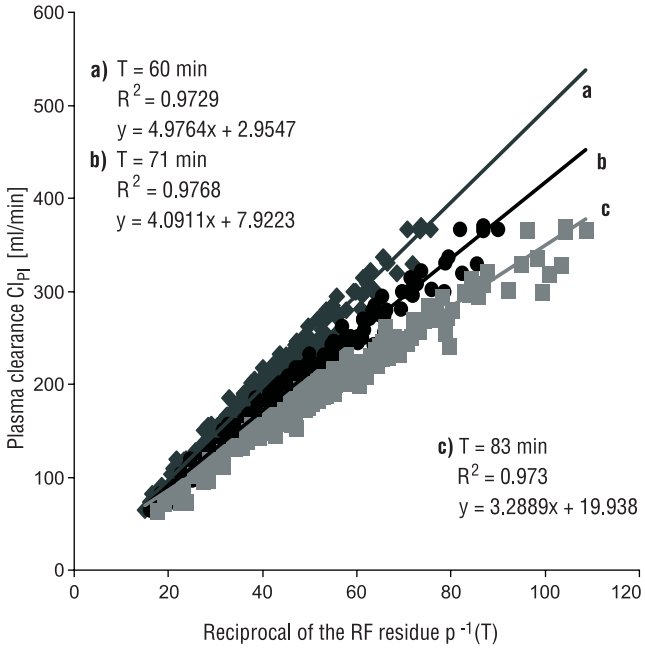

Figure 2. Linear correlations for plasma clearance (Cl_{Pl}) v. reciprocal of the radiopharmaceutical residue for three blood sampling times: a (◆) — 60 min, b (●) — 71 min and c (■) — 83 min post injection.

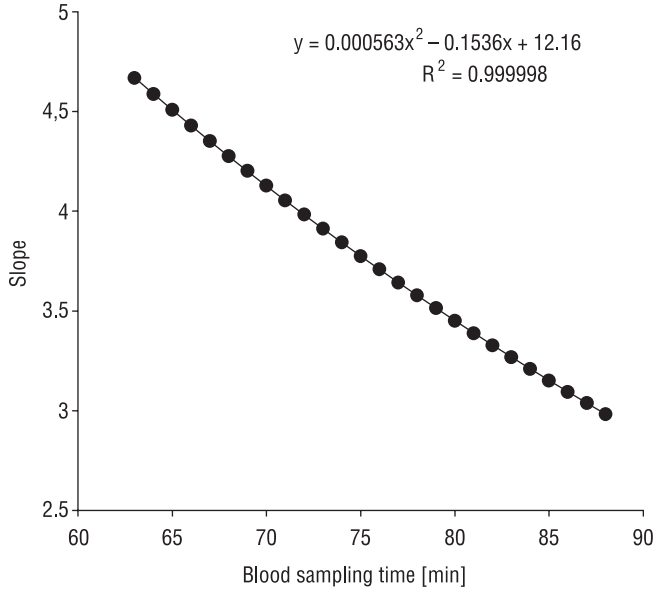

Figure 3. Slope of the plasma clearance v. reciprocal of the radiopharmaceutical residue regression equation of blood sampling time.

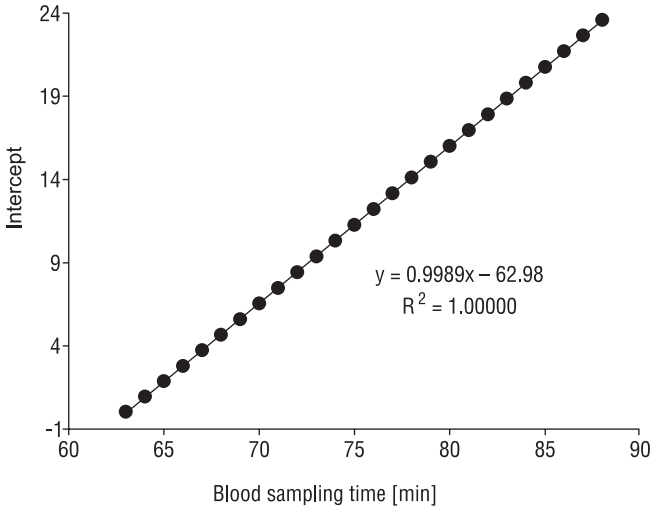

Figure 4. Intercept of the plasma clearance v. reciprocal of the radiopharmaceutical residue regression equation as a function of blood sampling time.

The least strong relationship was for T = 100 min and Y = 60 min (r = 0.94). The strength of the correlations allows borderline values of T and Y between 60 and 100 min, both for blood sampling and urine voiding. In Figure 6 there are presented lines of regression (without data points, for clarity of presentation) between ^{99m}Tc-HEPIDA concentration in the plasma and the integral for other pairs of Y and T values (see figure for details). For the time range that was earlier established as optimal for blood sampling (from 60 to 83 min post injections) the correlation coefficients for each moment of Y, selected between 60 and 100 min, exceed the value of 0.95. From further inspection of Figure 6 it follows that parameters of regression lines depend both on the moments of T and Y. The lines also cross over and this suggests that their parameters, derived earlier as G(T,Y) and H(T.Y) depend on the two moments

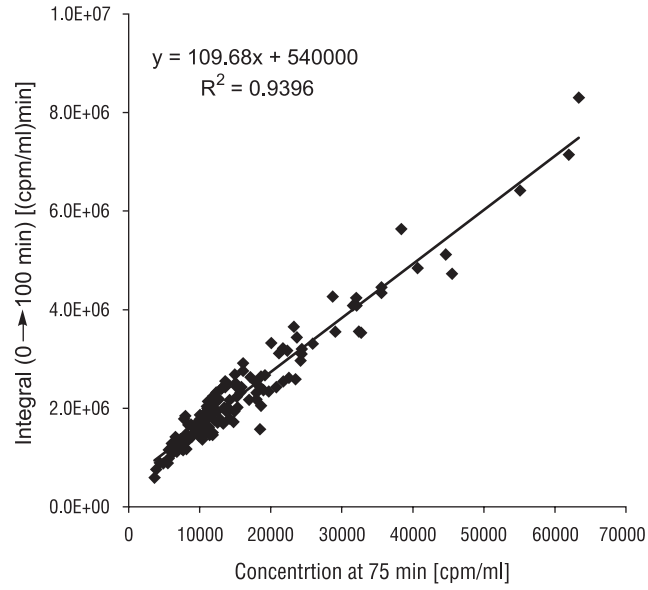

Figure 5. Regression line of activity concentration time integral (0 to 100 min post inj.) v. instantaneous concentration of radiopharmaceutical in plasma at 75 min post injection.

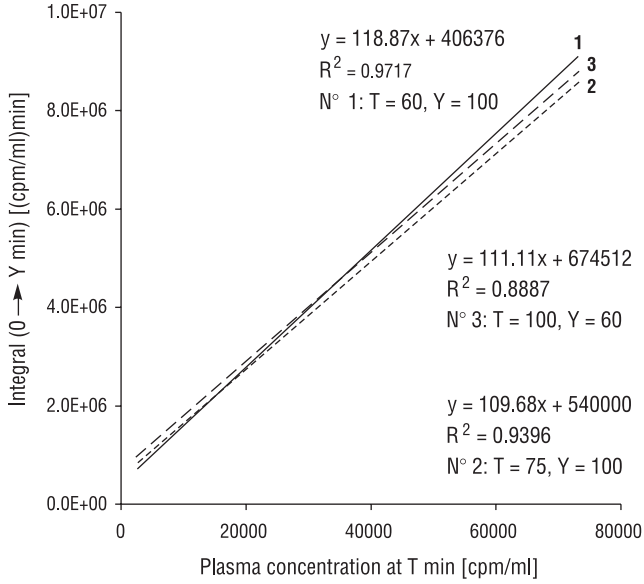

Figure 6. Regression lines of integrals of plasma concentration v. instantaneous concentration of radiopharmaceutical in plasma. The regressions were calculated for three pairs of T and Y. Line 1 — T = 60 min, Y = 100 min; Line 2 — T = 75 min, Y = 100 min; Line 3 — T = 100 min, Y = 60 min.

in a non-linear fashion. The respective equations, derived from the data, are:

$$G(T, Y) = (-0.2503Y^2 + 88.17Y + 1362)T - 3830Y + 332746 \quad (5a)$$

$$H(T,Y) = (-2.362 \times 10^{-3} Y^2 + 1.136Y + 6.219) \times 10^{-2} T + (0.6983 - 0.6983Y)Y + 9.497 \quad (5b)$$

for 63 < T < 88 min and 60 < Y < 100 min post injection, respectively.

Verification. In Figure 7 there is an orthogonal correlation displayed between the values of plasma clearance (Cl_{Pl}) of ^{99m}Tc-HEPIDA, determined by means of the reference method (multisample procedure), and a single sample simplified procedure using equation (4). It is easy to see that agreement between the two series is very close, more than satisfactory. For blood sampling times (T) of 60 min and 75 min, the values of Cl_{Pl} pairs do not diverge significantly from the line of identity; for T = 90 they do not fit the latter.

In Figure 8 orthogonal correlations are presented for specific hepatic clearance of ^{99m}Tc-HEPIDA, (Cl_{Hp}) determined similarly by

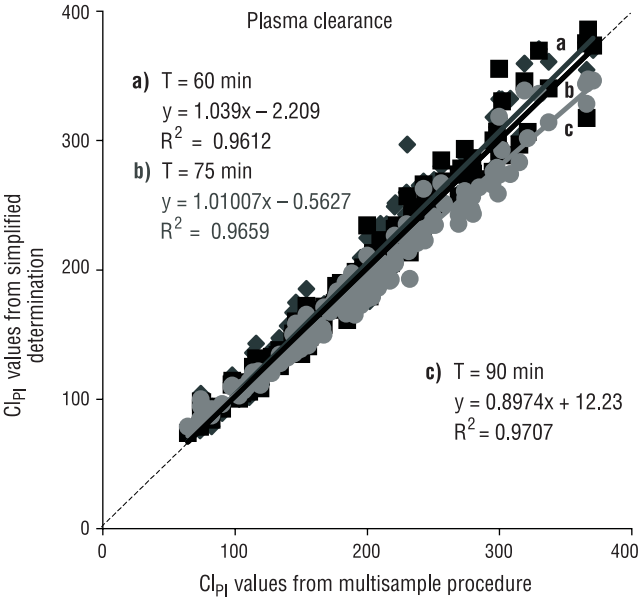

Figure 7. Orthogonal correlation between plasma clearance (Cl_{Pl}) values determined by means of multisample — and those measured applying the simplified procedure. Three values of blood sampling time: a (◆) — 60 min, b (■) — 75 min and c (●) — 90 min post injection. Dashed line–line of identity.

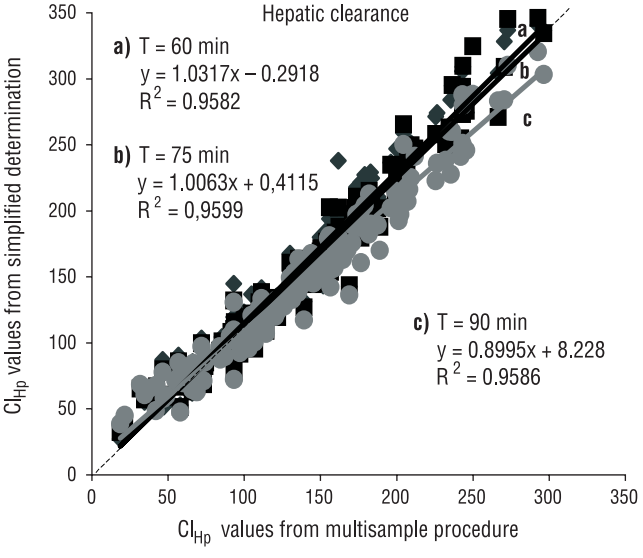

Figure 8. Orthogonal correlation between hepatic clearance (Cl_{Hp}) of ^{99m}Tc-HEPIDA, determined by means of multisample — and those measured applying the simplified procedure. The blood sampling time: a (◆) — 60 min, b (■) — 75 min and c (●) — 90 min post injection. One urine voiding time 95 min post injection. Dashed line–line of identity.

means of the reference and simplified method, using T sampling times of 60, 75 and 90 min post injection. As for the plasma clearance, agreement of the pairs is exemplary. Similarly the regression lines for T = 60 and 75 min fit the line of identity whereas the regression for T = 90 diverges from the latter in the sense that the values calculated by means of the simplified method systematically underestimate Cl_{Hp} if the values determined by multi-sample procedure are taken as the reference standard.

Discussion

Previous theoretical considerations indicated there should be a possibility to elaborate a simplified method for determination of the plasma, specific urinary and hepatic clearances of ^{99m}Tc-HEPIDA. In the study reported here parameters and equations were derived that fulfil the theoretical expectations. Before discussing the results of the present study one has to devote attention to the precision of the hepatic clearance determination.

The hepatic clearance is taken to be the difference between the plasma and the urinary clearance of the radiopharmaceutical. It is easy to see that due to superposition of the partial errors with which each of the clearances is measured, the coefficient of variation of their difference should be larger than that for each of the two components separately. Taken as a first approximation that for each of Cl_{Pl} and Cl_{Ur} the coefficients of variation are equal, then the coefficient of variation of the difference, i.e. of Cl_{Hp} should be larger by a factor of ~1.5 than that of Cl_{Pl}.

Simplified determination of Cl_{Pl}. The relationship between plasma concentration of ^{99m}Tc-HEPIDA (reciprocal of the residual) and Cl_{Pl} has been found to be linear, with no significant deviation of the regression from that simple function (r = 0.98 for T = = 75 min, almost the same tightness of correlation for the time range of blood sampling between 63 and 88 min).

This linearity of the relationship could be explained in two ways:

1. There is one dilution compartment for ^{99m}Tc-HEPIDA. Such a simplified concept was assumed for theoretical consideration in the preceding paper of this series [6]. However, the decline of Tc-HEPIDA in blood plasma with time cannot be described by a single exponential and a two-component exponential function is indispensable, which questions the first assumption.
2. There are two dilution compartments for ^{99m}Tc-HEPIDA in the body: plasmatic and extraplasmatic (e.g. interstitial). From a consideration and solution of the two-compartment open model it follows that if the penetration of the compound between the two compartments is very fast, faster than the total elimination of the radiopharmaceutical from the plasma by two routes — hepatic and urinary, then such linearity may obtain for the relationship between the total plasma clearance and reciprocal of the residual.

Solution of the distribution and excretion for a two-compartment model of ^{99m}Tc-HEPIDA indicates that transfer constants between the two compartments are 4–5 times larger than the total elimination constant from the plasma. This characteristic of ^{99m}Tc-HEPIDA is different from that seen for compounds used for renal clearance studies, in particular for ^{99m}Tc-EC (ethylenecysteine), for which the penetration constants between the 2 compartments

are comparable with the elimination constant. One has to mention here that the relationship between the reciprocal of residual and plasma clearance for ^{99m}Tc-EC is not linear [7, 8].

For the derived relationship between Cl_{Pl} and plasma concentration of ^{99m}Tc-HEPIDA (at a given time T=71 min), the error of regression amounts to 11 ml/min, and for the range of blood sampling times 60–83 min it does not exceed 11.2 ml/min or ~12 ml//min. This amounted to 5% for normal values of Cl_{Pl} (above 230 ml//min) and increases to 25% for values of Cl_{Pl} of the order of 70 ml//min. The latter precision may be deemed insufficient for monitoring of the patient's conditions during therapy of serious liver damage. In this case a reference multi-sample determination should be indispensable. One should add here that total error of determination will certainly exceed that of the regression alone and will be, therefore, larger. Assessment of the latter for the total range of the observed values requires further study.

Simplified method for determination of the urinary clearance (Cl_{Ur}) of ^{99m}Tc-HEPIDA. The presented results demonstrate unambiguously that there are very tight correlations ($r > 0.94$) between instantaneous concentration of ^{99m}Tc-HEPIDA in plasma (60–90 min and the integrals of the function, describing decline of the concentration with time in the range from injection until voiding of the urine in the same interval. For the least tight correlation, for which $r = 0.94$, the standard error of the regression, on which prediction error may be based, amounts only to about 0.1 per cent of the integral value, calculated from instantaneous concentration in plasma equations (e.g. 5a and 5b). In other cases the relative standard error is still smaller. It should be remembered, though, that results of this study, related to simplification of Cl_{Pl} determination, indicate that blood sampling should be optimally taken between 60 and 83 min post injection. When ^{99m}Tc-HEPIDA concentration in plasma is determined within this range of post-injection times the correlation coefficient between the respective integral of plasma concentration function and the former is not smaller than 0.95, irrespective of the time of urine voiding if the latter took place between 60 and 100 min (post injection). It should also be noticed that the tightest correlations were obtained when: a) voiding took place later than blood sampling ($Y > T$) and b) when interval T-Y was increasing. Therefore this should form a rule in the practice of clearance determination. If, however, the patient had to void urine before blood sampling took place, he (she) should be requested to void for the second time after blood withdrawal, and both urine samples should be mixed. The second time of voiding should be used for clearance calculation.

Verification of the method. As demonstrated in Figures 7 and 8 there are very close agreements between reference values of Cl_{Pl} and Cl_{Hp} on the one hand and those obtained by means of the simplified procedures on the other. The best agreement was obtained when blood had been sampled at the exact time of 75 min. A similar quality of agreement was seen when the sampling time was forwarded to 60 min. At later times, e.g. 90 min, the simplified method yielded values which were evidently lower than the reference values for both Cl_{Pl} and Cl_{Hp}. This could be due to a shorter than optimal interval between blood sampling and urine voiding. This strengthens one of the conclusions reached above that the longer the interval between two samplings (blood, urine), the better the accuracy of the simplified procedure. These circumstances should be taken into account in practice.

The clinical usefulness of the clearances of ^{99m}Tc-HEPIDA is a separate matter that will be dealt with in a forthcoming paper.

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