Clinical nuclear medicine

Nuclear Medicine Review 2009
Vol. 12, No. 1, pp. 14–22

ISSN 1506–9680

VIA MEDICA

Assessment of accuracy and precision of ^{99m}Tc-HEPIDA clearances determined by means of a simplified method

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[Received 6 VI 2009; Accepted 12 VI 2009]

Abstract

BACKGROUND: The aim of the present study was the assessment of the accuracy and precision of our own simplified method for the determination of ^{99m}Tc-HEPIDA liver clearance.

MATERIAL AND METHODS: It has been assumed that archived results of plasma clearance (Cl_{Pl}) and hepatic (Cl_{Hp}), determined by means of multisample methods, could be legitimately used as a reference standard.

The accuracy and precision of the simplified method was assessed by means of a Monte Carlo method alternatively utilizing three blood sampling times (T) of 68, 75 and 83 minutes post i.v. administration of ^{99m}Tc-HEPIDA. The corresponding alternative three urine voiding times (Y) were: 75, 80, and 95 min p.i.

The analysed model was created accepting values of Cl_{Pl} and Cl_{Hp}, of administered activity A_p and parameters of biexponential function, describing the concentration $C(t)$ decrease of the radiopharmaceutical (RF) in plasma during time as real values. Using the function $C(t)$ for each individual, the plasma concentrations of RF at three sampling times, urinary clearance ($Cl_{Pl} - Cl_{Hp}$), and voided activity ($A_{Ur}(Y)$) were calculated.

Simulated random errors were added to the assumed blood sampling times T and to voiding time Y. To the activity A_p and $A_{Ur}(Y)$, and RF plasma concentrations random errors were added, assuming normal distribution with relative SD from 0 to 5% and then clearance values were computed. For each process there were 5000 repeated simulated determinations.

The accuracy of the simplified methods was assessed by comparing mean values of simulated clearance computations with the reference. Comparison of standard deviations with mean uncertainties enabled us to gain insight into the degree of agreement of the estimator of relative uncertainty with the coefficient of variation as a measure of precision.

RESULTS: There were strong correlations between the reference clearance values and the mean values of determinations by means of the simplified procedure ($r > 0.93$). The correlations were practically insensitive to the uncertainty of pipetting. The lines of regression differed slightly from the lines of identity, giving an indication that there was a systematic error involved; it amounted to +4 ml/min at Cl_{Pl} = 60 ml/min and to –7 ml/min for Cl_{Pl} of 370 ml/min. For Cl_{Hp} a bias of +6 ml/min was found for a clearance value of 16 ml/min and –13 ml/min at $Cl_{Hp} > 300$ ml/min.

At uncertainty of pipetting of 2%, a precision of 6–7% was found for Cl_{Pl} of 300 ml/min. For Cl_{Pl} of 200 and 150 ml/min the corresponding precisions were 7–8% and 10%, respectively.

For Cl_{Hp} of 200, 150 and 100 ml/min the corresponding precisions were 10, 12 and 17%, respectively. These precisions are 5 percent worse than those that were obtained from determinations by means of multisampling procedures.

Key words: hepatic ^{99m}Tc-HEPIDA clearance error, hepatic ^{99m}Tc-HEPIDA clearance determination

Nuclear Med Rev 2009; 12, 1: 14–22

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Introduction

The determination of plasma clearance (Cl_{Pl}) and hepatic clearance (Cl_{Hp}) of ^{99m}Tc-HEPIDA (dimethyl-acetanilide-iminodiacetic acid) by multisampling method is an efficacious overall procedure for evaluation of liver parenchyma damage [1–3]. The analysis of the metrological characteristics demonstrated that determination of the clearances by multisample methods proved to be very accurate and precise [4].

In the Nuclear Medicine Department of the Medical University of Lodz, a new simplified method for the determination of ^{99m}Tc-HEPIDA plasma clearance and hepatic clearance was elaborated [5,6]. The method requires withdrawing one blood sample at predefined time post iv. injection of ^{99m}Tc-HEPIDA and for hepatic clearance additional determination of activity excreted with urine. The clinical value of the simplified ^{99m}Tc-HEPIDA clearances has been positively assessed [7]. However, using these simplified methods raises questions concerning the metrological characteristics and, in particular, calls for evaluation of their precision and accuracy.

The aims of the studies

The principal aim of the study was the assessment of the basic metrological characteristics of the accuracy and precision of the determination of ^{99m}Tc-HEPIDA plasma (Cl_{Pl}) and hepatic clearance (Cl_{Hp}) by a simplified method and the investigation into how some factors, which should be seen as potential sources of errors, affect these characteristics. Additionally, another objective of these studies was to select a proper estimator of precision of the clearances.

Theoretical basis

In a simplified method, as in the multisampling one, hepatic clearance Cl_{Hp} of ^{99m}Tc-HEPIDA is understood as the difference between two clearances: the plasma clearance (Cl_{Pl}) and renal clearance Cl_{Ur}. A simplified method for determination of plasma clearance (Cl_{Pl}) is based on the experimentally developed equation [6]:

$$Cl_{Pl} = \frac{5.63 \times 10^{-4} T^2 - 0.1536 T + 12.16}{p(T)} + 0.9989 T - 62.98 \quad (1)$$

where: T is the time at which a single blood sample is obtained in the range from 63 to 83 min (optimally at 75 min post injection);

$$p(T) = \frac{1000 \times C(T)}{A_p}$$

where: A_p is the activity injected *i.v.* to a patient, and $C(T)$ is the pharmaceutical plasma concentration at time T.

To determine the renal clearance one should know: a) the activity eliminated with the urine $A_{Ur}(Y)$ from the injection to time Y, at which urinary bladder emptying takes place, and b) the integral S in the same time period of the bi-exponential curve $C(t)$ (t signifies the continuous flow of time), which describes the changes of the radiopharmaceutical concentration in the plasma. The activity $A_{Ur}(Y)$ collected at time Y in urine can be directly measured. The integral (S) of $C(t)$ from 0 to Y, as it has been demonstrated [5, 6], is related linearly (equation 2) to the radiopharmaceutical concentration $C(T)$ in blood plasma sampled at T:

$$S = H \times C(T) + G \quad (2)$$

The parameters H and G depend on the moment of blood sampling at T and the moment of the urinary bladder emptying Y, and can be calculated from the following equations:

$$G(T, Y) = (-0.2503 Y^2 + 88.17 Y + 1362) T - 3830 Y + 332746 \quad (3)$$

$$H(T, Y) = (-2.362 \times 10^{-3} Y^2 + 1.136 Y + 6.219) \times 10^{-2} T + \\ + (0.6983 - 0.0019 Y) Y + 9.497 \quad (4)$$

As can be seen, the plasma concentration $C(T)$ at sampling time T, together with the activity given to the patient (A_p), is used for the determination of plasma clearance. Furthermore, it is also used for determination of the integral S, which together with the activity A_{Ur} (Y) leads to the renal clearance Cl_{Ur}, which is needed for determination of Cl_{Hp}.

In the case of the determination of ^{99m}Tc-HEPIDA clearances, there are a few factors which could affect the error of the measurement. They are the following:

1. The statistical character of the dependencies shown in equations in (1), (2), (3) and (4) causes an incidental prediction error with a normal distribution, and the value of which can be given by the standard error of estimation (SEE). In case of plasma clearance the error varies from 14.4 to 14.6 ml/min; in the case of hepatic clearance (Cl_{Hp}), evaluation of the error is more complicated, but possible [6].
2. The procedure of pipetting. Uncertainty here is usually of 2%. However, this value may change in a wider bracket even up to 5%.
3. Blood sampling time measurement and the moment of urinary bladder emptying. Blood samples are taken usually at established times after the injection but the whole process takes about 5 seconds. There are, however, cases in which blood sampling process lasts as long as 1 minute, so one might wish to know when the process has begun and when it has ended. Similarly, urinary bladder emptying takes up to 5 minutes.
4. The stochastic character of radioactive decay. This error is defined according to a Poisson distribution and is controlled in such a way that the precision of the results is not worse than 1%.

These factors overlap each other and lead to the fact that the final result of the determination of clearances is burdened with an error, which could be directly assessed by repeated measurements of the given quantity. However, in the case of clearance determination, this is impossible. For this reason the analysis of metrological characteristics requires the use of Monte Carlo methods.

For estimation of the accuracy of clearance measurements, a multisampling Monte Carlo method was used, based on the simulation of respective determinations, and metrological characteristics were obtained. The present study presents the results of the same method for the evaluation of a simplified procedure for clearance determination.

Material and methods

To establish a model for accuracy and precision assessment, the archive results of 172 patients of hepatic (Cl_{Hp}) ^{99m}Tc-HEPIDA clearances were taken. The clearances were determined by a multisampling method and they, as really true, served as reference values. Plasma clearance values ranged from 64 ml/min to 365 ml/min: the hepatic clearances ranged from 16 ml/min to 306 ml/min. There were also given values of activities A_p administered, and the parameters of bi-exponential function $C(t)$ describing the changes of radiopharmaceutical concentration in the plasma *vs*. time. It was assumed that these data show real values and real processes of concentration decay. The data from the patients' records allowed the calculation of real values of radiopharmaceutical concentration in the plasma at three moments of time T 68 min, 75 min, and 83 min, p.i. It was also possible to calculate the real value of the activity eliminated with urine $A_{Ur}(Y)$, accumulated up to time Y, taken respectively as 75 min, 80 min and 95 min after iv. administration of the radiopharmaceutical.

Simulation of measured values

Time measurements

Random values of rectangular distribution were added to the above-mentioned values of sampling time T and to time of bladder empting Y. Half of range of distribution ΔT assumed values of 0 s, 2.5 s, 5.0 s, 10 s, 20 s, and ΔY range assumed values of 0 min, 3 min and 6 min. The concentration of radiopharmaceutical in plasma samples were calculated from the function varied at moments $C(T + \varepsilon)$, $-\Delta T \leq \varepsilon \leq \Delta T$. However it has been assumed that the sampling took place at an undisturbed moment of time T. The determination of activity eliminated with the urine was treated similarly.

Pipetting procedure

Three random values of normal distribution representing three independent activity measurements were added to real values of A_p and A_{Ur}. To the established (calculated above) radiopharmaceutical concentration in plasma, a random value from the normal distribution was added — it corresponded to the error caused by pipetting during the preparation of one plasma sample. Relative standard deviations of normal distribution were 0%, 1%, 2%, 3%, 4%, and 5% which corresponded to relative fluctuations of pipetting. From three measured values of given activity A_p and of A_{Ur} mean values and standard deviations were calculated, which were used for computing the clearances and uncertainty of the measurements.

Stochastic character of radioactive decay

To the previously calculated (modified) activity values of A_p and $A_{Ur}(Y)$ as well as plasma concentration values, random errors of normal distribution were added with 1% relative standard deviation, which corresponded to errors caused by the stochastic character of radioactive decay and measurements of samples with a precision not worse than 1%.

The prediction of regression

The obtained values A_p and $A_{Ur}(Y)$ and $C(T)$ were put into the equations (1), (2), (3), and (4) and values of clearances were calculated. Random values of normal distribution within standard error of estimation (SEE ≈ 14.5 ml/min) were added to the calculated values.

Multiplicity of simulations

For each individual, 5000 clearance simulation determinations were carried out obtaining each time the values of both clearances and superposition standard deviation (computed on the basis of a total differential) (SSD) i.e. a standard deviation computed in accord with the superposition law. The obtained 5000 values allowed further the determinaion of:

1. Mean clearances values of Cl_{Pl} and Cl_{Hp}.
2. Root mean square (RMS) errors of both clearances.
3. Standard deviations (SD) computed from 5000 values of clearances.
4. Mean SDD values.

Assessment of accuracy

To evaluate proper accuracy of measurement, mean values of Cl_{Pl} and Cl_{Hp} were correlated with reference values (see "Material and methods"), and the obtained line of regression compared with the identity line. As tools of evaluation, the following indicators were used: coefficient of determination R^2, standard error of estimation (SEE), and the distance of regression line from the identity line for the minimum (D_{16}) and maximum clearance values (D_{306}). These parameters of R^2, SEE, and both distances were defined as agreement indicators. The units of the parameters, with the exception of R^2, is ml/min.

Assessment of precision

For assessment of precision, coefficients of variation were taken. The latter were used for analyzing changes caused by varying the factors which contributed to these errors.

The choice of the estimator of uncertainty of a single clearance determination

To select a proper measure for the estimation of uncertainty of a single clearance determination the mean values of SDD were compared with the standard deviations (SD) and the root mean square errors (RMS) of the given clearances values.

Results

The results presented have been obtained for Cl_{Hp} and for conditions most often prevailing during routine clinical work, namely T = 75 min, Y = 80min, ΔT = 2.5 s, ΔY = 3min, and $\Delta p/p$ = 2%.

Accuracy

Figure 1 presents the correlation with the regression line between the real plasma clearance and mean values taken from the simulated determinations obtained by the simplified method. Figure 2 shows similarly the correlation with the regression line between real values of Cl_{Hp} and its mean values from simulated determinations, and comparison with the identity line. As can be seen, both correlations are very close (of which the correlation for Cl_{Pl} is more close). However, the regression lines intersect with the lines of identity, which indicates that low clearance values, determined by the simplified method, are overestimated and its high values are underestimated. Such a discrepancy be-

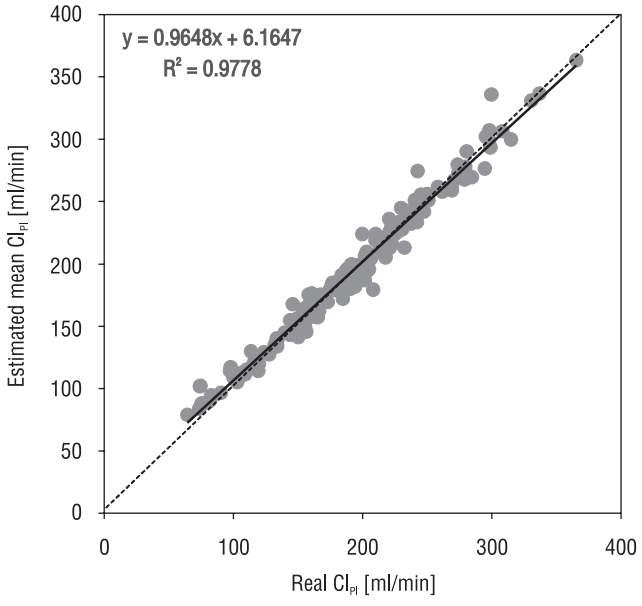

Figure 1. The correlation of real clearances of Cl_{Pl} and mean values of simulated determination by the simplified method.

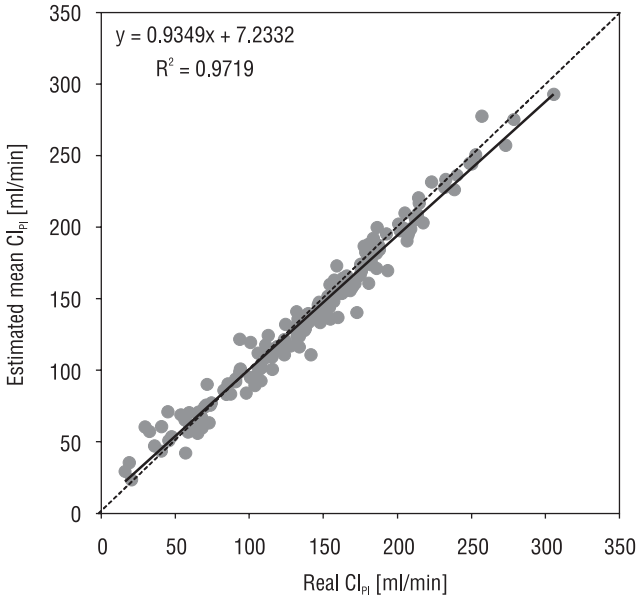

Figure 2. Correlation of real clearance of Cl_{Hp} and mean values of simulated determination by the simplified method.

tween these lines is more clearly visible for the hepatic than for the plasma clearances.

Table 1 shows assembled the values of agreement indicators of regression lines with the identity line for hepatic clearances; the moment the blood sampling is taken at three different times p.i. and bladder voiding process takes place later. It seems clear that the moment of blood sampling does not influence the change of these indicators. However, it can be seen, that the later the blood sampling and bladder voiding takes place, the more clearly apparent the discrepancy between the line of identity and the regression line.

Table 2 shows values of agreement indicators for lines of regression with lines of identity for hepatic clearances when varying the uncertainty of the pipetting process. These data indicate that uncertainty of pipetting does not influence the general accuracy of hepatic clearance determination.

Table 3 shows the assembled indicators of agreement of regression lines with lines of identity for hepatic clearances Cl_{Hp} obtained by the simplified method at varied uncertainty of time at which the blood sampling had been taken. It can be seen that, the uncertainty of ΔT does not practically change the accuracy of Cl_{Hp} determination.

Table 4 shows the assembled indicators of agreement of regression between real values and mean values from simulated determinations at varied moments of time for blood sampling (T) and urinary bladder voiding (Y), and uncertainty ΔY of time at which urinary bladder voiding took place. As can be seen from the table the correlation between the time for blood sampling and bladder voiding is accurate, but there is a greater discrepancy between the line of identity and the line of regression. However, the uncertainty of time measurement at which urine bladder voiding took place, does not affect the accuracy of determination.

Precision

Figure 3 shows the changes of root mean square (RMS) error and of standard deviation as a function of the value of hepatic ^{99m}Tc-HEPIDA clearance Cl_{Hp}, when determined by the simplified method. It follows from the graph that standard deviation of Cl_{Hp} is in good agreement with the corresponding values of mean square errors. For some clearance determinations, however, values of square errors are larger than the standard deviations. This could be due to a systematic error. There are similar relations between mean square errors and mean values of SSD.

Figure 4 shows how the coefficient of variation and the relative mean of SSD changes with hepatic clearance value. It can be clearly seen that both quantities could be used as error estimators.

Figure 5 shows, how the coefficient of variation for four clearance values changes when the pipetting is performed with varying relative uncertainty. The Figure 5 demonstrates — as expected — that if the uncertainty of pipetting is increasing, the precision of hepatic ^{99m}Tc-HEPIDA clearance determination (Cl_{Hp}) is deteriorating. Such changes are particularly clear for small values of the clearances.

Figure 6 shows the coefficients of variation for the same hepatic clearances at varied uncertainty of the time for blood sampling ΔT (for $T = 75$). It can be clearly seen that the uncertainty of blood sampling time does not materially affect the uncertainty of hepatic clearance determination.

Table 5 presents the assembled values of coefficients of variation for four hepatic clearances obtained by the simplified method assuming that blood was taken at $T = 75$min and the bladder was emptied at $Y = 80$ min at varied uncertainty of bladder voiding time.

In Table 6 again there are assembled values of the coefficient of variations for the same four hepatic clearances versus varied moments of blood sampling time and at different moments of urine voiding time Y (uncertainty $\Delta T = 2.5$ s and ΔY=3min, respectively). As can be clearly seen, the uncertainty of time measure ΔY does

Table 1. The values of agreement indicators of the regression line and the identity line for hepatic clearances obtained at different moments of time of blood sampling and bladder voiding

Agreement indicators	Value of indicators for different *T* [min] and *Y* [min]		
	T = 68; *Y*= 75	*T* = 75; *Y* = 80	*T* = 83; *Y* = 90
R^2	0.9674	0.9719	0.9727
SEE	9.99	9.22	9.03
D_{16}	5.98	6.19	6.72
D_{306}	–11.9	–12.7	–13.9

Table 2. Values of agreement indicators for regression line with the identity line for hepatic clearances versus uncertainty of pipetting

Agreement indicators	Values of indicators of agreement for different relative uncertainty of pipetting (%)					
	0	1	2	3	4	5
R^2	0.9718	0.9722	0.9719	0.9716	0.9716	0.9717
SEE	9.24	9.25	9.22	9.27	9.18	9.18
D_{16}	6.12	6.20	6.19	6.19	6.22	6.18
D_{306}	–12.76	–12.71	–12.67	–12.67	–12.56	–12.48

Table 3. Values of agreement indicators for the regression line with the identity line for hepatic clearances as obtained at varied uncertainty of blood sampling time *ΔT*

Agreement indicators	Values of indicators of agreement obtained at several uncertainties of sampling time *ΔT* [s]				
	0	2.5	5.0	10.0	20.0
R^2	0.9718	0.9717	0.9715	0.9718	0.9716
SEE	9.24	9.22	9.29	9.24	9.26
D_{16}	6.24	6.19	6.23	6.14	6.26
D_{306}	–12.75	–12.67	–12.80	–12.66	–12.75

Table 4. Values of agreement indicators for regression line with the identity line for hepatic clearances at different blood sampling times *T* [min], and bladder voiding *Y* [min], and varied uncertainty of bladder voiding time *ΔY*

Agreement parameter	Values of indicators of agreement for several *T* [min] and *Y* [min] and varied uncertainty of bladder emptying time *ΔY* [min]								
	T = 68; *Y*= 75			*T* = 75; *Y* = 80			*T* = 83; *Y* = 95		
	ΔY = 0	*ΔY* = 3	*ΔY* = 6	*ΔY* = 0	*ΔY* = 3	ΔY=6	*ΔY* = 0	*ΔY* = 3	*ΔY* = 6
R^2	0.9675	0.9674	0.9674	0.9708	0.9716	0.9715	0.9729	0.9727	0.9731
SEE	9.95	9.99	9.99	9.26	9.26	9.29	9.00	9.03	8.96
D_{16}	6.01	5.98	5.99	6.20	6.26	6.21	6.67	6.72	6.66
D_{306}	–11.97	–11.90	–11.82	–12.74	–12.75	–12.67	–13.87	–13.90	–13.8

not practically affect the precision of the hepatic clearance determination.

Discussion

Determination of clearances, mostly renal, using isotope techniques has been known for decades. The theoretical foundations of these methods as based upon a single intravenous injection of non radioactive compounds and few blood samplings, has been given by Sapirstein [8]. There are simplified methods for the determination of renal clearances, which require a single injection of the radiopharmaceutical and single blood sample [9–12]. Regardless of the good theoretical foundations of such procedures, very few studies have been devoted to their metrological characteristics and, in particular, to their accuracy and precision.

These characteristics for the determination of hepatic ^{99m}Tc-HEPIDA clearance (Cl_{Hp}) have been previously analysed when multisampling methods were used. Applying a simplified method for the determination of hepatic ^{99m}Tc-HEPIDA clearance (Cl_{Hp}) and an examination of its usefulness for the assessment of liver function lead to the conclusion that investigation of the precision and accuracy is vital.

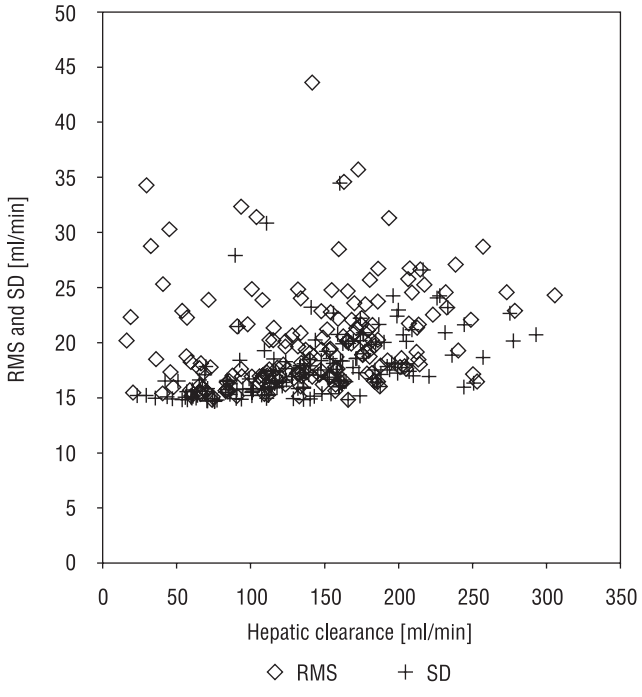

Figure 3. Root mean square error and standard deviation depending on the value of hepatic clearance. RMS — root mean square error; SD — standard deviation.

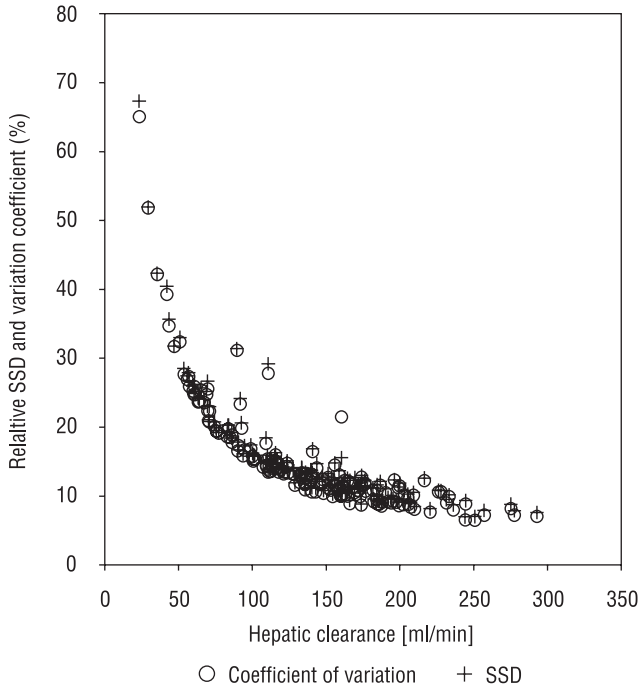

Figure 4. Coefficient of variation and relative mean SSD depending on the determined value of Cl_{Hp}. SSD — superposition standard deviation.

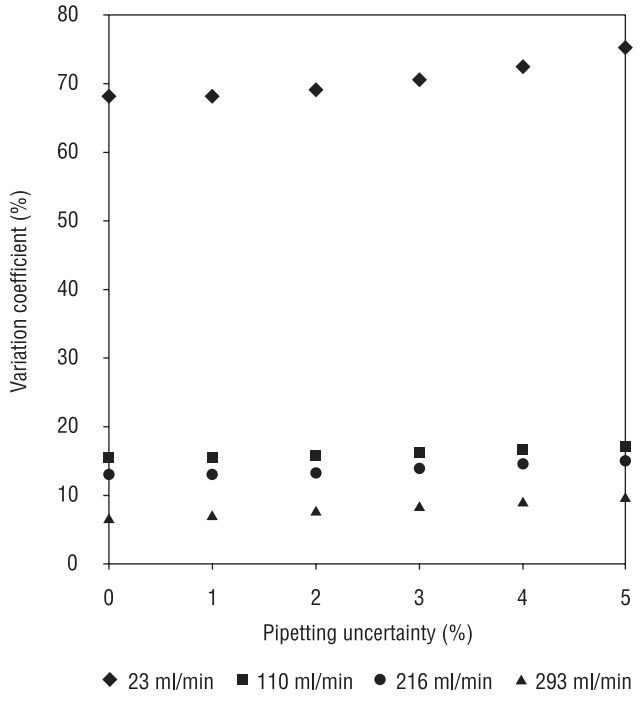

Figure 5. The changes of coefficient of variation for four values of Cl_{Hp} depending on uncertainty of pipetting.

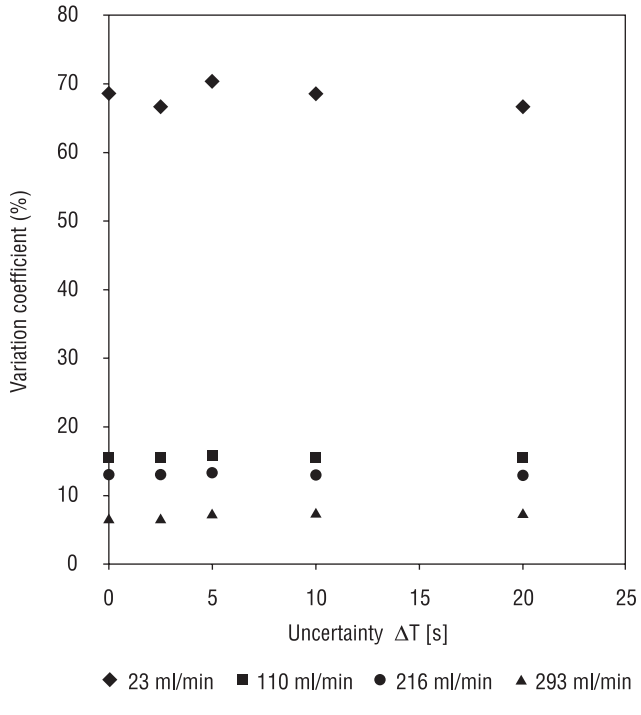

Figure 6. The changes of coefficient of variation for four values of Cl_{Hp} depending on the moment of blood sampling.

Accuracy

The results obtained from the simulation based on the model outlined above, demonstrate that mean values of 5000 virtual determination of the same clearance correlate very highly with the real values. However, from inspection of Figures 1 and 2 it can be seen that the regression lines do not coincide completely with the lines of identity. This might indicate that the determined values are biased. When the blood sample is taken at 75 min, the obtained values of plasma clearance (below 175 ml/min) are systematically overesti-

Table 5. Values of coefficients of variation [%] of four hepatic clearances determined by a simplified method, versus uncertainty of bladder voiding time [min]

Hepatic clearance [ml/min]	Values of variability coefficient [%] for four Cl_{Hp} at three uncertainties of bladder voiding ΔY [min]		
	0	*3*	*6*
23	67.9	67.3	67.2
110	15.9	15.9	15.9
216	12.6	12.6	12.8
293	7.6	7.6	7.6

Table 6. Values of coefficients of variation [%] of the four hepatic clearances determined by a simplified method and assuming three blood sampling and corresponding bladder voiding times

Hepatic clearance [ml/min]	Values of variability coefficient [%] for four Cl_{Hp} at several blood sampling T [min] and bladder voiding Y [min] times		
	$T = 68; Y = 75$	$T = 75; Y = 80$	$T = 83; Y = 95$
23	70.5	67.3	65.7
110	16.1	15.9	16.2
216	12.3	12.6	13.0
293	7.5	7.6	7.8

mated by 4 ml/min, while high values (above 200 ml/min) are systematically underestimated by approximately 9 ml/min. Low values of hepatic clearances (below 110 ml/min) are overestimated (up to 6 ml/min), whereas values higher than 110 ml/min are underestimated (up to13 ml/min). When blood is taken at 83 min both systematic errors increase to 6.7 ml/min and 14 ml/min, respectively (Table 1). Similar changes are seen for the determination of the plasma clearances. Analysis of covariance enabled the derivations of a formula providing a value for the systematic error (ε) for each individual clearance and for the optional moment of blood sampling ranging from 68 to 83 min.

The equations are as follows:

a) for the plasma clearance:

$$\varepsilon_{Pl} = (-2.8 \times 10^{-5} T^2 + 3.703 \times 10^{-3} T - 0.1561) Cl_{Pl} + \\ + 5.7 \times 10^{-3} T^2 - 0.7789 T + 32.58$$

b) for the hepatic clearance:

$$\varepsilon_{Hp} = (-1.87 \times 10^{-5} T^2 + 2.201 \times 10^{-3} T - 0.1247) Cl_{Hp} + \\ + 2.698 T^2 - 0.348 T + 18.16$$

As follows from the subsequent tables, the systematic errors do not follow the relative uncertainty of pipetting (Table 2), the uncertainty of blood sampling measures (Table 3), or the uncertainty of urinary bladder voiding (Table 4).

Precision

The distribution of results of measurements, which are responsible for an imprecise determination, results from the interference of incidental errors. Precision, as a measure of agreement of results, is measured by the coefficient of variation, which is a quotient of standard deviation: mean value. The presented model makes it possible to find a standard deviation and mean value out of 5000 results, and therefore the coefficient of variation, and to estimate the importance of the sources of variation. This study also enabled the comparison of the standard deviation with the root mean square (RMS) errors, and thus to decide which quantity should be taken as an overall uncertainty of hepatic or plasma clearance determination.

As Figure 3 shows, for the overwhelming majority of Cl_{Hp} values the standard deviations are practically identical to the values of respective RMS errors; however, for individual values of Cl_{Hp} there are some differences which reach as much as 20 ml/min. Similar observations apply to RMS error and the standard deviation for plasma clearance. This small difference between RMS errors and standard deviations is probably due to small systematic errors, which are not incorporated into the standard deviation. Values of the coefficients of variation (CV) obtained for various values of the Cl_{Hp} in conditions typical for routine analytical work while determining the uncertainty determination are presented in Figure 4. A similar variation of CV was seen for Cl_{Pl}, and — as anticipated — the values of coefficient of variations for both clearances decline with the absolute value. The CV for Cl_{Hp} and Cl_{Pl} above 200 ml/min and 150 ml/min, respectively, do not change significantly, ranging from 12% to 10%. The precision becomes worse at low clearance values, and the resulting uncertainty may, to some extent, jeopardize the unambiguous classification of patients with Cl_{Hp} around 80 ml/min. At lower values of Cl_{Hp} irrespective of the absence of good overall precision, there is no real problem of interpretation that liver parenchyma performance is a poor one.

The results of further studies make it clear that the coefficient of variation rises with the increasing uncertainty of pipetting and this observation applies to low values of both Cl_{Hp} and Cl_{Pl} (Figure 5). When uncertainty of pipetting rose from 1 to 5%, the coefficient of

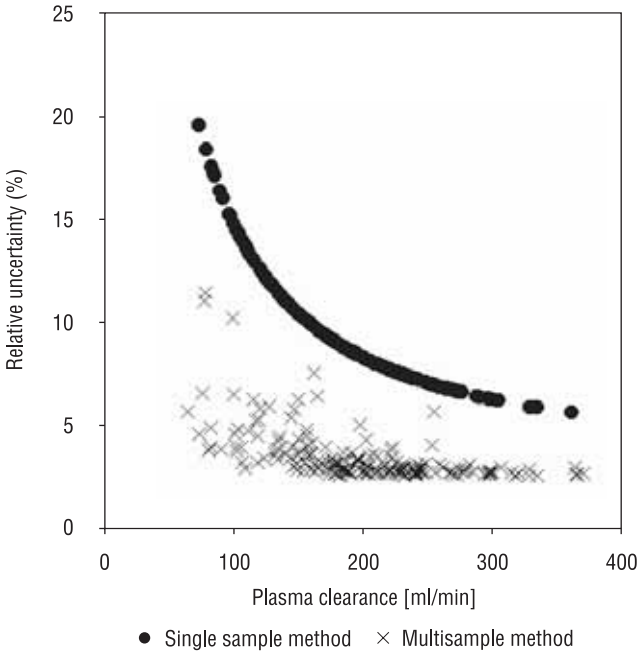

Figure 7. The comparison of precision of plasma clearance determination by multisample and single sample methods.

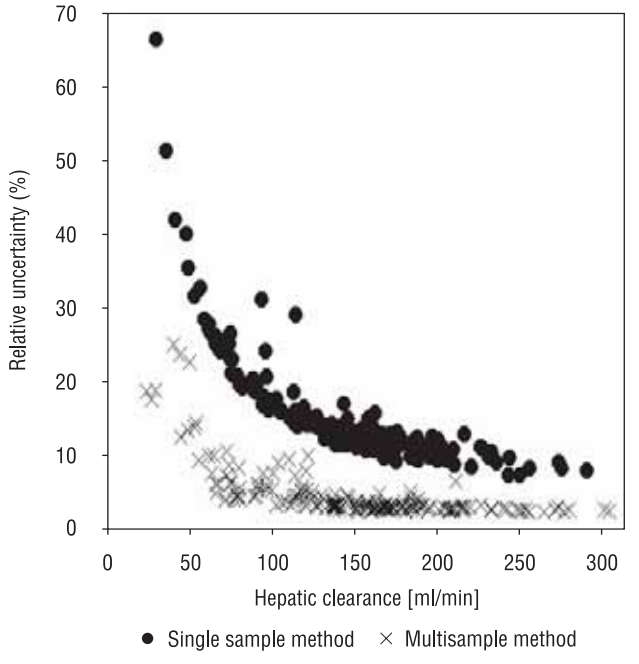

Figure 8. The comparison of precision of hepatic clearance determination by multisample and single sample methods.

variation for plasma clearance of 70 ml/min and hepatic clearance Cl_{Hp} = 22 ml/min increased from 68% to 75%, respectively. For Cl_{Pl} = 366 ml/min and Cl_{Hp} = 306 ml/min the coefficient of variation increased only from 8% to 12%.

As shown in the following tables and figures the timing precision of blood sampling and urinary bladder voiding does not affect the precision of the determination.

To summarize, the coefficient of variation is a good measure of precision and uncertainty of a single determination, based on the law of error propagation, and as was shown above, the applied model allowed the comparison of the standard deviation with a mean value of superpositional standard deviation (SDD).

Figure 4 shows that within the whole range of Cl_{Hp} the relative mean of SSD is identical to the coefficient of variation. Similar observations are seen for Cl_{Pl}. This allows, therefore, the replacement of the customary standard deviation with the superpositional uncertainty and the use this measure for the evaluation of precision.

To assess fully the precision of the simplified procedure for Cl_{Pl}, and Cl_{Hp} measurement, one should compare the latter with the precision of a standard multisample method. Such a comparison has been shown in Figures 7 and 8. The uncertainty of clearance determined according to the law of superposition of errors was taken as a precision for both methods.

Values of precision from the multisampling method were taken from the previous studies [4]. It can be seen that hepatic clearance determined by both methods is less precise than overall plasma clearance, and the results of a simplified method for both clearances are from two to five times less precise than those obtained by the multisampling method. However, it is interesting to note that for a simplified method there is a clear dependence of precision upon the determined clearance value, while for the multisampling method for clearances with values above 170 ml/min for Cl_{Pl}, and for 100 ml/min for Cl_{Hp} the precision remains constant. For this reason, the simplified method should be used for scanning and preliminary classification of a patient. However, for the monitoring of patients' condition, the mutlisample method should be used.

Conclusions

1. The accuracy of simplified methods for determination of ^{99m}Tc--HEPIDA clearances is acceptable.
2. Precision of Cl_{Pl} determination by a simulated method depends predominantly on its value and ranges from 5% at 250 ml/min to 20% at low values of the clearance.
3. Precision of Cl_{Hp} — using a simple method — is somewhat less satisfactory than that of Cl_{Pl} and in the range from 100 to 200 ml/min it varies from 17 to 10%.

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