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Original

^{99m}Tc-HEPIDA hepatic clearance as a diagnostic tool: usefulness of a single sample plasma and hepatic clearance of ^{99m}Tc-HEPIDA for assessment of hepatic parenchyma performance

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Abstract

BACKGROUND: A simplified method of ^{99m}Tc-HEPIDA clearance determination, both plasma and hepatic, depends upon measuring the radiopharmaceutical concentration in plasma of a blood sample taken once in the time range from 68–83 min after injection of compound, and measurement of activity voided (excreted) with urine about five minutes after blood sampling. The aim of the present study was to analyze the clinical usefulness of both clearances, as determined by the simplified method in view of the diagnostic usefulness of both clearances (particularly of hepatic clearance) as determined by the respective multisampling method.

MATERIAL AND METHODS: For the analysis, archived data of studies in 134 individuals (48 healthy individuals and 86 patients with chronic liver parenchyma damage) were used, in which plasma clearance (Cl_{Pl}) and hepatic clearance (Cl_{Hp}) ^{99m}Tc-HEPIDA were determined by the standard multisample method — the values of such determined clearances constituted clearance referential values for further comparative analyses.

The clearances Cl_{Pl} and Cl_{Hp} were determined by the simplified method separately for three blood sampling times of: 60, 75 and 90 min, using the same archived data for calculation of corresponding concentrations of ^{99m}Tc-HEPIDA in plasma. For urinary clearances — which were necessary for calculation of Cl_{Hp} — archived data were utilized on activity contained in voided urine (at about 95 min.).

The clinical reference system used here was the semi-quantitative assessment of liver function, performed on the basis of commonly used basic biochemical indices (AST, ALT, GGTP, bilirubin, albumin and gammaglobulin in serum, proteinogram and prothrombin index). For each test there were 4 categories of results (sub-ranges) selected, which were ranked from 0 to 3. For each patient the ranks for the results of each test were summed, giving a total sum (called SP). These latter sums of ranks served as a reference system, characterizing liver condition (performance) in each individual.

RESULTS: Clearance, Cl_{Pl} and Cl_{Hp}, values, obtained by a simplified method, were correlated with respective values determined by the multisampling method, and with ranks (SP) representing classification of degree of hepatic parenchyma damage — SP. On the basis of the attribute independence χ^2 test, the coherence of clearances (simplified determination) with SP was assessed. Also, analysis of variance of SP-values and clearance was performed using Spearman's theory for testing the correlation of non-continuous variables.

By factorial analysis a factor responsible for changes in individual quantities (results of biochemical tests and ^{99m}Tc-HEPIDA

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clearances) was computed. Its loading was determined for each individual quantity.

During analysis for each moment of blood sampling tight correlations of clearance values, obtained by the simplified method, were determined with referential values. The closest correlation was obtained for blood sampling at 75 min. It was found that there are negative correlations between values of hepatic and plasmatic clearances and SP. The values of r obtained for Cl_{Hp} are close to those obtained for analogical correlations by multisampling methods. However, the values of correlation coefficient obtained for Cl_{Pl} by single sample method are greater than those for Cl_{Pl} determined by multisampling method.

CONCLUSIONS: Factor loading, known as "liver incapacity", is greater for Cl_{Hp} determined by single sample method, but lower than comparable hepatic clearance loading determined by the multi-sample procedure. Values of incapacity factor for Cl_{Pl} are lower than for Cl_{Hp}, but the lowest value was obtained for Cl_{Pl} determined by the multisampling method.

Obtained values χ^2, r and loading of incapacity factor speak in favour of the correlations between the degree of hepatic parenchyma performance and the values of clearances determined by the simplified method. However, this correlation is closer for Cl_{Hp} than for Cl_{Pl}. In view of such a distinct correlation, there is good justification for the implementation of the simplified method for the determination of hepatic clearances used in diagnostic analysis of hepatic performance.

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

Introduction

Values of plasma (Cl_{Pl}) and hepatic (Cl_{Hp}) ^{99m}Tc-HEPIDA clearance determination by multisampling methods are useful for the assessment of degrees of hepatic parenchyma damage [1–3]. The multisampling method is precise and satisfactory but time consuming [4]. In our laboratory a simplified method of both hepatic and plasma clearance determination has been developed. By this method, hepatic clearance (Cl_{Hp}) is determined as the difference between plasma clearance (Cl_{Pl}) and urinary clearance (Cl_{Ur}).

For the simplified method of determination of plasma clearance an experimentally developed empirical equation is used, which combines this clearance with ^{99m}Tc-HEPIDA concentration $C(T)$ in plasma blood, sampled at the moment T post injection:

$$Cl_{Pl} = \frac{5.63 \times 10^{-4}\, T^2 - 0.154T + 12.16}{p(T)} + 0.9989T - 62.98 \quad (1)$$

where: $p(T) = 1000 \times C(T)/A_p$, A_p — injected activity.

This equation shows a close correlation when a blood sample is taken once in time range between 68 and 83 min, optimally at 75 min after injection.

To determine the urinary clearance, one should know the activity excreted with the urine $A_{Ur}(Y)$ from the time of injection to the moment Y, at which urinary bladder emptying takes place, and integral S of the biexponential curve

$$C(t) = Ae^{-at} + Be^{-bt},$$

which describes the changes of radiopharmaceutical concentration in the plasma. The activity $A_{Ur}(Y)$ should be determined by radioactivity counting. The integral S, as has been demonstrated in previous studies [5, 6], is related by linear dependence to the radiopharmaceutical concentration, $C(T)$ in blood plasma taken at time T:

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

The parameters H and G depend on the moment of blood sampling T and on the moment of urinary bladder emptying Y, according to the empirical equations presented below:

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

$$G(T, Y) = (-0.2503Y^2 + 99.17Y + 1362)T - - 3830Y + 332746 \quad (4)$$

It has been shown, that with the activity given to the patient A_p, the blood sample might be used for determination of plasma clearance, and with the activity $A_{Ur}(Y)$ to obtain urinary clearance and later — Cl_{Hp}.

The principal aim of this study was to check whether the simplified method of plasma and hepatic clearance determination is useful for clinical assessment of liver parenchyma function. Additionally, for full evaluation of the method, its capacity was compared to that of a multisampling method.

Material and methods

The studied group

The studied group consisted of:

1. Patients treated for chronic liver diseases in the Hospital Department of Infectious Diseases of the Medical University of Lodz:
   - — chronic viral hepatitis, type B and C — 28 individuals (10 females, 18 males);
   - — liver cirrhosis — 18 individuals (7 females, 11 males);
   - — alcoholic diseases — 16 individuals (7 females, 9 males);
   - — other diseases — 24 individuals (9 females, 15 males).

   Altogether there were 86 patients, 33 females and 53 males, with ages varying between 18–68 (average 45) years.
2. Healthy volunteers, altogether 43 individuals — 22 females and 21 males in three age brackets:
   - — 17 persons (8 males, 9 females, age bracket 19.4–24.3) average 22.4 y;
   - — 12 persons (6 males, 6 females, age bracket 31.5–38.8) average 35 y;
   - — 14 persons (7 males, 7 females, age bracket 50.8–55.5) average 52.7 y.
   - — 5 patients (3 males, 2 females) middle age, in which liver disease was excluded upon clinical investigation.

Together, the second group consisted of 48 healthy persons (24 males and 24 females). The study on 43 volunteers was approved by the Ethical Committee of the Medical University of Lodz.

In all individuals participating in the study there were seven basic biochemical indices determined, which are used in hepatological diagnostics of the liver diseases: activities of asparagine

Table 1. The ranges of clearance values obtained by the reference method in both investigated groups: healthy individuals and patients

Clearance	Ranges of clearance values [ml × (min × 1.73m²)⁻¹]			
	Healthy individuals		Patients	
	Min	Max	Min	Max
Cl_{Pl}	162	299	65	307
Cl_{Hp}	118	248	19.1	249

aminotranspherase (AST), alanine aminotranspherase (ALT) and gamma glutamyl transpeptidase (GGTP), concentration of bilirubin in blood serum, gamma globulin and albumin concentration in blood serum and prothrombin index.

^{99m}Tc-HEPIDA clearances were determined applying the reference multisampling method and stored in each individual record. The clearance values obtained in healthy individuals and patients are assembled in Table 1. In further studies these values were used for comparison with those determined by the single sample method ("clearance reference values").

The results of biochemical indices and all data useful for clearance determination are also stored in the patients' archives.

The assessment of liver condition = = reference system

The evaluation of liver performance was deduced on the basis of the results of seven basic biochemical indices using a clinical algorithm as reported by Białkowska [2] and later modified by Frieske et al. [3]. According to the algorithm, for each biochemical test four sub-intervals of index values (ranges) were applied. The values of biochemical determinations have been attributed to each of these ranks (from zero to three) as defined in Table 2.

For each patient, the ranks contributed to each individual biochemical index were added yielding the final sum of ranks (SP). These allowed for classification of patients into four groups:

— group I — absence of hepatic damage (SP = 0);
— group II — marginal hepatic damage (SP 1–5);
— group III — substantial hepatic parenchyma damage (SP 6–10);
— group IV — severe hepatic parenchyma damage (SP > 10).

Clearance determination by simplified method

Applying the values of activity A_p given to the patient, radiopharmaceutical concentrations in blood samples taken at 60, 75 and 90 min. after injection and the activity eliminated with urine, three separate clearance values were determined by a using the simplified method. Urine voiding was assumed to take place at about 95 min. post injection, but in many cases it took place earlier. Necessary measured values were taken from the records of those participating in analysis and were processed according to previously given equations (1), (2), (3).

Selection of a factor determining the changes of measured quantities

With data obtained in all patients and volunteers, factorial analysis has been performed aimed at identification of a factor that most adequately characterizes the variability of measured quantities characterising liver function: these included hepatic and plasmatic clearance determined by both simplified and multisampling methods and each individual biochemical indicator. The analysis was performed by application of the program STATISTICA.

The assessment of clinical usefulness/capacity of determined clearances

To evaluate the usefulness of plasmatic clearance and specific hepatic clearance, the classification of individuals into groups was applied, based upon SP. The ranges of the clearance values were divided into four equal groups. By considering biochemical classification and all statistical requirements it was possible to create a 3 × 4 contingency table (group 3 and 4 were combined). Statistical analysis was performed by the χ^2 test of independence of attributes.

Investigation of correlation between values of clearances and sums of ranks

Variance analysis of individual SP and obtained clearance values was performed. The analysis applied Spearman's correlation theory for (discrete) non-continuous variables.

Analysing differences between mean values

To assess the differences in mean values obtained in males and females a t-Student's test was utilized taking the α value = 0.05.

Results

Clearance values determined by a single sample method

The ranges of plasma and hepatic clearance values determined by simplified method are presented in Table 3.

Table 2. Ranks attributed to individual biochemical indicators based on determined results

AsAT [U/l]	AlT [U/l]	GGTP [U/l]	Bilirubin concentration [mg/dl]	Albumin concentration [mg/dl]	Gglob concentration [mg/dl]	Protrombin index (%)	Rank
10–41	8–35	M: 11–49 F: 7–32	≤ 1.2	> 3.5	≤ 1.5	80–120	0
42–99	36–99	M: 50–99 F: 33–99	1.2–1.9	3.5–3.16	1.51–2	60–79	1
100–300	100–300	100–200	2–3	3.15–2.8	2.01–2.5	4–59	2
> 300	> 300	> 200	> 3	< 2.8	> 2.5	< 40	3

M — male; F — female

Table 3. The ranges of plasma and hepatic clearance values determined by single sample method for three times of blood sampling, as obtained in healthy individuals and patients

Blood sampling time [min]	Values of lower and upper limits of clearances [ml/min/1.73m²] for both investigated groups							
	Healthy individuals				Patients			
	Cl_{Pl}		Cl_{Hp}		Cl_{Pl}		Cl_{Hp}	
	Min	Max	Min	Max	Min	Max	Min	Max
60	137	325	99	261	80	338	37	276
75	166	320	125	253	80	348	40	290
90	153	299	110	231	72	300	26	253

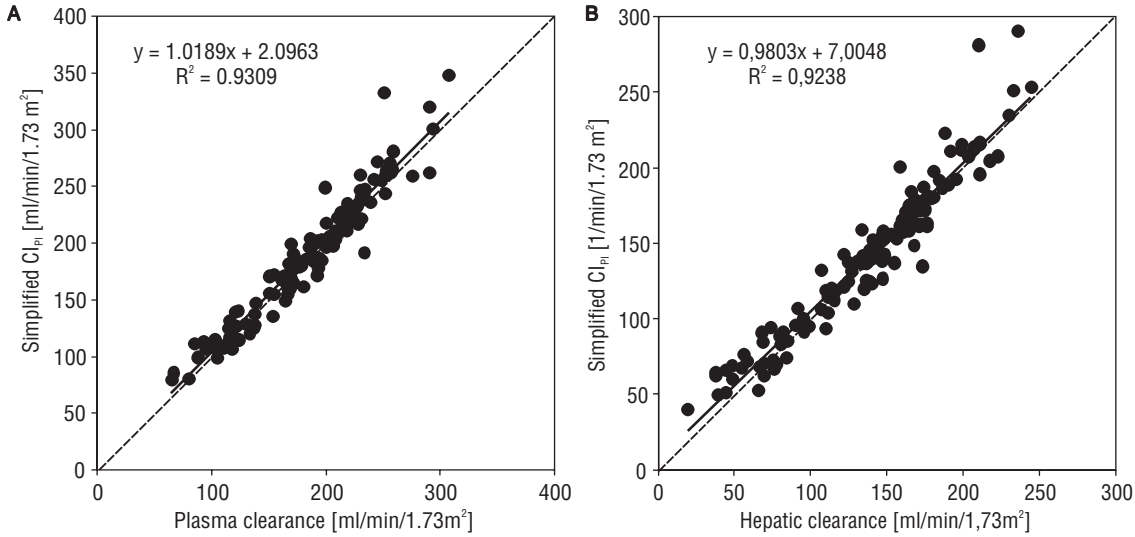

Figure 1.A. Correlations between plasma; **B.** Correlation between hepatic — clearances determined by a single sample method with their referential values.

Comparing the values presented in Table 3 and in Table 1, it may be concluded that values of clearances determined by a simplified method are slightly shifted against the ranges of referential values. The shift for each moment of blood sampling differs with regard to both measured quantity and direction (plus, minus).

Figure 1 shows the correlation between plasmatic (A) and hepatic (B) clearance values, as determined by sampling the blood 75 min. after injection *vs.* their referential values. As was demonstrated the correlations are very close and regression lines lie near to the identity line.

Table 4 shows assembled correlation coefficient values (r) and the mean standard estimated errors (SEE) for correlations of clearance values determined from one blood sample taken at three different times after injection vs. their referential values. As follows from the table the clearances determined by blood sampling at 75 min. are most closely correlated with the respective referential values. For other times of blood sampling the correlations are similar, although somewhat less close.

Values of biochemical indices

The ranges of values for biochemical indices, obtained in all studied individuals, varied considerably (presented in the Table 5).

On the basis of biochemical tests and the reference system, groups with different degrees of liver parenchyma damage were obtained; their sizes are shown in Table 6. To meet all statistical requirements, groups III and IV were combined. Therefore the 3×4 contingency tables were made for the attributes independence χ^2 test.

Table 7 presents assembled values of attributes independence χ^2 test including the degree of hepatic parenchyma damage based upon biochemical tests and the values of clearances determined from the single blood sample taken at different times after injection. There is also shown the χ^2 values obtained in similar analysis of referential clearance values. As can be seen, all values presented in the table support the hypothesis that both plasma and hepatic clearances are not independent of the degree of hepatic parenchyma damage. Additionally, there is clearly closer correlation (with greater values of χ^2) of hepatic clearance than plasma clearance. However, both Cl_{Pl} and Cl_{Hp} determined at different times of blood sampling are similarly related to the degree of hepatic parenchyma damage.

Figure 2 presents correlations between the total sum of ranks and the values of clearances as determined by the simplified method, applying ^{99m}Tc-HEPIDA concentration in plasma taken at 75 min post *iv.* injection.

Table 4. The values of correlation coefficient r and standard estimation error SEE for correlations between clearances determined by the single sample method and referential clearances values (for three blood sampling times)

Parameter	Parameter values for Cl_{Pl} and Cl_{Hp} at three different blood sampling times					
	60 min		75 min		90 min	
	Cl_{Pl}	Cl_{Hp}	Cl_{Pl}	Cl_{Hp}	Cl_{Pl}	Cl_{Hp}
r	0.951	0.955	0.965	0.961	0.955	0.947
SEE [ml/min/1.73m^2]	17.2	15.4	14.2	13.9	14.0	14.3

Table 5. Ranges of values of biochemical indices obtained in 134 individuals

Limits	Minimum and maximum limits of value ranges of participial biochemical indices						
	AsAT [U/l]	AlT [U/l]	GGTP [U/l]	Bilirubin [mg/dl]	Albumin [mg/dl]	Gglob [mg/dl]	Prothrombin index (%)
Min	7.06	11	4.2	0.20	1.83	0.55	55
Max	295	308	1629	5.22	4.85	2.98	119

Table 6. Sizes of groups with several degrees of liver parenchyma damage

Group	Size
I — lack of damage	48
II — marginal damage	42
III – substantial damage	31
IV —	13
Together	134

Table 7. Values of χ^2 of independence of attributes on liver parenchyma damage degree and clearance values determined by a simplified method and their referential values

Clearance	Values of χ^2 variable independence obtained values determined for the blood samples taken at different times and for referential clearance values			
	60	75	90	Referential
Cl_{Pl}	55.99	53.3	54.21	46.27
Cl_{Hp}	61.92	63.1	47.1	61.34

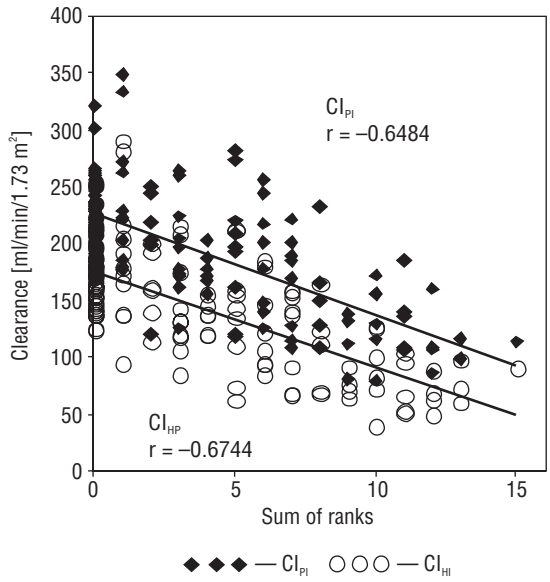

Figure 2. Correlation between the sum of ranks and clearance values obtained by a simplified method.

Table 8 illustrates assembled values of coefficients of correlation between the total sum of ranks (SP) and the values of clearances based upon the concentration of ^{99m}Tc-HEPIDA in the blood plasma sampled at different times after injection. As follows from Fig. 8, these correlations are close but their closeness is better for hepatic than for plasma clearance.

Table 9 presents the values of assembled factor loading responsible for the hepatic parenchyma damage, given in individual quantity measures used for assessment of the clearing capacity of that organ. The values of clearances to which these values refer were determined by a simplified method with blood sampling at 75 min. Very similar — factor loading values were obtained for Cl_{Pl} and Cl_{Hp} determined by a simplified method from blood sampled at two different times. The obtained results of factorial analysis show that Cl_{Hp}, determined by a multisampling method, is the attribute most closely connected with the degree of liver function.

Table 10 shows mean values and standard deviations of Cl_{Hp} and Cl_{Pl} in females and males (simplified method) and the same values obtained by the multisample method. The mean values of hepatic clearances obtained by a simplified method, and by a multisample method, differ from each other and, as in studies applying multisampling methods, the mean values in females are lower than in males.

Table 8. Values of correlation coefficient r between sum of ranks (SP) and clearance values determined by the simplified method for different blood sampling times and for referential clearance values

Blood sampling time [min]	Correlation coefficient	
	r_{Pl}	r_{Hp}
60	–0.6498	–0.6744
75	–0.6484	–0.6744
90	–0.6262	–0.6488
Referential	–0.585	–0.6529

Table 9. Factor loadings in individual tests applied for assessment of liver

Measured quantity	Factor loading	Measured quantity	Factor loading
Cl_{Pl} – Ref.	–0.9034	AlT	0.6752
Cl_{Hp} – Ref.	–0.9355	AsAT	0.7813
Cl_{Pl} – simpl.	–0.9138	GGTP	0.3346
Cl_{Hp} – simpl.	–0.9197	Albumin	–0.7247
Bilirubin concentration	0.9276	GGLB	0.602
		Prothrombin index	–0.5714

Discussion

Our earlier studies showed explicitly that logic and experience favour determination of net hepatic clearance of ^{99m}Tc-HEPIDA instead of previously determined plasmatic clearance of the radiopharmaceutical [3, 7] for the assessment of the degree of liver parenchyma damage. Further studies demonstrated that the value of Cl_{Hp} determined by a multisample method better reflected the degree of liver function damage than the value of $Cl_{Pl,}$ even if their values are less precise. However, a multisample method is time consuming and, for some patients, even uncomfortable, which is why we have elaborated a simplified method of clearance determination for both plasma and hepatic clearances [4, 5].

To implement the method in laboratories of nuclear medicine, it is necessary to investigate the usefulness of results obtained by that method. This was the principal aim of these studies.

Patient selection

One argument in favour of using the studied group was the wide range of impairment of liver function, which was confirmed by the results of laboratory tests and values of clearances obtained by the multisampling method.

In the documentation concerning clearance determination, there were results of radiopharmaceutical concentrations in blood plasma sampled at different times - among others at 60, 75 and 90 min after injection. The compound concentrations in plasma sampled at these three times were applied separately for clearance determination by the single sample method, even though the times blood sampling were outside the denoted time range (from 68 to 83 min p.i.) previously given in papers [5, 6].

Reference system

The analysis of the usefulness of a simplified single sample method for the assessment of liver function requires a reference system in which the degree of liver functionality has been determined either in a real or nearly real way. Such a reference system was created on the basis of results of biochemical tests.

Even if the applied rank procedure changed the measured results from the scale of absolute values into results on the rank scale, the results are still useful if further analysis uses the proper mathematical apparatus (tools), namely statistical tests referring to the variable of the discrete type, here using Spearman's correlation test instead of Pearson's criteria.

Correlation of hepatic parenchyma damage and values of determined clearances

From analysis it follows that both clearances (Cl_{Pl}, Cl_{Hp}) demonstrate a close correlation with regard to the degree of hepatic parenchyma damage determined on the basis of the reference system. High values of χ^2, above 20, explicitly show that these features are dependent — the likelihood of random non-association of these attributes is less than 0.1%. It should be noted that higher values of χ^2 were obtained for hepatic clearances, which shows that their values reflect the degree of hepatic parenchyma damage in a better way than the total plasma clearances.

Correlations between the clearances and the degree of liver function damage are also confirmed by Spearman's correlation analysis, which is appropriate for results expressed on a rank scale. The correlation analysis confirms a closer correspondence of Cl_{Hp} than that of Cl_{Pl}.

Table 10. Mean values and standard deviations of hepatic and plasma clearances as determined by the simplified method from concentration of ^{99m}Tc-HEPIDA in plasma sampled at different times after injection, and those determined by a referential multisampling method

	Clearance [ml/min/1.73m^2]															
	60 min				75 min				90 min				Referential			
	Cl_{Pl}		Cl_{Hp}		Cl_{Pl}		Cl_{Hp}		Cl_{Pl}		Cl_{Hp}		Cl_{Pl}		Cl_{Hp}	
Sex	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Average	233	217	183	163	231	212	183	161	207	194	162	145	224	201	180	157
S.D.	40	29	36	26	35	25	33	24	33	24	30	23	32	25	30	23
p	0.059 (+)		0.016 (–)		0.015 (–)		0.006 (–)		0.0501 (+)		0.018 (–)		0.014 (–)		0.0063 (–)	

M — male; F — female

The factorial analysis also enabled us to select a factor which most adequately characterized the variation of biochemical quantities, which in turn reflected the degree of liver function. This factor was temporarily called "incapacity". If the incapacity is higher, correlated values take higher values. With greater incapacity, the values of bilirubin and clearance concentration are lower.

So called factor loading informs us about the degree of dependence of studied attributes with the postulated factor. The more the value of the loading of factor approaches unity, the closer the association of the quantity with the hypothetical factor (incapacity). The sign of the loading value informs us whether the factor causes a positive correlation (increase of the value) or negative correlation (decrease).

The values of factor loading presented in Table 9 show that incapacity appears more adequately characterized by a multisampling clearance method than by the simplified method. However, the plasma clearance there has a lower factor loading, which proves that this quantity does not reflect the liver incapacity as well as the specific hepatic clearance. It should also be noted that of all ^{99m}Tc-HEPIDA clearances, the values of Cl_{Pl} determined by a multisampling method are the least connected with liver damage, and the values of χ^2 and r of determined Cl_{Pl} clearance are lower in comparison with analogous values of Cl_{Pl} and Cl_{Hp} obtained by a standardized and simplified method. This results in the least uncertainty burden of the plasma clearance obtained by a multisampling method, which in a way variables of renal cleaning is shown clearly. It should however be clearly underlined that the hepatic clearance demonstrates the degree of liver functionality better than Cl_{Pl} , even though the former one is determined with greater uncertainty.

Comparing the values of χ^2, coefficients of correlations and loading of incapacity, it can be observed that hepatic clearance, determined by a simplified method, shows a degree of hepatic parenchyma damage which is close to that of the Cl_{Hp} value obtained by a multisampling method.

Clearances values and sex

Investigations of Frieske et al. [3] inform us about differences between mean hepatic clearance values obtained in healthy individuals of both sexes. The inter-sexual variances in excreting capacity of the liver and the range of clearance values obtained by a simplified method in healthy individuals pointed to an investigation of the differences between mean clearance values by a simplified method. The respective mean values of both clearances (Cl_{Pl} and Cl_{Hp}) for females and males are presented in Table 10. In the table the mean values of Cl_{Pl} and Cl_{Hp} obtained in healthy individuals are given, together with those obtained by the multisample method. As follows from the table and the t-Student test, mean values of hepatic clearances differ significantly ($p < 0.05$); in males they are greater than in females. With regards to mean values of plasma clearance, the differences were analysed only on the basis of the concentration in blood plasma. However, there were significant differences only in the case of blood sampled at 75 min, but in the case of blood sampling at 60 and 90 minutes no significant differences were noted. The results of estimations from plasma concentrations when the time of sampling is outside the denoted time range, in which the marked equation is very close, might be inaccurate. In this case the accepted norm was exceeded slightly. The differences in the postulated range from 68–83 min between mean values for both sexes are significant.

Comparison of mean values of clearance determination from one sample method with those taken from multisampling procedure might result in a lack of essential differences. Therefore, normative values determined by multisampling method are valid for determination by simplified method.

Conclusions

1. Both clearances (Cl_{Pl} and Cl_{Hp}), when determined by means of simplified procedure, reflect the functional condition of the liver.
2. Hepatic ^{99m}Tc-HEPIDA clearance determined by a simplified procedure reflects liver condition more adequately than the plasma counterpart.
3. The simplified procedure of ^{99m}Tc-HEPIDA clearances may be recommended for diagnostic purposes.

While determining the clearances in a simplified way, the blood sampling should take place between 68 an 83 min post *i.v.* injection of ^{99m}Tc-HEPIDA; optimal time value seems to be 75 min.

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