Original

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Comparison of ^{99m}Tc-HEPIDA and ^{99m}Tc-MBrIDA from the standpoint of hepatic clearance determination — preliminary communication

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Abstract

BACKGROUND. In order to evaluate the functional capacity of the liver by means of clearance determination, the derivative of iminodiacetic acid (^{99m}Tc-HEPIDA) has been used in recent decades. Because of recent problems with manufacturing and delivery of ^{99m}Tc-HEPIDA, an investigation was undertaken with the aim of testing whether a more widely available ^{99m}Tc-MBrIDA could be used for clearance determination and whether hepatic clearance measured with the use of this compound provides a similarly useful test of hepatic function.

MATERIAL AND METHODS. Comparative investigations were performed in 73 patients of both sexes. The state of the efficiency of liver parenchyma was determined based on seven widely used biochemical tests, i.e. levels of: bilirubin, albumin, and gamma globulin; activity of AST, ALT, GGTP, and prothrombin index. The clearances of both radiopharmaceuticals, ^{99m}Tc-HEPIDA and ^{99m}Tc-MBrIDA, were determined by means of multisample technique. The results of determination were correlated among themselves and with the results of biochemical tests. The set of results of all estimations allowed a factorial analysis to be performed to find a common factor and to compute the values of factor loadings in particular tests.

RESULTS. Obvious correlation between plasma and hepatic clearances of both radiopharmaceuticals was obtained and between plasma clearance of ^{99m}Tc-MBrIDA and hepatic clearance of ^{99m}Tc-HEPIDA. Correlation coefficients of ^{99m}Tc-MBrIDA clearance and the biochemical test results attained somewhat lower values than for ^{99m}Tc-HEPIDA clearance. Similarly, values of χ^2 test of independence of ^{99m}Tc-MBrIDA clearances and test results were also less close than for ^{99m}Tc-HEPIDA clearances. Factorial analysis showed that common factor loading is greatest for hepatic clearance of ^{99m}Tc-HEPIDA; the values of two loadings of ^{99m}Tc-MBrIDA clearances are very close, but somewhat lower than those for ^{99m}Tc-HEPIDA.

CONCLUSIONS. From the performed investigations it is possible to conclude that ^{99m}Tc-MBrIDA clearances may be used for the evaluation of liver parenchyma performance, even if the results may not be as certain as those obtained using ^{99m}Tc-HEPIDA.

Key words: ^{99m}Tc-HEPIDA clearances, ^{99m}TcMBrIDA clearances, hepatic capacity measurements

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Introduction

The derivatives of iminodiacetic acid (IDA) labelled with ^{99m}Tc have been used for decades for dynamic studies of the biliary system. Six derivatives fulfil the demands expected from clinically useful radiopharmaceuticals [1]. The most common two substances: ^{99m}Tc-MBrIDA (^{99m}Tc-N-(3-bromo-2, 4, 6, trimethylacetanilide) and ^{99m}Tc-HEPIDA [^{99m}Tc-N-(2, 4 dimethylacetanil-

ide) iminodiacetic acid] have also been used for the evaluation of the functional capacity of the liver by means of clearance studies [2–4, 9–11].

The derivatives of IDA are picked up from the blood and eliminated with bile to the intestines. A disadvantage of ^{99m}Tc-HEPIDA, where clearance determinations are concerned, lies in the fact that variable fraction of the compound is excreted with urine. To obtain a meaningful result, when hepatic clearance of the radiopharmaceuticals is required, a urinary clearance has to be determined in parallel. Therefore, the procedure became more laborious and susceptible to larger errors because hepatic clearance can be obtained only by subtracting the urinary component from the total plasma clearance. However, the hepatic clearance measured in this way was shown to be a reliable clinical test for the assessment of the functional capacity of the liver [9–11]. The results of ^{99m}Tc-HEPIDA clearance determination provide useful data for classification of the degree of liver function impairment and can be used for monitoring hepatic function. However, there have recently been problems with the manufacture and delivery of ^{99m}Tc-HEPIDA.

The present investigation was undertaken with the aim of testing whether a widely available ^{99m}Tc-MBrIDA could be used for hepatic clearance determinations and whether hepatic clearance measured with the use of this compound could provide a similarly useful test of hepatic function.

Materials and methods

The ^{99m}Tc-MBrIDA was purchased from the Radioisotope Centre POLATOM. To determine whether this radiopharmaceutical could be a useful substitute for ^{99m}Tc-HEPIDA, clearance determinations were made using both substances, and both plasma and urinary clearances were measured. The results were compared to each other and were juxtaposed to biochemical tests widely used for the assessment of liver parenchyma function.

Group of investigated patients

The investigations were made on 73 patients of both sexes, with age varying between 20.5 and 77.1 years (mean 52 years). In all subjects a clinical diagnosis of chronic hepatitis of varying etiology had been established, with a wide range of functional impairment of the organ. These patients were directed to the Department of Nuclear Medicine for diagnostic reasons; however, the second determination of the clearance was made for research purposes. The plans and justification for the latter were submitted for consideration to the Regional Ethical Commission, which granted the approval.

The clearances were determined according to the procedure described earlier [6–8]. The method was based on a multisampling procedure; the first test was made with ^{99m}Tc-HEPIDA, and another was made two days later using ^{99m}Tc-MBrIDA for the same purpose. The last blood sample was taken at 90 minutes post administration of radiopharmaceuticals; the urine was collected immediately, and after urine voiding the fraction of the latter retained in the bladder was determined by ultrasonographic method. The activity of both radiopharmaceuticals was determined by measuring the volume of urine voided and by measuring the concentration of activity in 1 ml of urine; the activity measurements were made using the Wizard System. The urinary clearance was calculated from voided activity and integrated plasma concentration of the ^{99m}Tc activity of each compound from injection to the time of voiding. The hepatic clearance of each radiopharmaceutical was obtained from subtraction of renal clearance from the corresponding plasma clearance.

The hepatic clearance was normalized to body surface derived from height and mass of the body using the formula of Haycock.

In each patient, the following biochemical tests were made (not later than 2 days after determination of the clearance) in the serum: bilirubin conc., activity of ALT, AST, and GGTP, concentration of albumin and gamma globulin, protrombine index, and serum proteinogram.

Over these two days, no changes in the clinical status were observed and no event was noted that could affect the functional status of the liver in the studied individuals.

Statistical processing of the data

The results of ^{99m}Tc-HEPIDA clearances were correlated with those obtained from ^{99m}Tc-MBrIDA investigations and the regression lines were obtained by means of orthogonal least square method.

The functional state of liver parenchyma was derived from the results of the laboratory tests of the seven above-mentioned biochemical indices. For purpose of evaluation, an algorithm, as defined by Białkowska and co-workers [3, 4] and further modified by Frieske et al. [9, 10], was used. Summarizing briefly the idea of the algorithm, there were 4 sub-ranges of each of the test values defined (based on the statistical distribution of the results for the test). A number (0 to 3) was attributed to the sub-ranges, resulting from the position of the data in the sub-ranges. The sub-ranges for all biochemical indices and corresponding numbers of points attributed are presented in Table 1.

Table 1. Weight for results of biochemical tests as depending on the measured values

AST [U/l]	ALT [U/l]	GGTP [U/l]	Concentration of bilirubin [mg/dl]	Concentration of albumin [mg/dl]	Concentration of Gglob [mg/dl]	Protrombine index (%)	Sum of points (SP)
1.10.1941	1.08.1935	M: 11–49 F: 7–32	do 1.2	> 3.5	do 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	40–59	2
> 300	> 300	> 200	> 3	< 2.8	> 2.5	< 40	3

For each of the patients, the sum of weight numbers (SP) was thus obtained, and all of them were subsequently correlated with clearance values. As a measure of correlation, the r coefficient of Spearman was used.

The sum of weight numbers (SP) allowed attribution of the investigated individuals into 4 groups: group 1, SP = 0 — no damage to the hepatic parenchyma; group 2, SP = 1–5 — marginal damage to the liver parenchyma; group 3, SP = 6–10 — substantial damage to the liver parenchyma; and group 4, SP > 10 — severe liver parenchyma damage.

Such a division of patients into 4 groups, and division of clearance values into 3 equal sub-ranges enabled application of the χ^2 test of independence of the attributes, i.e. of biochemical evaluation and results of clearance determinations.

Utilization of all measured values made possible a factorial analysis with the aim of finding a common factor, named here *liver performance*, and to attribute a load of each measured quantity to the performance. For this purpose, Statistica software was used.

Results

The values of plasma-hepatic and urinary clearances while using the two radiopharmaceuticals, as observed in the studied individuals and contained in the above-defined ranges, are presented in Table 2.

In Figure 1, the distributions of urinary clearances for the two radiopharmaceuticals are presented. It may be seen that urinary clearances of ^{99m}Tc-MBrIDA are much lower than the corresponding clearances of ^{99m}Tc-HEPIDA.

Figures 2 and 3 present correlations between plasma and hepatic clearances for the two radiopharmaceuticals. Figure 4 presents the correlation between ^{99m}Tc-HEPIDA hepatic and ^{99m}Tc-MBrIDA plasmatic clearances. There is obvious correlation between the mentioned quantities.

Figures 5 and 6 show a correlation between sums of weight points obtained from biochemical studies and corresponding plasma and hepatic clearances (^{99m}Tc-HEPIDA and ^{99m}Tc-MBrIDA). These graphs and values of the Spearman correlation coefficients confirm that these values are correlated.

In Table 3 the clearance values and values of the χ^2 test of independence of the group of patients are assembled.

Using two radiopharmaceuticals, the classification of patients with different degrees of liver parenchyma damage is very similar (see Table 4). The highest χ^2 value was obtained for the hepatic ^{99m}Tc-HEPIDA clearance, and the lowest was for plasma clearance for the same substance. The remaining χ^2 values for ^{99m}Tc-MBrIDA are identical. The obtained χ^2 values speak for rejection ($p > 0.05$) of the hypothesis that the clearance values and the results of the biochemical tests are independent of each other.

Table 2. The lowest and highest values in 3 types of clearances determined in the studied patients, using ^{99m}Tc-HEPIDA and ^{99m}Tc-MBrIDA

	The lowest and highest values of clearances [ml/min]					
	^{99m}Tc-HEPIDA			^{99m}Tc-MBrIDA		
	Plasma	Hepatic	Urinary	Plasma	Hepatic	Urinary
Max	251.3	197.5	102.5	449.4	440	13.6
Min	75.7	17.8	19.7	52.7	48.7	2.2

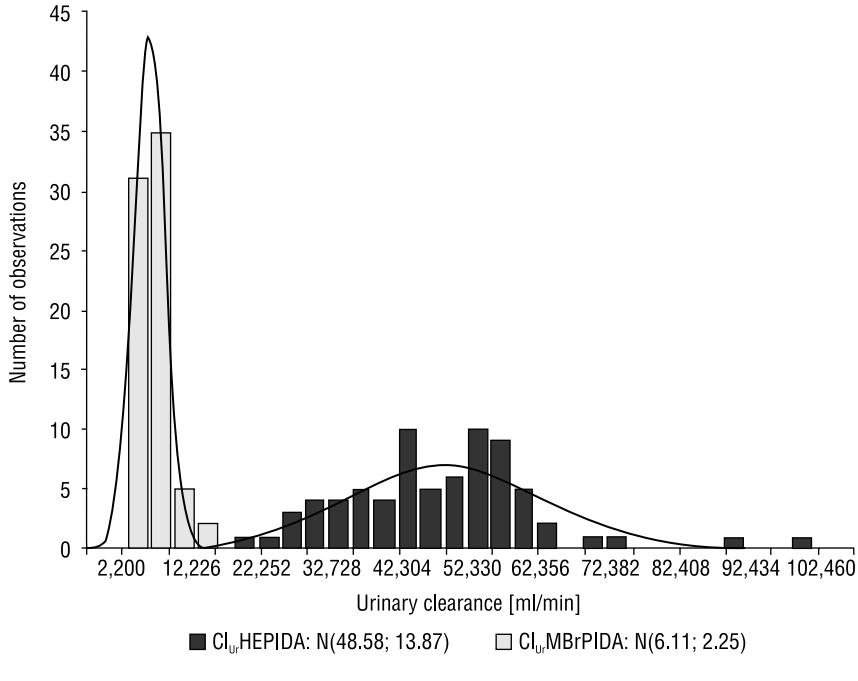

Figure 1. Histograms of urinary clearances of ^{99m}Tc-HEPIDA and ^{99m}Tc-MBrIDA.

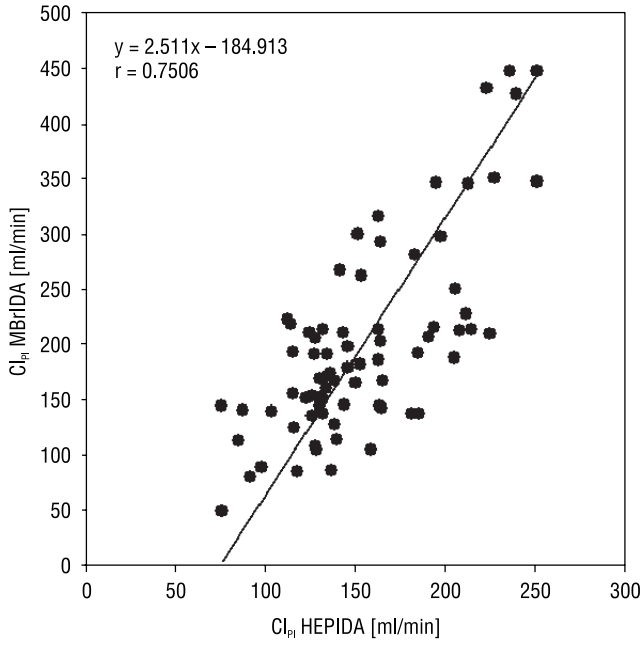

Figure 2. Correlation and regression line between plasma clearances of ^{99m}Tc-HEPIDA and ^{99m}Tc-MBrIDA.

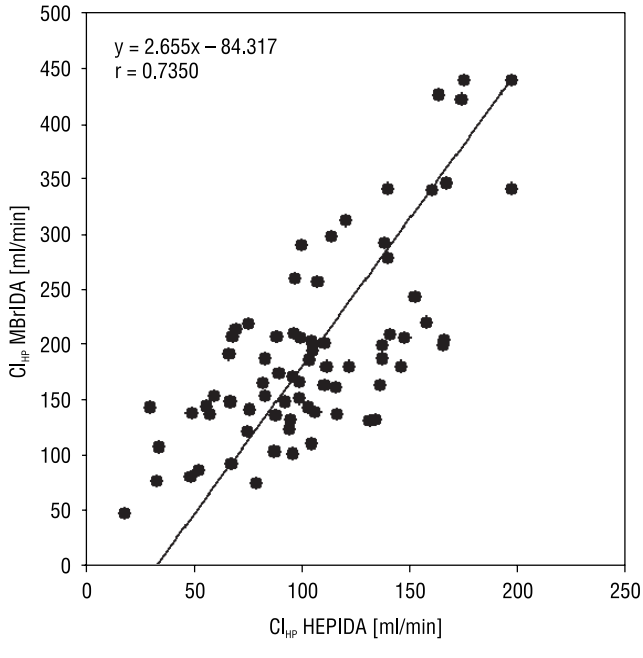

Figure 3. Correlation and regression line between hepatic clearances of ^{99m}Tc-HEPIDA and ^{99m}Tc-MBrIDA.

In Table 5, the factor loadings for hepatic performance have been assembled (biochemical tests, clearances of both radiopharmaceuticals). The results are in agreement with those of the correlation studies and χ^2 tests. It should be mentioned that the highest factor loadings contribute the hepatic and plasmatic ^{99m}Tc-HEPIDA clearances; the values of two loadings of ^{99m}Tc-MBrIDA clearances are very close, but clearly somewhat lower than those for ^{99m}Tc-HEPIDA are.

The factor loadings of individual biochemical tests are evidently much lower.

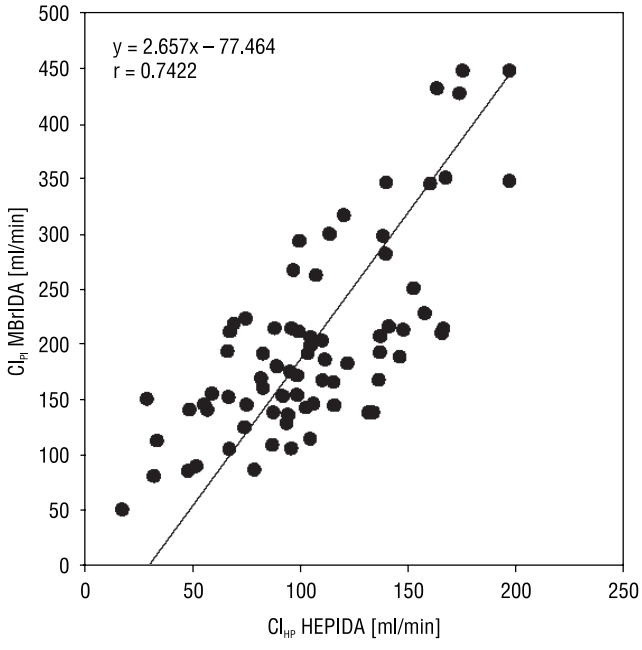

Figure 4. Correlation and regression line between hepatic clearance of ^{99m}Tc-HEPIDA and plasma clearance of ^{99m}Tc-MBrIDA.

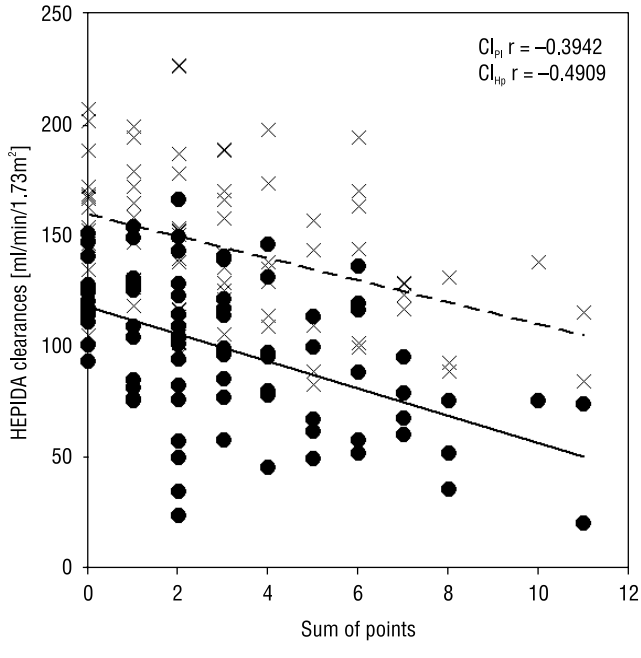

Figure 5. Correlation of Sum of points and clearances of ^{99m}Tc-HEPIDA: × and dashed line–plasma, ● and solid line–hepatic.

Discussion

For years, ^{99m}Tc-HEPIDA was used for hepatic clearance determination. The usefulness of this radiopharmaceutical for the assessment of hepatic parenchyma performance by determination of hepatic clearance had been documented in earlier publications [2–4, 9–11]. It was demonstrated that hepatic clearance is superior for this purpose than plasma clearance is [9–11]. The results of the hepatic clearance determination, as observed in the present study, are in full agreement with the previous studies. This test has

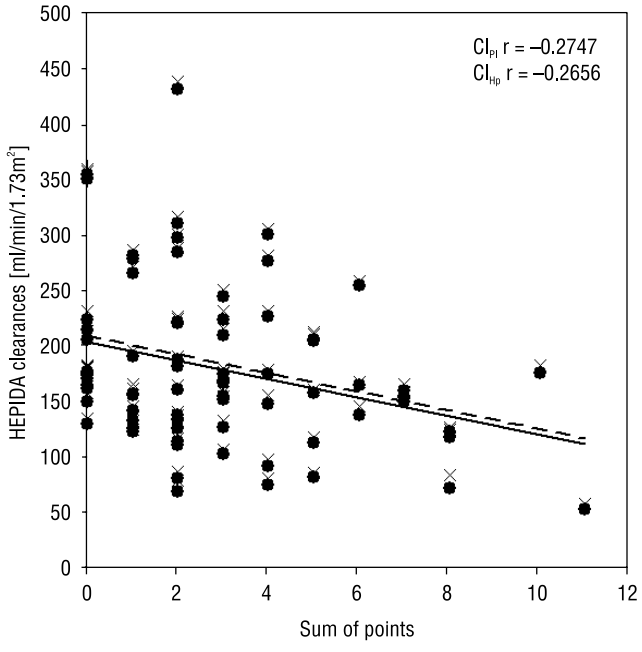

Figure 6. Correlation of Sum of points and clearances of ^{99m}Tc-MBrIDA: × and dashed line–plasma, ● and solid line–hepatic.

Table 3. The χ^2 values of the test for independence of clearance results and grouping of patients on the basis of biochemical tests

Clearance	Value of χ^2
Hepatic ^{99m}Tc-HEPIDA	11.36
Plasma ^{99m}Tc-HEPIDA	6.447
Hepatic ^{99m}Tc-MBrIDA	7.79
Plasma ^{99m}Tc-MBrIDA	7.79

Table 4. Classification of patient groups as related to ranges of hepatic ^{99m}Tc-HEPIDA and plasmatic ^{99m}Tc-MBrIDA clearances

Clearance range [ml/min/1.73 m²]	Group of patients acc. to classification based on biochemical tests		
	0	1	2 + 3
^{99m}Tc-HEPIDA			
≤ 129	1	8	6
129 <…≤ 177	7	26	6
177 <	6	13	0
^{99m}Tc-MBrIDA			
≤ 150	2	16	5
150 <...≤ 250	10	22	6
250 <	2	9	1

Table 5. Values of factor loading for "Liver performance", as observed for individual tests

The diagnostic test	Value of factor loading
^{99m}Tc-HEPIDA Hepatic clearance	0.901487
^{99m}Tc-HEPIDA Plasma clearance	0.877251
^{99m}Tc-MBrIDA Hepatic clearance	0.833514
^{99m}Tc-MBrIDA Plasma clearance	0.828202
Bilirubin plasma concentration	–0.027502
AST	–0.445999
ALT	–0.399829
GGTP	–0.542289
Total protein	0.035845
Albumin	0.288152
GGlb	–0.237470
Protrb. index	0.359329

therefore been selected as a standard for comparison with ^{99m}Tc-BrIDA clearances.

As may be seen in Figure 2, the average value of urinary clearance of ^{99m}Tc-HEPIDA is ab. 50 ml/min; however, distribution of this quantity is wide with a standard deviation = 14 ml/min. This flat distribution with high variation coefficient indicates that, in a single patient, finding a value of this clearance in the range from 30 ml/min to 60 ml/min is almost equally probable and cannot be guessed in advance.

In contrast, as can be seen in Figure 1, the distribution of urinary clearances of ^{99m}Tc-MBrIDA is very narrow and on average equals 5.6 ml/min with σ = 2.3 ml/min. Such a narrow distribution justifies the expectation that urinary clearance in an individual patient is easy to predict. By subtracting this average value from the plasma clearance one can obtain the hepatic clearance of ^{99m}Tc-MBrIDA. The probable error (two standard deviations — 5 ml/min) will not have any serious impact on the interpretation of the hepatic clearance. This situation justifies resignation of urine collection and determination of the urinary clearance of ^{99m}Tc-MBrIDA.

There are also further justifications for determination of ^{99m}Tc-MBrIDA clearance only. Thus:

1. Plasma clearance of ^{99m}Tc-MBrIDA correlates more closely with ^{99m}Tc-HEPIDA hepatic clearance than with the hepatic ^{99m}Tc-MBrIDA clearance (Figures 2 and 3). This results most likely from the fact that hepatic clearances are calculated as the difference between the plasma and corresponding urinary clearances. This subtraction results in propagation of errors and therefore the error of ^{99m}Tc-BrIDA hepatic clearance is subject to greater error than the corresponding plasma clearance alone. This is the reason for the fact that ^{99m}Tc-MBrIDA clearance is more widely scattered around the regression line than the plasmatic clearance of this substance.
2. The χ^2 test indicates that both the plasma and hepatic clearance of ^{99m}Tc-MBrIDA display the same agreement with damage to hepatic parenchyma, as based on biochemical tests. This justifies selecting the more simple determination of the two.
3. A negligible difference between the factor loadings of both ^{99m}Tc-MBrIDA clearances implies that they are equally suited for assessment of liver performance.

These preliminary studies demonstrated that ^{99m}Tc-MBrIDA clearances reflect the functional state of liver parenchyma; however, their factor loading is somewhat smaller than that of ^{99m}Tc-HEPIDA, and correlations of the former with the sum of the points of biochemical assessment are less close (Figures 5 and 6, Table 3). Nevertheless, these differences do not appear to be substantial.

Conclusions

1. ^{99m}Tc-MBrIDA clearances may be used for evaluation of liver parenchyma performance, despite the fact that the results may not be as certain as those obtained using ^{99m}Tc-HEPIDA for the same purpose.
2. The results of this study seem quite convincing that for evaluation of liver performance, plasma clearance of ^{99m}Tc-MBrIDA is sufficient.
3. Further studies of the clinical usefulness of ^{99m}Tc-MBrIDA plasma clearance seem advisable.

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