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Specific ^{99m}TC-hepida hepatic clearance — essential value ranges from a clinical stand-point

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Abstract

BACKGROUND: Determinations of plasma ^{99m}Tc-HEPIDA clearance (Cl_{Pl}) have been performed in some centres for 30 years to assess liver parenchyma damage, mostly for monitoring of organ performance in the course of various diseases. The main disadvantage of such a procedure rests with the fact that elimination of the compound from the system occurs not only via the liver and gall ducts, but also via the urinary route; the contribution of the latter compound being quite variable. This circumstance may lead to false assessment of liver parenchyma performance. A method has been developed therefore for assessment of specific hepatic clearance of ^{99m}Tc-HEPIDA (Cl_{Hp}). Using this method it was demonstrated that results of Cl_{Hp} correlated better with independently assessed degrees of liver impairment than did the values of Cl_{Pl}.

MATERIAL AND METHODS: To delineate ranges of Cl_{Hp} that would provide valuable clinical information 134 individuals were studied, of whom 48 served as healthy controls and 86 had varying degrees of livers function impairment, resulting from various chronic diseases affecting the organs functional capacity. The latter was assessed on the basis of a series of commonly used biochemical indicators.

RESULTS AND CONCLUSIONS: For delineation of meaningful ranges of ^{99m}Tc-HEPIDA specific hepatic clearance ROC curve method was used. The following results were obtained: $Cl_{Hp} \geq 150$ ml min^{-1} 1.72 m^{-2} — excludes with high probability presence of substantial liver parenchyma damage; $Cl_{Hp} \leq 120$ ml min^{-1} 1.72m^{-2} — indicates a substantial impairment of liver function (damage).

Values of $Cl_{Hp} \leq 90$ ml min^{-1} 1.72 m^{-2} are highly specific for serious liver damage, of intensity typical for cirrhosis of the organ.

Key words: ^{99m}Tc-HEPIDA plasma clearance, specific ^{99m}Tc-HEPIDA hepatic clearance, clinically essential range

Introduction

At our university ^{99m}Tc-HEPIDA plasma clearance (Cl_{Pl}) was introduced into clinical practice long ago, in the nineteen-eighties [1]. The test has been used for evaluation of the liver's parenchyma impairment as well as for monitoring the clinical condition in chronic, and more seldom in acute diseases of the organ [2–5]. The main advantages of the procedure are: total lack of invasive intervention and presentation of results in the form of a single number, which is easier to interpret in global assessment of liver damage than results of a large group of various diagnostic laboratory tests. These advantages, however, had been accompanied by a complication, which is the partial elimination of ^{99m}Tc-HEPIDA from the plasma by the urinary route [6, 7]. According to the manufacturers attached information the latter elimination should be modest, in the range of 5–8%. However, our own measurements yielded values that disclosed high variability of the renal clearance of the radiopharmaceutical. Thus, in healthy individuals the percentage leaving the body with urine varied between 9 and 28 percent of the total plasma clearance, and more interestingly perhaps, in subjects with chronic liver disease the percentage reached, in selected cases, 80. It is obvious that such variability could lead to serious misinterpretation of liver condition if Cl_{Pl} would be (and had been) used for interpretation of liver parenchyma

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damage, at least in some cases with advanced malfunction of the organ.

A method had been developed in our laboratory for determination of the specific hepatic ^{99m}Tc-HEPIDA clearance (Cl_{Hp}) which was defined as the difference between the plasma and urinary clearance of the compound [9–11]. It was also shown that values of Cl_{Hp} correlate more closely than those of Cl_{Pl} with the results of biochemical assessment (score) of liver parenchyma damage in spite of the fact that precision of Cl_{Hp} determination is somewhat lower than of Cl_{Pl} [12].

There was no dependence of Cl_{Hp} on age in healthy controls; however, there was a slight difference between mean values of the clearance after normalization to body surface for males and females. The difference, however, is really very small, and perhaps may reflect more the bias in normalization than be a real phenomenon [12].

In this paper research is presented aimed at the interpretation of results of Cl_{Hp}, i.e. at delineation of ranges of clearance values which are essential from the clinical practice point if view.

Material and methods

The study involved 134 individuals ageing from 18 to 70 years; they were divided into two groups: group I — 48 healthy volunteers (24 males and 24 females) in the age range 19 to 55 yrs. II group — 86 patients (53 males and 33 females) in the age range 19 to 70 yrs, with various chronic liver diseases (chronic viral hepatitis — 28 pts, alcoholic hepatitis 16 patients, liver cirrhosis — 22 persons, and lipid degeneration of the liver, lipid hepatitis and some hepatic disorders of not disclosed aetiology — 20 patients). The study was granted permission from the Ethical Commission of the University.

Assessment of liver parenchyma injury in all individuals was performed on the basis of clinical data (qualitatively) and semiquantitatively on the basis of 7 biochemical determinations used commonly in diagnostics of chronic liver diseases, namely: concentration of bilirubin in the plasma, activity of enzymes (ALAT, AspAT and GGTP), concentration of albumins, G-globulins in the plasma and value of the prothrombin index. On the basis of these determinations all individuals were divided in four subgroups, taking intensiveness of liver parenchyma involvement: 0 — healthy individuals and 1–3 — patients with mild, intermediate and severe impairment of the liver function. This separation into subgroups was based upon two classifications: a clinical one, being a modified Białkowska classification, based on clinical experience in interpretation of the biochemical determinations (there was an arbitrary element involved) and our own classification based on statistical distributions of (Gaussian or geometric) results of biochemical determinations; the results were classified according to the distance from the mean values, given in terms of standard deviations. Both classifications and results obtained have been presented in an earlier publication [12].

After intravenous administration of the ^{99m}Tc-HEPIDA with activity of — 40 MBq, for each person the plasma (Cl_{Pl}) and urinary (Cl_{Ur}) clearance was determined, and Cl_{Hp} calculated as the difference of the two former. For determinations published earlier [9–11] multisample procedures were used. All clearances were standardized to the body surface acc. to Du Bois algorithm [13].

Results

Mean values of Cl_{Hp} and numbers of determinations in each subgroup are presented in Figure 1.

ROC curves were created (Figure 2) with the aim to delineate optimal values of Cl_{Hp} for classification of the results indicating lack of substantial impairment of liver function (0 plus presence of mild- subgroup 1) *vs.* substantial and severe (subgroups 2 and 3) impairment of liver function.

These curves permitted the selection of the threshold values that provided good efficacy (sensitivity, specificity) for the detection of substantial liver damage for both classifications used (see above). At the threshold value of 150 ml min^{-1}1.72 m^{-2} sensitivity of the test is acceptable and amounts to 85 and 93 percent for the clinical and our own classification, respectively. The corresponding negative predictive values (lack of damage at and above the threshold) were 87 and 92%, respectively. In other words, at and above the value of Cl_{Hp} — 150 ml min^{-1}1.72 m^{-2} there would be few false negative diagnoses. However, rather low specificity of the test for both classifications (66 and 62%, resp.) means that at such selection of the threshold there would be quite a large percentage of false positive diagnoses of substantial impairment of the liver function (PPV — 62 and 63% for the clinical and own classification, resp.).

A much better specificity has been attained for the threshold value of 120 ml min^{-1} 1.72 m^{-2}; it amounted to 94 and 93% for two classifications used (PPV 87 and 88%, resp.).

From this consideration it follows that probability to see lack of substantial liver damage at or below this threshold is quite low. However, as the sensitivity of damage detection for this value is quite low (62 and 69% for the clinical and our own classification, resp.; NPV 79 and 80% correspondingly) this threshold cannot be a dividing criteria for those individuals with and without the liver damage.

Figure 3 presents ROC curve aimed at selection of optimal values of Cl_{Hp} for differentiation of severe liver damage, typical for

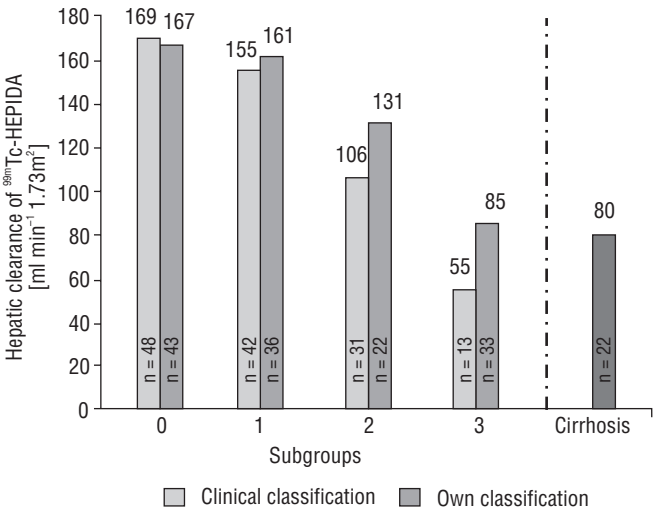

Figure 1. Mean values of specific hepatic ^{99m}Tc-HEPIDA clearance (Cl_{Hp}) in subgroups of varying degrees of liver involvement: 0, 1, 2, 3 (according to clinical and our own classification), the mean value for patients with diagnosed cirrhosis being indicated separately.

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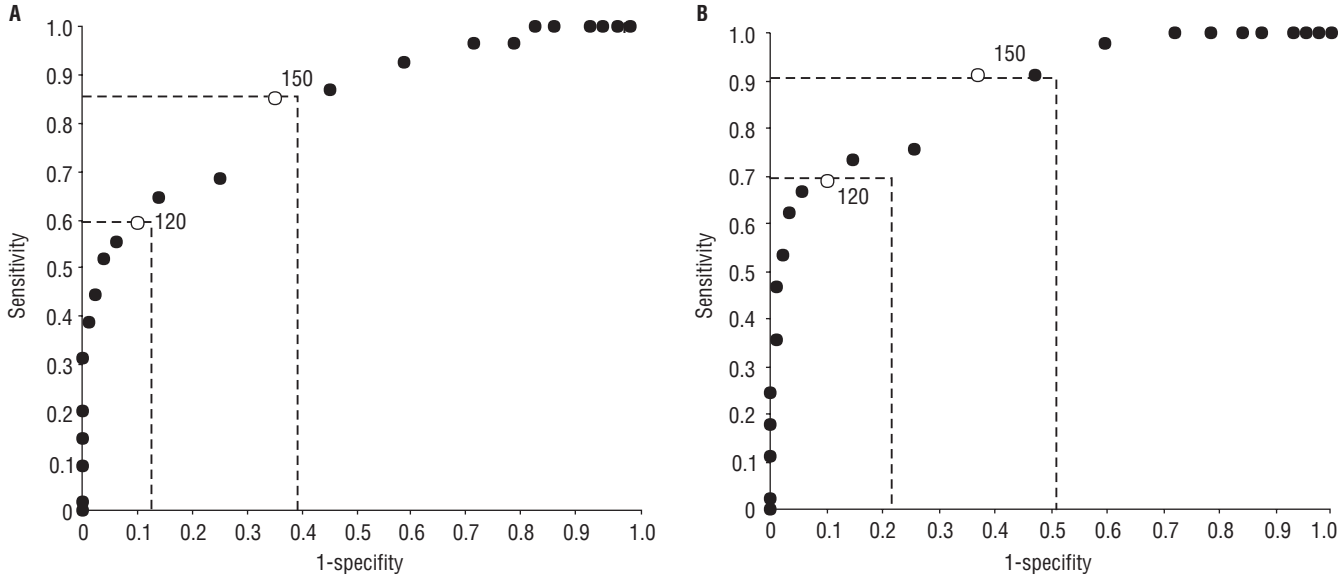

Figure 2. ROC curves for classification of the results indicating lack of substantial impairment of liver function (subgroup 0, 1) *vs.* substantial and severe impairment of liver function (subgroup 2, 3). **A.** Clinical classification; **B.** Our own classification.

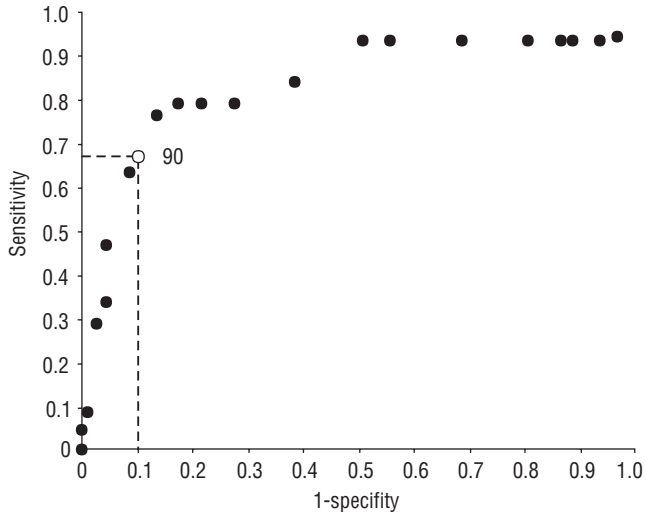

Figure 3. ROC curve for differentiation of patients with liver cirrhosis from other individuals, on basis of Cl_{Hp} values.

cirrhosis, diagnosed clinically and histopathologically from all the other individuals.

The analysis of that curve pointed to the value 90 ml min^{-1} 1,72 m^{-2} of Cl_{Hp} as a highly specific threshold for differentiation of patients with liver cirrhosis (specificity 89%, sensitivity 68%). Values of Cl_{Hp} below 90 ml min^{-1} 1.72 m^{-2} strongly suggest severe damage of the liver, typical for cirrhosis.

Discussion

In every day clinical practice, when using a quantitative diagnostic test, there is an obvious necessity to have a range of "normal" values. Appropriate interpretation of test results is a prerequisite for its utility.

The results of plasma clearance of ^{99m}Tc-HEPIDA have been interpreted so far on the basis of normal values and ranges characterizing different degrees of liver parenchyma damage, as obtained from a study by Studniarek [2]. However, for obvious reasons these reference values do not apply to the results of specific hepatic clearance of the compound [9–12]. The basic aim of the present study was to develop such values for $Cl_{Hp.}$

In studies devoted to the selection of diagnostic criteria there are various ways reported to arrive at a decision threshold for clinical assessment of a patient's condition. One of most useful methods is analysis of diagnostic efficacy on the basis of ROC curves. The essence of this method is visualization of the relation between sensitivity and specificity of a test and values of a decision threshold. This enables a selection for a given population of such a border value of the test which yields optimal constellation of sensitivity and specificity.

It is the obvious desire of a researcher to elaborate a test that could be characterized by both high values of these attributes. On the other hand, one has to remember how a negative result of a test with high sensitivity, even at lower specificity, excludes a disease with high probability. A positive result of a highly specific test, even of limited sensitivity, strongly suggests the presence of the disease in question.

In the present study two decision thresholds were proposed for Cl_{Hp} of ^{99m}Tc-HEPIDA, that while using both classifications of liver damage, permit a clinician to practically exclude or confirm a substantial impairment of liver function. The results of the test falling between the two thresholds do not provide an unequivocal answer.

However, they suggest that damage may be present and imply further monitoring of the patient by this and other relevant methods.

There was also a threshold suggested, below which severe damage to the liver, at intensity represented a.o. by cirrhosis, seems very likely.

Finally, one has to keep in mind that all the above considerations apply to patients without diagnosable cholestasis.

Conclusion

1. Values of hepatic clearance, essential from the clinical stand point, of liver damage assessment may be specified as follows:
— ≥ 150 ml min^{-1} 1.72 m^{-2} — exclude substantial liver damage with high probability;
— ≤ 120 ml min^{-1} 1.72 m^{-2} — indicate substantial damage to liver parenchyma.
2. Values of hepatic clearance ≤ 90 ml min^{-1} 1.72 m^{-2} are highly specific for severe damage to the organ of intensity corresponding to that of cirrhosis.

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