VIA MEDICA

Nuclear Medicine Review 2001
Vol. 4, No. 1, pp. 35–38

ISSN 1506–9680

Original

^{99m}Tc-HEPIDA plasma clearance as a diagnostic tool. Total plasma v. specific hepatic clearance

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Abstract

BACKGROUND: ^{99m}Tc-HEPIDA total plasma clearance has been used for assessment of hepatic parenchyma damage. However, the radiopharmaceutical used is being partly cleared from plasma also by the urinary tract. As the share of the latter route in total elimination of the compound is not well known, the aim of the study was to investigate the percentage of ^{99m}Tc-HEPIDA eliminated by the kidneys and by the liver.

MATERIAL AND METHODS: To this aim total plasma clearance of the compound and urinary part were determined by the methods employed here in 117 patients and in 16 healthy volunteers. The pure hepatic clearance was calculated as the difference between total plasma and the urinary clearance of ^{99m}Tc-HEPIDA.

RESULTS: The urinary clearance in patients amounted from 2.6 to 78% of total clearance; in the healthy volunteers the corresponding range was from 8.6 to 28%. Pronounced spread of the urinary clearance (coefficient of variation = 35%) and lack of correlation between the urinary and total clearance make it necessary to take account of urinary elimination in each patient in whom reasonably accurate assessment of hepatic clearance is required.

CONCLUSION: Further studies on the diagnostic efficacy of pure hepatic clearance and its change with age in healthy patients appear necessary.

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

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This project was financed by the Medical University of Łódź, grant Nº 502–11-691.

Introduction

Determination of ^{99m}Tc-HEPIDA (dimethylacetanilidiminodiacetic acid with ^{99m}Tc complex) total plasma clearance is a diagnostically useful procedure in assessing the presence or even degree of liver parenchyma damage [1–3]. From results of earlier studies it follows that the clearance is evidently reduced in most cases of acute and chronic liver ailments. Sporadically, however, we were able to see that the value of the clearance did not conform to the clinical assessment of patients' condition. These observations, at first, seemed to suggest that technical failure affecting determination of the total clearance could be responsible. However, critical appraisal of the analytical methodology did not reveal any obvious justification for the discrepant results. This prompted a search for more fundamental reasons for the inconsistencies.

From own observation, made during cholescintigraphic investigations in patients and from relevant literature [4–6], it became clearly apparent that a fraction of administered ^{99m}Tc-IDA complexes is eliminated via the urinary tract. Up to the present time it has been tacitly assumed that extra hepatic clearance of ^{99m}Tc-HEPIDA is approximately constant [1]. On closer examination of the available data this assumption could be questioned. Pronounced variability of the fraction of ^{99m}Tc-HEPIDA, eliminated via urinary path, could introduce considerable uncertainty in the estimation of hepatobiliary elimination of the compound, when the latter is being identified with the total plasma clearance. This could happen because total plasma clearance of ^{99m}Tc-HEPIDA must be the sum of hepatic and urinary clearances. (There is no evidence of accumulation of the complex in any other system of the body.)

Taking the above considerations into account we undertook a study on the magnitude and variability of the ^{99m}Tc-HEPIDA fraction cleared from plasma by the urinary route.

The aim of the study was therefore:

— estimation in consecutive patients of the fraction of ^{99m}Tc-HEPIDA eliminated via the urinary tract, expressed as absolute clearance [ml(min × m^2)$^{-1}$] as well as percentage of the total plasma clearance of the complex [%];

— determination of the "pure" hepatic ^{99m}Tc-HEPIDA clearance and its relation to the respective clearance;

— measurements of normal values of the clearances in a group of young healthy volunteers.

Material and methods

The study was conducted in the course of a normal clinical routine on 115 consecutive patients with chronic hepatic ailments (cirrhosis, chronic viral hepatitis of B and C type, autoimmune hepatitis, alcoholic liver damage), treated at the Hospital Department of Infectious Diseases of the Medical University of Łódź. The age of the patients varied from 18 to 72 years (av. ~ 45 y). There were 46 females and 69 males in the group. In 6 patients of the group, clearance determinations were performed twice.

The group of young volunteers included initially 21 subjects. After laboratory studies 5 were excluded due to presence of hepatic virus antigens in plasma (4 subjects) or elevated concentration of bilirubin in the serum (1 subject). ^{99m}Tc-HEPIDA clearances were thus determined in 16 healthy volunteers (7 males, 9 females). Their ages varied from 19 to 25 years (av. ~ 22 y). The study on the volunteers was conditioned on their informed consent and was approved by the Ethics Committee of this University.

In both groups altogether 137 determinations were made of each of the total plasma, urinary and hepatic clearances of ^{99m}Tc-HEPIDA.

For this purpose ^{99m}Tc-HEPIDA was prepared from a kit supplied by OBRI POLATOM of Świerk, Poland.

In patients and volunteers clinical examinations and laboratory studies were performed. The latter included:

On the basis of these analyses, anamnesis and clinical examinations the volunteers were characterised as healthy and patients' illnesses were diagnosed and their severity assessed (to be reported separately).

At about 45 min prior to ^{99m}Tc-HEPIDA intravenous injection, both patients and volunteers were given pure water to drink in amounts of ~ 8 ml per kg body mass. Directly before injection of the ^{99m}Tc-complex each subject voided urine.

^{99m}Tc-HEPIDA was administered intravenously, as a single bolus, at activity of about 37 MBq and a weighted sample of the dose was retained as a representative standard of the quantity injected. The blood was withdrawn at 5, 10, 15, 20, 30, 45, 60, 75 and 90 min post-injection, centrifuged and 1 ml plasma of each sample taken for activity measurements. About 5 min after last blood sampling (i.e. c. 95 min post-injection of the radiopharmaceutical), the patients and volunteers voided urine (as completely as possible). The urine was diluted in a calibrated flask to 1000 ml and 1 ml samples were taken for activity measurements. All activity determinations were corrected for radioactive decay of ^{99m}Tc.

For description of the time course of plasma concentration C(t) of ^{99m}Tc-HEPIDA as a function of time the equation:

$$C(t) = A_1 e^{-b_1 t} + A_2 e^{-b_2 t}$$

was used. Parameters A_i and b_i (i = 1.2) were determined using an iterative least square procedure and the computer program described earlier [8, 9].

Total plasma clearance, Cl_{Pl}, was calculated from the formula:

$$Cl_{Pl} = \frac{A_P}{\int_0^\infty c(t)dt}$$

where Ap — injected activity of the radiopharmaceutical.

The urinary clearance of plasma from ^{99m}Tc-HEPIDA , Cl_{Ur}, was calculated from the formula:

$$Cl_{Ur} = \frac{A_{Ur}(T)}{\int_0^T c(t)dt}$$

where $A_{Ur}(T)$ denotes activity excreted with urine at time T(≈95 min post injection).

The "pure" hepatic clearance Cl_{Hp}. was calculated as a difference:

$$Cl_{Hp} = Cl_{Pl} - Cl_{Ur}$$

The clearance values were normalised to body surface, calculated from the Du Bois formula.

Results

Determined values of the total plasma clearance in the patients varied from 65 to 310 ml/(min × 1.73 m^2). In the healthy volunteers the corresponding range spanned values from 187 to 255 ml × (min × 1.73 m^2)$^{-1}$. In the latter group values for males and females did not differ significantly (p = 0.115).

The urinary clearance of ^{99m}Tc-HEPIDA varied in the patients from 4.5 to 120 (mean 50 + 18) ml × (min × 1.73 m^2)$^{-1}$. In the healthy volunteers the same quantity varied from 20 to 63 (mean 45 + 12) ml × (min × 1.73 m^2)$^{-1}$. The histogram of the values in all individuals studied is shown in Figure 1. In both groups Cl_{Ur} shows considerable variability; the coefficient of variation amounted to 35 and 27 per cent in the patients and volunteers, respectively.

In Figure 2 there is presented the urinary clearance as a function of the total plasma clearance of ^{99m}Tc-HEPIDA. There does not seem to be any correlation between the two variables.

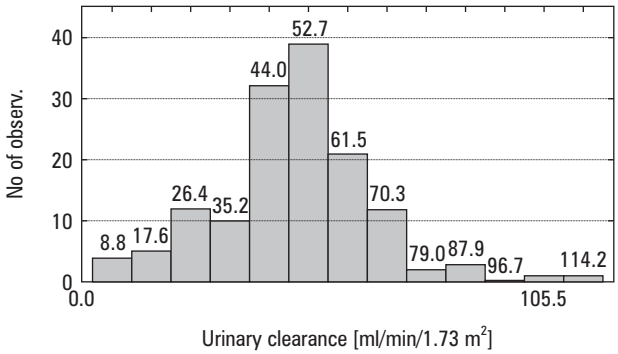

Figure 1. Histogram of distribution of experimental urinary clearance obtained in 135 patients.

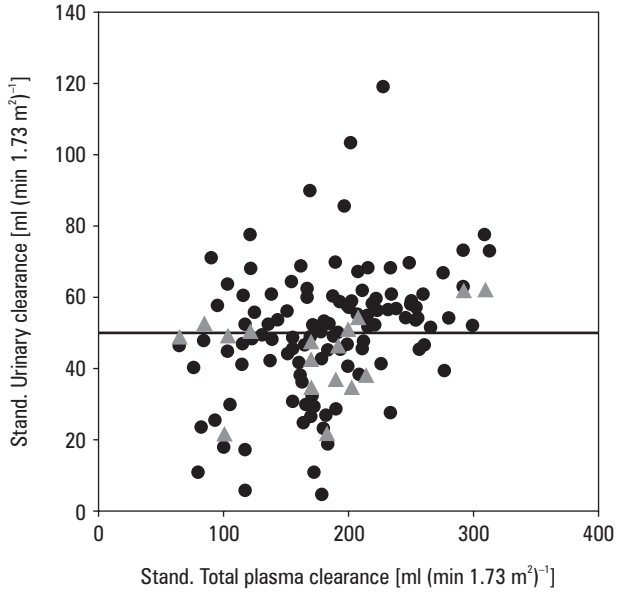

Figure 2. Relationship between urinary (ordinate) and total plasma clearance (abscissa) of ^{99m}Tc-HEPIDA; ● — patients, ▲ — volunteers.

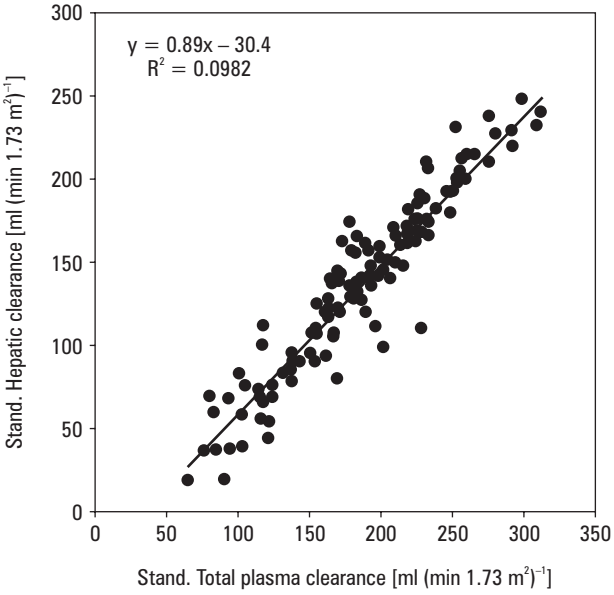

Figure 4. Correlation between hepatic and total plasma clearance of ^{99m}Tc-HEPIDA.

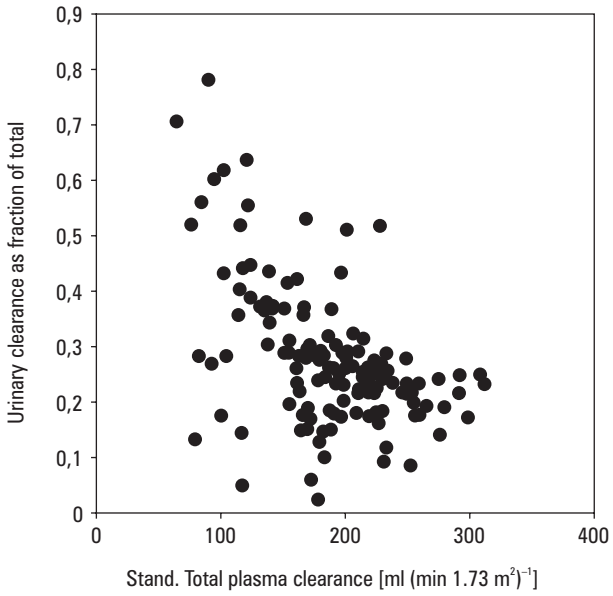

Figure 3. Relationship between standardised total plasma clearance of ^{99m}Tc-HEPIDA and urinary clearance as a fraction of the former.

The share of the total plasma clearance taken by urinary elimination rate of ^{99m}Tc-HEPIDA varied considerably. It spanned the range from 2.6 to 78% in the patients and from 8.6 to 28% in the healthy participants of the study. A relationship between the latter quantity (fraction of Cl_{Pl} taken by Cl_{Ur}) and absolute magnitude of the standardised total plasma clearance is displayed in Figure 3. There seems to be a crude correlation, probably hyperbolic; however, due to large variability the relationship is of very limited utility from the standpoint of potential statistical correction in individual patients of the total plasma clearance for contribution of the urinary elimination.

The pure hepatic clearance Cl_{Hp}, of ^{99m}Tc-HEPIDA varied in patients from 19 to 250 ml × (min × 1.73 m²)$^{-1}$. In the healthy volunteers the range was much narrower: 140 to 230 (mean 175 + 26) ml × (min × 1.73 m²)$^{-1}$.

There is a significant positive correlation ($R^2 = 0.898$) between total plasma clearance and the hepatic clearance (Fig. 4, $p < 0.001$).

Regardless of the small number of healthy volunteers studied, a significant difference ($p = 0.037$) between mean values for males and females (2.14 ± 22.0) v. (165 ± 22) ml × (min × 1.73 m²)$^{-1}$, respectively could be demonstrated. This conclusion has to be taken as tentative for the time being and should be verified in a more extensive study. There appears also an obvious justification for investigating the potential effect of age in subjects of either sex.

Discussion

Values of the total plasma clearance of ^{99m}Tc-HEPIDA in healthy volunteers are in reasonable accord with the data published by Studniarek [1]. A somewhat narrower range in the present study, reflected mostly in the upper boundary of the values, can be explained by the smaller number of individuals included in our investigation and, perhaps, by a narrow age distribution of our volunteers as compared with the age-span reported by Studniarek (71 males: 17–70 y). The values in patients with diagnosed impairment of liver function are also in agreement with the reported data [1–3].

The present study confirmed substantial participation of kidneys in extraction and elimination of ^{99m}Tc-HEPIDA from blood (plasma) as inferred from hepatobiliary scintigraphic diagnostics with the use of ^{99m}Tc-IDA derivatives [4, 5]. However, the present study demonstrated large variability of the urinary contribution to the total plasma clearance of ^{99m}Tc-HEPIDA. The coefficient of variation of the urinary elimination rate in patients (± 35%) suggests a necessity to make quantitative correction in each individual studied for this elimination

route in assessing hepatic component (Cl_{Hp}) from the total plasma clearance measurements. As demonstrated in our study, this can be easily done by collecting urine in the interval 0-T ($T \approx 90$ min). This makes it possible to determine the urinary clearance, which can be subtracted from the total clearance, yielding values of the Cl_{Hp}. A statistical correction by subtracting a mean Cl_{Ur} value cannot be advocated in view of large individual variability, which must deteriorate the precision of Cl_{Hp} indirect assessment. The scatter of the data around the correlation line between per cent urinary excretion and the total plasma clearance (Fig. 4) supports this contention.

The results presented in this paper support the initial hypothesis that in individual patients the assessment of hepatic elimination function from total plasma clearance of ^{99m}Tc-HEPIDA may be obscured by variable component of the urinary clearance.

Conclusions

1. Adequate assessment of liver capacity for extraction from plasma of ^{99m}Tc-HEPIDA and elimination via biliary route requires determination of both the total plasma and urinary clearance of the radiopharmaceutical.
2. Further studies are required for better characterisation of the normal range of hepatic plasma clearance of ^{99m}Tc-HEPIDA in healthy volunteers of both sexes and wider age range.
3. Magnitude of "pure" hepatic clearance of ^{99m}Tc-HEPIDA in parenchymal liver disorders of various nature and its diagnostic efficacy require further studies.

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