originales

Rev. Esp. Med. Nuclear 22, 4 (244-249), 2003

A new method for quantification of hepatobiliary scintigraphy using ^{99m}Tc–mebrofenin. A comparative study

J.M.P. LIMA[a], J.J.P. LIMA[b], J. ISIDORO[a], P. LAPA[a]

[a]*Serviço de Medicina Nuclear, Hospitais da Universidade de Coimbra, 3000 Coimbra, Portugal.* [b]*Serviço de Biofísica e Biomatemática, IBILI, Faculdade de Medicina de Coimbra, 3000 Coimbra, Portugal.*

Summary.—A method based upon the application of mathematical techniques of deconvolution on the classical compartmental model for the quantitative study of liver function from hepatobiliary scintigraphy using ^{99m}Tc–*mebrofenin* data is proposed. The theory in which the method is based upon is presented and a comparison with a published methodology of obtaining the hepatic extraction after scintigraphic sudies has been performed using the results on 36 rats studies obtained with the two methods. A highly significant correlation between the two techniques was verified. The characterisitics of the two methodologies, the proposed one based upon a theoretical approach and the other one on an empirical approximation are discussed. Comments are made on the interest and limitations of the presented technique that may be an useful tool for the evaluation of hepatic insufficiency.

KEY WORDS: Hepatobiliary scintigraphy. Deconvolution analysis. Hepatic function.

UN NUEVO MÉTODO PARA LA CUANTIFICACIÓN DE GRAMMAGRAFÍA HEPATOBILIAR UTILIZANDO 99MTC–MEBROFENINA. UN ESTUDIO DE COMPARACIÓN

Resumen.—Se propone un método basado en la aplicación de técnicas matemáticas de deconvolución sobre el modelo compartimental clásico para el estudio cuantitativo de la función hepática con datos de gammagrafía hepatobiliar con 99mTc–mebrofenina. Se presenta la teoría sobre la cual se basa el método y se hace una comparación con una metodología publicada para la obtención de la extracción hepática después de hacer estudios grammagráficos utilizando los resultados de 36 estudios en ratas, obtenidos con los dos métodos. Se comprobó una correlación altamente significativa entre las dos técnicas. Se discuten las características de las dos metodologías, la propuesta basada en un enfoque teórico y la otra en un enfoque empírico. Se comenta el interés y limitaciones de la técnica presentada que puede ser una herramienta útil para la evaluación de la insuficiencia hepática.

PALABRAS CLAVES: Gammagrafía hepatobiliar. Análisis de deconvolución. Función hepática.

Recibido: 15-05-02.
Aceptado: 20-06-02.

Correspondencia:

J.M. PEDROSO DE LIMA
Serviço de Medicina Nuclear
Hospitais da Universidade de Coimbra
3000 Coimbra, Portugal
E-mail: smnhuc@mail.telepac.pt
jlima@huc.min-saude.pt

INTRODUCTION

Studies of liver function based on scintigraphic data using compartmental modelling have been tried by several groups[1-5]. Results from these *classical models* are usually presented as *rate constants* for the hepatic extraction from the plasma and, in the case of hepatobiliary scintigraphy, also for the hepatic excretion. Other measured parameters are the disappearance half-life ($T_{1/2}$) and mean of the residence time for the radio-pharmaceutical molecules. The method proposed is based upon the application of mathematical techniques of deconvolution over the classical compartmental model. The quantification of parameters with physiologic meaning, in hepatobiliary scintigraphy may be obtained by using ^{99m}Tc–*mebrofenin*. After a venous puncture this agent (or any of the last generation ^{99m}Tc–IDA derivatives) is transported in blood mainly loosely bound to albumin. In the space of Disse, ^{99m}Tc–*mebrofenin* is taken up by the hepatocyte and excreted into the intestine through the bile, without modifications[6]. This radio-pharmaceutical has high specificity for hepatocyte uptake (98 %), rapid blood clearance, fast intra-hepatic transit and no enteric absorption. Sixty minutes after intra-venous administration of ^{99m}Tc–*mebrofenin* in normal volunteers, the percentage in the extra-vascular space is only 0.6 % and inferior to 1 % in urine[7]. Based on compartmental modelling and considering the characteristics of ^{99m}Tc–*mebrofenin* a theoretical method for

quantification of hepatobiliary scintigraphies based upon deconvolution was developed. A comparison with a published methodology of obtaining the hepatic extraction from scintigraphic data[8] has been performed on the results on 36 rats studies obtained with the two methods.

THEORY OF THE METHOD

Consider an open three compartments model of the hepatobiliary system, in a steady state and with no reflux (fig. 1). An activity A_0 of a radiopharmaceutical is administered in the blood compartment at t = 0 with immediate mixture and homogeneous concentration. All the reactions between compartments are first order.

k_1 and k_2 are rate constants, $a_p(t)$, $a_h(t)$ and $a_b(t)$ are respectively the instant activity values in the compartments of total blood, total hepatic parenchyma and total excretion, as shown in fig. 1. The differential equations that represent the instant variation of activity with time in the three compartments are:

$$\frac{da_p}{dt} = -k_1 a_p$$

for the blood compartment

$$\frac{da_h}{dt} = k_1 a_p - k_2 a_h$$

for the liver parenchyma compartment and

$$\frac{da_b}{dt} = k_2 a_h$$

for the total excretion compartment.

The integration of these equations lead to

$$a_p(t) = A_0 e^{-k_1 t} \qquad (1)$$

for the blood activity compartment.

For the activity in the liver parenchyma compartment it comes

$$a_h(t) = \frac{k_1 A_0}{k_2 - k_1} e^{-k_1 t} - \frac{k_1 A_0}{k_2 - k_1} e^{-k_2 t}$$
$$= A_p e^{-k_1 t} + A_h e^{-k_2 t} \qquad (2)$$

with

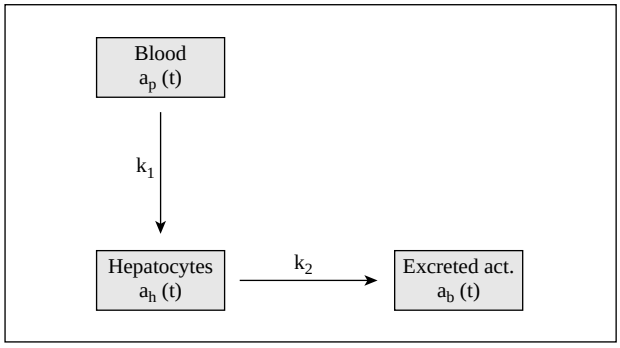

FIG. 1.—*Model of three compartments for quantification of hepatobiliary scintigraphy.*

$$A_p = \frac{k_1 A_0}{k_2 - k_1} = -A_h \qquad (3)$$

The activity in the total excretion compartment is:

$$A_b(t) = A_o + A_b e^{-k_1 t} + A_p e^{-k_2 t} \qquad (4)$$

Where

$$A_b = -\frac{k_2 A_0}{k_2 - k_1}$$

We are mainly interested in Eqs. 1 and 2. To execute the study in rats, activity-time curves for blood and liver, after ^{99m}Tc–*mebrofenin* injection, are necessary. On a region of interest (ROI) drawn over the gamma camera image of the heart, a fraction α of the total blood activity is detected and a function obtained, formally identical to Eq. 1 but with a value at zero time given by

$$A'_0 = \alpha A_0$$

The activity externally detected in the hepatic ROI is a summation of the activity existing in the liver parenchyma, in the hepatic blood and also in the bile in transit to the intestine. Activity in the interstitial space was not considered in our model. This is realistic since the percentage of tracer in the extra-vascular space, for the last generation of hepatobiliary radio-pharmaceuticals is minimal (0.6 %, 60 minutes after injection). In our model the activity in the bile in transit, detected on the hepatic ROI, is assumed to be negligible which is true in the first times. Then, if fractions β and γ respectively of the total hepatic activity and of the total blood activity

are detected on the liver ROI and considering Eqs. 1 and 2, the activity detected on this ROI is

$$a'_h(t) = \beta A_p e^{-k_1 t} + \beta A_h e^{-k_2 t} + \gamma A_0 e^{-k_1 t} \quad (5)$$

that is,

$$a'_h(t) = A'_p e^{-k_1 t} + A'_h e^{-k_2 t} \quad (6)$$

where

$$A'_p = \beta \frac{k_1 A_0}{k_2 - k_1} + \gamma A_0 \quad (7)$$

and

$$A'_h = -\beta \frac{k_1 A_0}{k_2 - k_1} \quad (8)$$

Assuming systems theory applicable, the function a_p (t) can be considered as an input function in a system and the function a_h (t) the response of the system to that input function. The response function can be considered as the result of the convolution of a_p (t) with a retention function, h (t), that is, the function that represents the theoretical hepatic time activity curve after an instantaneous injection of the radio-pharmaceutical at the hepatic artery (or portal vein), with no re-circulation. Thus,

$$a'_h(t) = a_p(t) \otimes h(t) \quad (9)$$

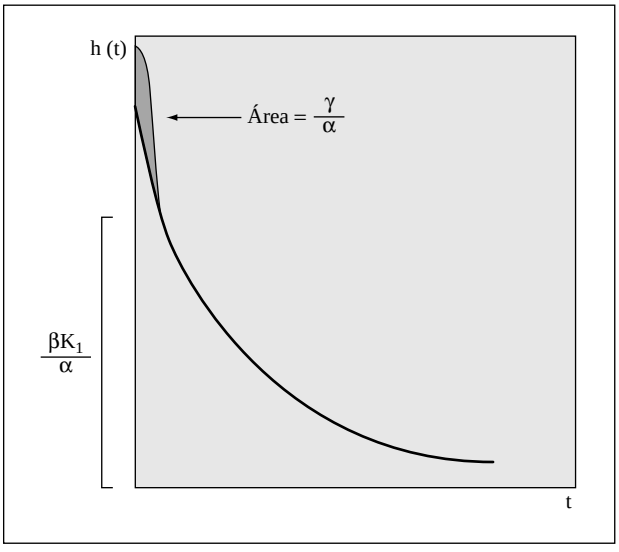

FIG. 2.—*Graphic representation of function h (t).*

where ⊗ means convolution. The retention function h (t) is characteristic of the system and independent of a_p (t). To know h(t), deconvolution of Eq. 9 has to be performed. Applying Laplace transforms to Eq. 9 it comes:

$$A_h(s) = A_p(s)\, H(s) \quad (10)$$

Where $A_h(s)$, $A_p(s)$ e H(s) are the Laplace transforms of $a'_h(t)$, $a'_p(t)$ and h (t), respectively.

Thus,

$$H(s) = Ah(s) / Ap(s) \quad (11)$$

Calculation of Laplace transforms of A_p (s) and A_h (s) and their substitution in Eq.31 leads to:

$$H(s) = \frac{A'_p}{A_0} + \frac{A'_h}{A_0}\, k_1 \frac{1}{s + k_2} + \frac{A'_h}{A'_0} \frac{s}{s + k_2} \quad (12)$$

Then h(t) is obtained by the inverse transform of H (s), that is:

$$h(t) = H^{-1}(s) \quad (13)$$

which leads to

$$h(t) = \left[\frac{A'_p}{} + \frac{A'_h}{}\right]\delta(t) + \left[-\frac{A'_h}{}(k_2 - k_1)\right]e^{-k_2 t} \quad (14)$$

and after the substitution of, e by their own expressions and making:

$$A = \frac{\gamma}{\alpha} \quad (10)$$

And

$$B = \frac{\beta\, k_1}{\alpha}$$

It comes

$$h(t) = A\delta(t) + Be^{-k_2 t} \quad (16)$$

Eq. 16 is the summation of an exponential function with a delta function of area A, situated at the origin. The graphic representation for this function is shown in fig. 2. The ratio "r" between

the area of the delta function and the value of the function Be^{-k_2t} at t = 0 is

$$(17)\ \frac{r = \gamma}{\beta\ k_1}$$

The value of γ, which is the fraction of the total blood activity simultaneously detected with the activity at the hepatocytes at the hepatic ROI, is

$$\gamma = r\beta\ k_1 \qquad (18)$$

β is the efficiency of the detection of radioactivity at the liver parenchyma, assumed as being unity (α and γ are relative values). Then:

$$\gamma = r\ k_1 \qquad (19)$$

In practice, the value of γ results almost exclusively from the hepatic blood activity because the contribution of blood activity in the organic structures located outside the liver in the FOV of the detector is minimal. Then, γ (and also " r ") are as big as the hepatocyte difficulty to take the radiopharmaceutical. This method may be an useful tool for the quantification of hepatic insufficiency. The presented method has some similarities with a nonparametric method for quantification of hepatobiliary scintigraphies proposed by Juni[8-10]. He also used a mathematical technique of deconvolution and got a similar retention function. But this method is not based on a compartmental modelling. Another difference is the interpretation of the meaning of the deconvoluted retention function. For Juni, this curve may be divided in two different parts: a vascular peak and an hepatic retention phase. The height of the vascular peak is proportional to the total activity injected (but the constant of proportionality is not known). The retention fase represents the initial extraction of the tracer. The area under the retention fase of the curve is proportional to the medium transit time. As considered for other organs (kidney and thyroid) it is assumed that the ratio between the initial height of the retention phase and the high of the vascular peak represents the (hepatic) extraction fraction at the first pass –HEF[11-13].

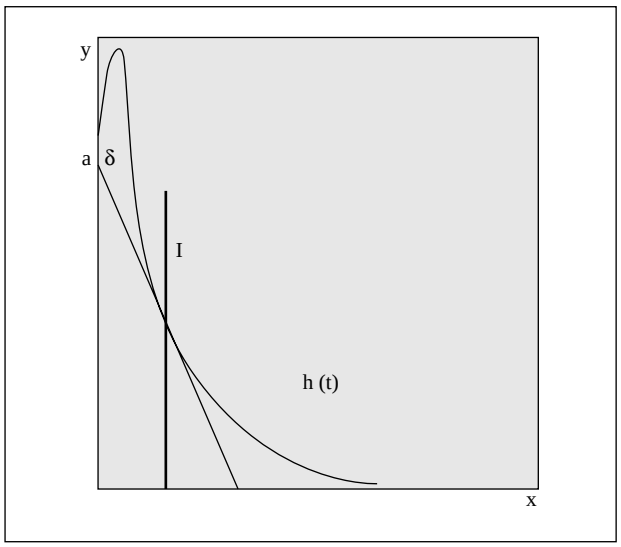

FIG. 3.—*Area of the vascular spike ("d function"). (I - vertical line drawn in the intersection of the deconvoluted liver curve with its exponential fitting; h(t) - deconvoluted liver curve; a – exponential fitting to the deconvoluted liver curve).*

MATERIAL AND METHODS

The two methods of quantification were applied to 36 hepato-biliary scintigraphies with ^{99m}Tc–*mebrofenin* done in *Sprague-Dawley* male rats, before and after bile duct ligation. The values from hepatic extraction fraction (HEF) of Juni's method and from "r", the ratio from the area of the initial spike (δ function) and the value obtained for Be^{-k_2t} when t = 0, were compared using a polynomial regression analysis software (*Statistica-4.5*). HEF were obtained according to published methodology14. To obtain "r" two areas were calculated (using *Excel-5.0* and *Origin-3.5 software*). One was defined by 1) the deconvoluted liver curve, 2) a vertical line drawn in the intersection of this curve with its exponential fitting, and 3) the *xx* e *yy* axes. The second area was defined by 1) the same vertical line, 2) the liver curve exponential fitting and 3) the *xx* e *yy* axes (fig. 3). The difference of the two areas gives the value of the initial spike area. The value of the function for t = 0 is the intersection of the exponential fitting with the yy axe.

RESULTS

Table 1 shows the values for HEF and "r" for ^{99m}Tc–*mebrofenin* obtained in the scintigraphic

Table 1
VALUES OF HEF AND " R " IN 36 RATS

Rat	*HEF (%)*	*"r"*
J1B4	17,56	5,081
J2B	83,29	0,162
J2B48	20,23	5,179
J3B2	79,85	0,521
J4B2	66,6	0,535
J6B2	97,73	–0,225
J7B2	96,23	–0,292
J7B48	99,02	–0,037
J8B2	94,21	0,058
J8B48	22,52	5,220
J9B2	40,42	2,137
J9B48	12,56	9,613
J10B0	115,24	–0,478
J10B2	52,24	1,123
J10B48	13,36	7,041
J11B2	71,5	0,392
J12B2	80,89	0,235
J13B2	76,33	0,250
J14B2	45,52	1,843
J15B2	84,22	0,103
J16B0	106,39	–0,562
J17B48	12,92	7,463
J18B48	19,23	6,043
J19C48	115,76	–0,600
J20C48	107,16	–0,407
J21B24	27,85	2,104
J22B24	29,78	4,029
J23B24	37,59	2,062
J24B72	13,69	8,098
J25B72	34,66	2,869
J26B72	11,64	10,114
J27B96	14,59	6,434
J28B96	19,64	6,710
J29B96	13,08	8,414
J30B96	13,41	7,803
J31B96	13,5	10,473

HEF: Hepatic Extraction Fraction; r: the ratio from the area of the d function and the value obtained for $Be^{-k_2 t}$ when t = 0.

hepatobiliary studies. The normalization of HEF to a maximum of 100 % was not considered in this study allowing the amplification of small alterations around the value considered for normal hepatic function. The same reason to use the original value of "r" when negative (no equalization to zero).

A highly significant correlation between the two techniques was obtained (R = 0,981; p = 0,0001).

DISCUSSION

Based upon the theory of systems we consider the function representing the activity at the blood compartment (partially detected in the cardiac region of interest) as the input function for the hepatic compartment. The function representing the activity in the hepatic compartment (detected in the hepatic region of interest) is the response function for that input function. As proved, after deconvolution, a function *h (t)* can be obtained representing the deconvoluted retention function, that is the response function which would be obtained if all the activity was instantaneously injected (Dirac delta function) in the hepatic artery (or portal vein). One of the advantages of this method over the classical modelling is to obviate the effect of tracer re-circulation. Another advantage is the possibility to evaluate, in relative terms, the non-effective hepatic blood flow (γ fraction) which is the fraction of blood with the radio-pharmaceutical not taken by the hepatocytes. The function *h (t)* has the shape of a vascular peak over a decreasing exponential function (the area of this vascular peak is inversely related to the effective capacity of the hepatocytes to uptake the radio-pharmaceutical). To express the impulse response function in an explicit way the real structure of the system has to be known[13]. On a non-compartmental approach the organ under investigation is described as a *black box* of unknown internal structure. The relationships established by Juni are empirical approximations not based on theoretical approaches. On the contrary, compartmental modelling is based on information obtained from experimental work based on a theoretical formulation. The two methods being compared represent two different approaches for the evaluation of dynamic systems. One is based on differential equations obtained from a mathematical model. In this model the topology of the system is postulated *a priori*. To the second approach (Juni method) the previous knowledge of the system is not necessary *(black box)*; its mathematical description is based on an integral equation and the impulse response function comes directly from the use of the time / activity curves. Besides this different approach on the interpretation of the hepatic retention curve, there is a good correlation between the results obtained with the two methods. The application of our method to the quantification of hepatobiliary scintigraphies may inform about the hepatic blood flow status and the functional capacity of the hepatocytes. This may be of clinical value in several situations such as hepatic insufficiency, intra and extrahepatic cholestasis and liver transplant function

evaluation[18]. Nevertheless, several factors may constraint its use in the clinical practice, where the real situation is usually very different of the ideal conditions considered for the theoretical models. Some of these factors are mentioned and discussed as follows: 1) We assume no back diffusion of the radio-pharmaceutical between compartments, namely between the hepatic compartment and the blood. This is probably true in normal situations[15] but not the case in certain hepatic diseases[16]. 2) The radio-pharmaceutical molecules not taken by the hepatocytes (functional shunt) do not have an instantaneous transit through the liver. So, that function *over* the exponential decreasing function is not a true Dirac function. 3) Another factor may be the existence of a distribution of rate constants leading to alteration of the curves and deterioration of its exponential behaviour[3,17] 4) The γ fraction consists not only of the non effective hepatic blood flow but also of blood existing in other tissues detected by the gamma camera and considered in the hepatic region of interest. 5) Detection efficiency changes with the distance to the detector system. Deep regions of the liver are detected less efficiently than more superficial aspects of the organ, located closer to the gamma camera detector. Then, ß is less than unity. 6) Sometimes, the drawing of regions of interest over the hepatic and cardiac areas may be difficult causing cross-talking phenomena.

REFERENCES

1. Galli G, Maini CL, Salvatori M, et al. The quantitative approach to the 99mTc-IDA radiohepatogram: clinical testing of three methods. Rays 1985;10;3:105-18.
2. Marshall EA, Diprose GK, Cosgriff PS. Transport dynamics of the hepato-biliary system: a mathematical model allied to Tc99m-IDA scintigraphy. Phys Med Biol 1987;32;6:719-35.
3. Frazer IA, Shaffer P, Love J, et al. Pharmacokinetic studies of DISIDA disposition. I - Animal studies. Eur J Nucl Med 1988; 14:431-5.
4. Love JE, Shaffer P, Fraser IA, et al. Pharmacokinetic studies of DISIDA disposition. II - Clinical studies. Eur J Nucl Med 1988; 14:436-40.
5. Gambhir SS, Hawkins RA, Huang S-C, et al. Tracer kinetic modelling approaches for the quantification of hepatic function with Technetium-99m DISIDA and scintigraphy. J Nucl Med 1989;30:1507-18.
6. Hladik III WB, Norenberg JP. Radiopharmaceuticals for hepatobiliary imaging. In: Henkin RE, Boles MA, Dillehay GL et al., eds. Nuclear Medicine. St Louis: Mosby-Year Book; 1996; p. 986-996.
7. Subramanian G. ^{99m}Tc - labeled hepatobiliary agents: design, synthesis and evaluation of iodine substituted HIDA derivatives. Final report submitted to the IAEA. Buenos Aires. Argentina. 1986; Nov. 10-13.
8. Juni JE, Thrall JH, Froelich JW, et al. The appended curve technique for deconvolutional analysis - method and validation. Eur J Nucl Med 1988;14:403-7.
9. Tagge EP, Campbell Jr DA, Reichle R, et al. Quantitative scintigraphy with deconvolutional analysis for the dynamic measurement of hepatic function. J of Surgical Research 1987;42: 605-12.
10. Juni JE. Scintigraphic measurement of hepatic function. In: Murray IP, Ell PJ, eds. Nuclear medicine in clinical diagnosis and treatment: New York; Churchill Livingstone 1994; p. 439-444.
11. Sejrsen P. Single injection, external registration method for measurement of capillary extraction. In: Crone C, Lassen NA, eds. Capillary permeability. The transfer of molecules and ions between capillary blood and tissue. Copenhagen; Munksgaard. 1970; p. 256-60.
12. Kuikka JT, Bassingyhwaighte JB, Henrich MM, et al. Mathematical modelling in nuclear medicine. Eur J Nucl Med. 1991;18:351-62.
13. Szabo Z. Noncompartmental analysis. In: Wagner, Szabo e Buchanan, eds. Principles of nuclear medicine, 2nd ed. Philadelphia. 1995; p 462-474.
14. Brown PH, Juni JE, Lieberman DA, Krishnamurthy GT. Hepatocyte versus biliary disease: a distinction by deconvolutional analysis of Technetium-99m IDA time-activity curves. J Nucl Med 1988;29:623-30.
15. Galli G, Orlando P. Massari P, et al. 99mTc-Diethyl-IDA: The extraction efficiency of the liver. Eur J Nucl Med. 1983;8: 187-90.
16. Pellegrini CA. Pathophysiology of Biliary Obstruction, In: Way LW, Pellegrini CA, eds Surgery of the gallbladder and bile ducts. Philadelphia: W. B. Saunders Company 1987; p. 103-117.
17. De Lima JJ. New possibilities of computer studies in nuclear medicine. In Willems JL, van Bemmel JH, Michel J, eds. Progress in computer-assisted function analysis: Amsterdam: Elsevier. 1988; p. 409-414.
18. Krishnamurthy GT, Krishnamurthy S, eds. Nuclear Hepatology. Berlin Heidelberg: Springer. 2000.