Kinetics of ^{111}In-labeled bleomycin in patients with brain tumors: Compartmental vs. non-compartmental models

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The kinetics of an indium-111 labeled bleomycin complex (^{111}In-BLMC) after rapid intravenous injection in patients with brain tumors was quantified by using compartmental and non-compartmental models. The models were applied to data obtained from 10 glioma, one meningioma, and one adenocarcinoma brain metastasis patients. Blood and urine samples from all the patients and tumor samples from three patients were collected. The mean transit time of ^{111}In-BLMC in the plasma pool was 14 ± 7 min without and 1.8 ± 0.6 h when accounting for recirculation, and 13 ± 4 h in the total body pool. The mean plasma clearance of ^{111}In-BLMC was 0.3 ± 0.1 ml blood/min and the mean half-life in urine was 3.5 ± 0.6 h. The mean transfer coefficients for the open three-compartmental model were: excretion from plasma = 0.02 ± 0.01, from depot to plasma = $(12 \pm 9)*10^{-4}$, from plasma to depot = 0.01 ± 0.01, from tumor to plasma = 0.39 ± 0.19 and from plasma to tumor = 1.11 ± 0.57, all in units minute^{-1}. The mean turnover time from the tumor was 4.5 ± 2.7 min and from the depot 20 ± 8 h. It is concluded that both compartmental and non-compartmental models are sufficient to describe the kinetics of indium-111 labeled bleomycin complex. The non-compartmental model is more practical and to some extent more efficient in describing the in vivo behaviors of ^{111}In-BLMC than the compartmental model. The compartmental model used provides estimates of both extraction and excretion from the plasma and tumor.

Key words: ^{111}In-bleomycin, brain tumors, modeling, compartmental models, exponential fit

INTRODUCTION

WHEN ANALYZING the time course of radioactively labeled compounds, in vivo compartmental and non-compartmental modeling are commonly used.[1-9] The basic considerations of compartmental models and detailed solving of a general three-compartmental model have been presented by Rubinow and Wintzer.[10] In non-compartment analysis (black-box analysis) no compartments are im-

plied, but the exponential representation of the functions of the system is employed.[11,12] These models are useful, for example, for investigating blood flow in one capillary and global blood circulation in an organ.[12-16]

The absorbed dose calculation of internal radiotherapy requires knowledge of the mean residence times in tissues and organs of the isotope used.[17] Conventionally compartmental models have been used in the definition of organ-specific residence times.[18,19] Modeling has also been used in oncology when investigating the biodistributions of different cytostatics.[20] Especially in chemotherapy it is necessary to know the amount of the chemotherapeutic agent in different parts of the body.

Bleomycin is a glycopeptide antibiotic with a molecular weight of approximately 1400 D. It has cell cycle-

Table 1 Clinical data on patients with brain tumors

Patient no.	sex	age	high/low	histology*	recurrence
1	male	53	high	GB4	primary
2	male	43	—	MA	primary
3	female	48	high	O2	recurrent
4	male	62	high	GB4	primary
5	male	44	high	AA3	primary
6	female	52	high	O2	recurrent
7	male	53	high	GB4	recurrent
8	male	41	high	AO3	recurrent
9	male	38	low	O2	primary
10	male	32	low	OA2	primary
11	female	70	—	MET	primary
12	male	66	high	GB4	primary

* Histology: GB = glioblastoma multiforme; O = oligodendroglioma; AA = anaplastic astrocytoma; AO = anaplastic oligodendroglioma; OA = oligoastrocytoma; MA = atypical meningioma; MET = adenocarcinoma; 2, 3, 4 = WHO grades

specific cytotoxic effects as it breaks the DNA in the G2 and M phases.[21] It is widely used as a chemotherapeutic agent in combination chemotherapy in the treatment of various solid malignant tumors.[22] The binding of indium-111 labeled bleomycin complex (^{111}In-BLMC) has been studied in mice tumors and cell lines.[23] The initial distribution of ^{111}In-BLMC is reported to be similar to that of cobalt-labeled bleomycin with a fast clearance from the blood into other organs and tissues, an early uptake in the kidneys, and excretion of a large part during the first 24–48 h.[24,25] Recently radiolabeled bleomycin complexes have been used as tracers in the diagnosis and staging of human head and neck cancers.[26] Huhmar et al.[27] have preliminarily reported ^{111}In-BLMC to be a useful SPECT tracer for the grading of human gliomas.

The aim of this work was to quantify the kinetics of ^{111}In-BLMC after rapid intravenous injection in patients with brain tumors. Compartmental modeling and the inlet-outlet theorem were used to study and simulate the biodistribution and kinetics of an indium-111 labeled bleomycin complex. The purpose was to compare the utility of two different models for quantitation of the kinetics of a small labeled molecule. The usefulness of the physiologic information provided by these models was especially studied. Furthermore, we wanted to clarify whether the application of more than one model to the same clinical data provides additional information.

MATERIALS AND METHODS

Patients

The models were applied to data from 12 brain tumor patients: 8 male and 2 female glioma patients and one male meningioma and one female adenocarcinoma patient with brain metastasis (Table 1). All the tumors were histologically classified according to the WHO classification.[28] Eight patients had high grade gliomas of which
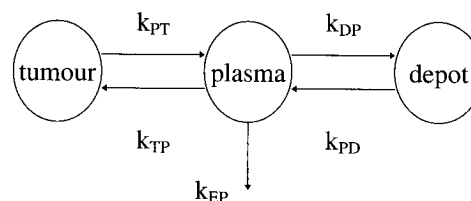

Fig. 1 The three-compartmental open model used to fit plasma and tumor ^{111}In-BLMC activity values. k = transfer coefficient; P = plasma; D = depot; T = tumor; E = excretion.

Table 2 Activities of ^{111}In-BLMC in plasma in patients at 1 h, 4 h and 24 h after the injection in per cents of the injected activity

Patient no.	1 h	4 h	24 h
1	19	6	0.8
2	10	4	0.5
3	45	15	1.4
4	14	5	0.5
5	38	15	1.6
6	20	6	0.4
7	40	15	1.3
8	30	12	0.7
9	25	10	1.0
10	20	7	0.5
11	25	14	1.1
12	36	12	0.8
mean ± S.D.	29 ± 11	11 ± 5	1.0 ± 0.5

four were primary and four were recurrent tumors. Two patients had novel low grade gliomas. All but one (No. 9) showed contrast enhancement on post-contrast T1-weighted MR images. The age of patients varied from 32 to 70 years; mean 50 years. Informed consent was obtained from every patient before injection of the tracer, and the research protocol was approved by the ethical committee of the hospital.

The bleomycin complex was supplied by H. Lundbeck a/s (Copenhagen, Denmark). Radiolabeling and formulation of ^{111}In-BLMC were performed by MAP Medical Technologies Ltd. (Tikkakoski, Finland) utilizing a modification of the procedure described by Hou et al.[23,29] The mean specific activity of ^{111}In-BLMC was 60 MBq/ mg. The radiochemical purity of the tracer was over 98%, as analyzed by thin layer chromatography (1 : 1 methanol and 10% NH_4Ac on SG plates). The total amount of injected substance varied from 2.0 to 3.3 mg, and that of the activity from 118 to 200 MBq. The injection time was less than one minute.

Sampling

Blood samples (5 ml) were collected at different time intervals. During the first hour after injection an average of five samples were drawn and during the next nine hours an average of four samples. Subsequently 6 to 7 samples

were drawn from each patient. Blood samples were collected from three patients (Nos. 1, 5 and 7) in 3–5 days. These patients were operated on 3–5 days after the injection, and tumor and plasma samples were collected during surgery to determine the tumor activity. The actual unit of the plasma ^{111}In-BLMC concentration was ppm. The activity of the plasma samples were measured in units Bq/ml, which was then divided by the original injected activity calculated for the plasma volume unit (that is Bq/ml). Consequently the final value has no dimension. Tumor samples were washed to withdraw the blood. From nine patients blood samples were collected one or two days after the injection. No tumor samples were available

from these patients. Urine samples were collected from all patients. The radioactivity in 1 ml whole blood and urine, and 1 g samples of the tumor were measured in a gamma counter (1282 Compugamma, LKB-Wallac, Finland) about 75 h after the injection.

Data analysis

The fitting of the exponential functions to the observed plasma activity data was performed by the method described by Guardabasso et al.[30] In this method the data obtained are iteratively fitted until the convergence criteria are met. The residual variance test and the runs test provide indices of the goodness of the fit.[30] The estimated error for each datum was $SD_{ij} = 1/\sqrt{data_{ij}}$. The following transit times were obtained from the exponential fittings (Appendix 1): mean transit time in plasma pool (t_1), mean sojourn time in plasma pool including recirculating activity (t_2) and mean transit time in total body ^{111}In-BLMC pool (t_3), which equals zero, the first and the second origomoments, respectively. The half-life of ^{111}In-BLMC in the urine was determined with the inverse of the regression coefficient of the semilogarithm of the urine time-activity curve. The clearance (CL) in units ml blood/min was obtained from the non-compartmental model defined by the equation,[11,31]

$$CL = \frac{m_0}{\sum_i \frac{A_i}{g_i}}, \qquad (1)$$

where m_0 is the amount of injected activity, and A_i and g_i are the constants and coefficients from the fitted exponential function, respectively.
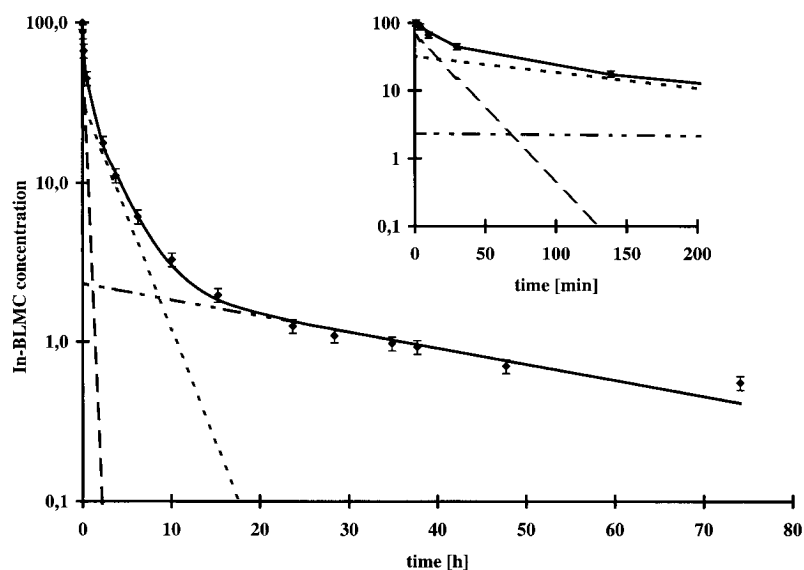
A three-compartmental model was applied, with the

Table 3 Mean transit times of ^{111}In-BLMC in patients. Mean transit time in plasma pool (t_1), mean sojourn time in plasma pool including recirculating molecules (t_2) and mean transit time in total body ^{111}In-BLMC pool (t_3)

Patient no.	t_1 [min]	t_2 [h]	t_3 [h]
1	29.7	2.2	21.3
2	7.2	1.7	12.9
3	15.2	2.1	13.2
4	4.2	0.9	10.2
5	11.8	2.3	17.7
6	21.9	1.5	6.4
7	15.4	2.0	10.4
8	7.5	1.2	10.7
9	7.3	1.1	15.0
10	15.8	1.8	14.8
11	15.3	3.2	10.6
12	17.0	1.5	7.3
mean ± S.D.	14 ± 7	1.8 ± 0.6	13 ± 4

Fig. 2 The plasma clearance of ^{111}In-BLMC represented as a sum of the 3-exponential curve (logarithmic scale) for one patient (No. 1). Error bars are ± 10% of the detected values. The corresponding mean half-lives were 14.3 min for the fast, 2.2 h for the intermediate and 30.1 h for the slow component. Small picture presents the first 200 minutes.
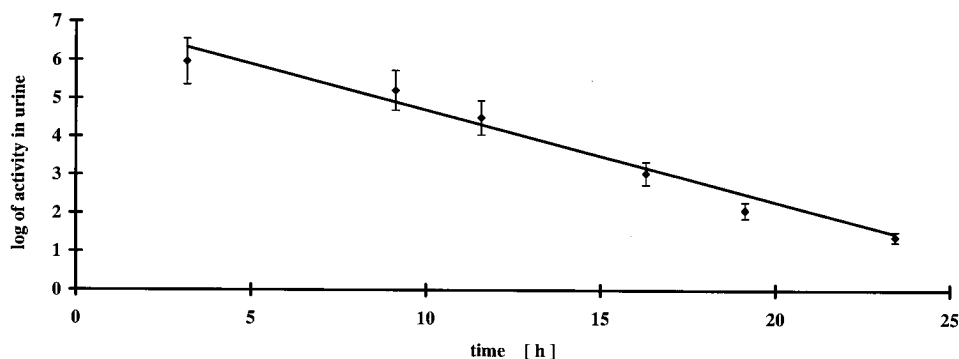
Fig. 3 Inverse of the regression coefficient equals to the half-life (2.8 h) of the urine time-activity curve for one patient (No. 2). Error bars are ± 10% of the detected values.

Table 4 Transfer coefficients for individual patients used to fit ^{111}In-BLMC values to the three-compartmental open model in units min^{-1}

Patient no.	k_{EP}	k_{PD}	k_{DP}	k_{PT}	k_{TP}
1	0.022	6.9E-04	0.016	0.346	1.446
2	0.041	8.3E-04	0.028	0.173	0.180
3	0.012	9.3E-04	0.006	0.297	0.797
4	0.035	11.0E-04	0.021	0.100	0.633
5	0.010	5.3E-04	0.008	0.580	1.351
6	0.029	15.0E-04	0.008	0.385	1.483
7	0.012	9.3E-04	0.005	0.150	0.271
8	0.019	28E-04	0.012	0.717	1.851
9	0.017	6.5E-04	0.016	0.353	0.962
10	0.026	5.8E-04	0.012	0.446	1.945
11	0.016	35E-04	0.013	0.441	1.334
12	0.015	7.2E-04	0.009	0.359	1.023
mean ± S.D.	0.02 ± 0.01	(12 ± 9) E-04	0.01 ± 0.01	0.39 ± 0.19	1.11 ± 0.57

k = transfer coefficient; P = plasma; D = depot; T = tumor; E = excretion

plasma, tumor and depot as compartments (Figure 1). The differential equations for the models created were solved by iterative computer methods to calculate the transfer coefficients. The program used was SAAM (Simulation Analysis and Modelling, version two).[32] The standard deviation used by SAAM for each datum was the fractional standard deviation (f) of the form $SD_{ij} = f*|data_{ij}|$. In this case f had the value 0.1. The iteration process by SAAM II proceeds until the converge criteria are fulfilled, the maximum number of iterations has been achieved or the transfer coefficients have reached their high- or low-limits predetermined by the user on the basis of edge criteria. The goodness of the fit is tested by minimizing a function of the reciprocal of the estimated variance and the square of the separation of the developed model and data values.[32] The turnover time of an individual compartment is defined as the reciprocal of the transfer coefficient which describes outflux from the compartment.[31]

Statistical analysis
In the compartmental models the χ^2-test was used to compare the differences between the goodness of the fits

of the models. In the case of non-compartmental models the F-test was applied to measure the discrepancy between the fit and observed values. The parameters derived from compartmental and non-compartmental models were compared by regression analysis.
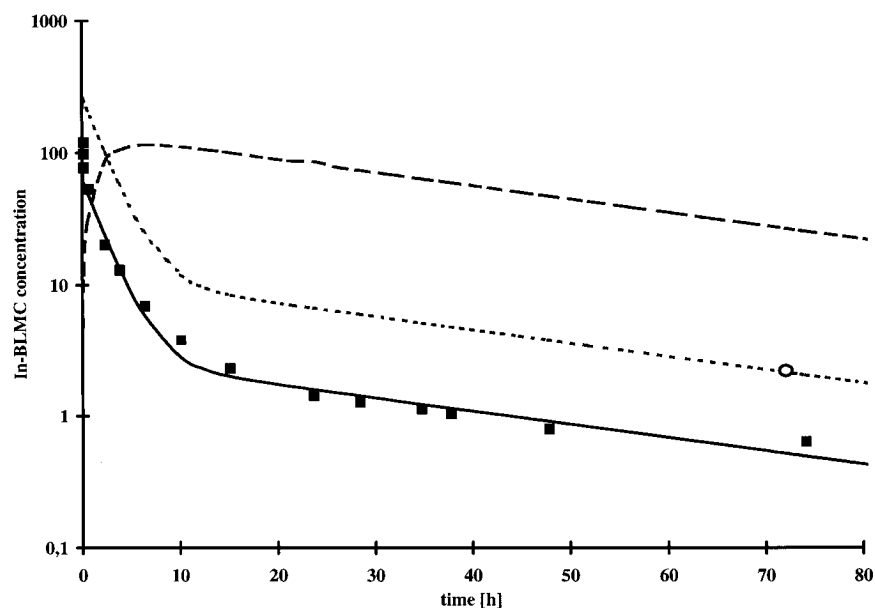
RESULTS

Non-compartmental models
The injected activity in plasma as percentages of the total injected amount at 1, 4, and 24 h after injection is shown in Table 2. The plasma clearance curve for ^{111}In-BLMC can be displayed as the sum of a three-exponential function (Figure 2). The mean half-lives were 5.6 ± 3.4 min for the fast, 1.7 ± 0.4 h for the intermediate and 18 ± 6 h for the slow component. The impact of the first component on the fittings was 69 ± 7% and the corresponding impact of the third was less than 5%. The mean transit times based on the fitting of exponential functions (Appendix 1) are shown in Table 3. The 3-exponential model was good (p < 0.01) for all patients. For one patient (No. 3) the fitted 3-exponential model was not significantly better than the
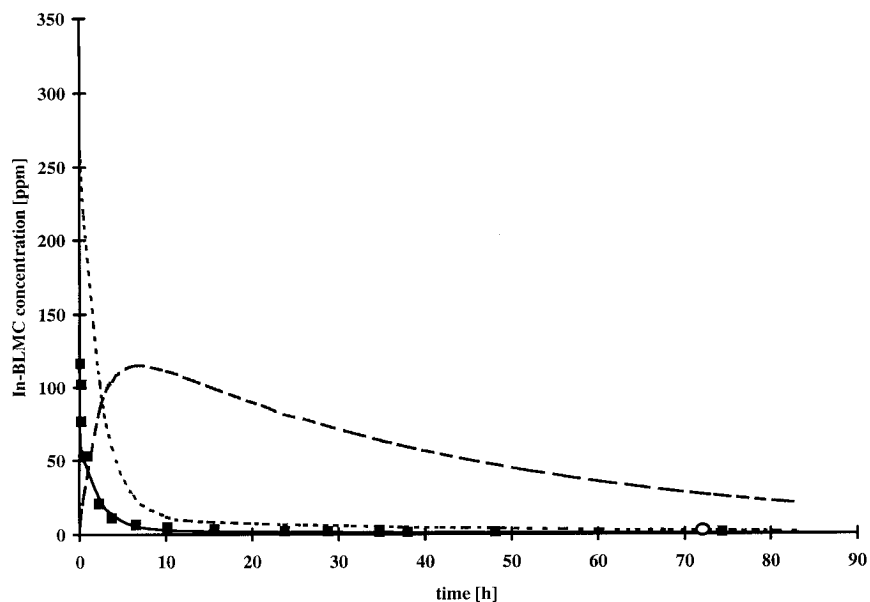
Fig. 4 Example of detected and modeled time-activity curves of ^{111}In-BLMC for one patient (No. 1). Lines (solid line presents plasma, long spot line presents depot and short spot line presents tumor) are results from the three-compartmental model and single points (rectangle marks plasma, circle marks tumor) are observed values. It is estimated that all the ^{111}In-BLMC is in the blood at time t = 0. In a linear scale (A), and in a logarithmic scale (B).

2-exponential fit. For the other patients the 3-exponential fit was significantly better than the 2-exponential fit (p < 0.01, F-test).

The mean clearance of ^{111}In-BLMC was 0.3 ± 0.1 ml blood/min. An example of the urine excretion curve is shown in Figure 3. The mean half-life of ^{111}In-BLMC in the urine was 3.5 ± 0.6 h.

Compartmental models

The transfer coefficients for the three-compartmental open model are shown in Table 4. The mean values are k_{EP} (excretion from plasma) = 0.02 ± 0.01, k_{PD} (from depot to plasma) = (12 ± 9)*10^{-4}, k_{DP} (from plasma to depot) = 0.01 ± 0.01, k_{PT} (from tumor to plasma) = 0.39 ± 0.19 and k_{TP} (from plasma to tumor) = 1.11 ± 0.57, all in units per minute. The corresponding time-activity curves of [111]In-
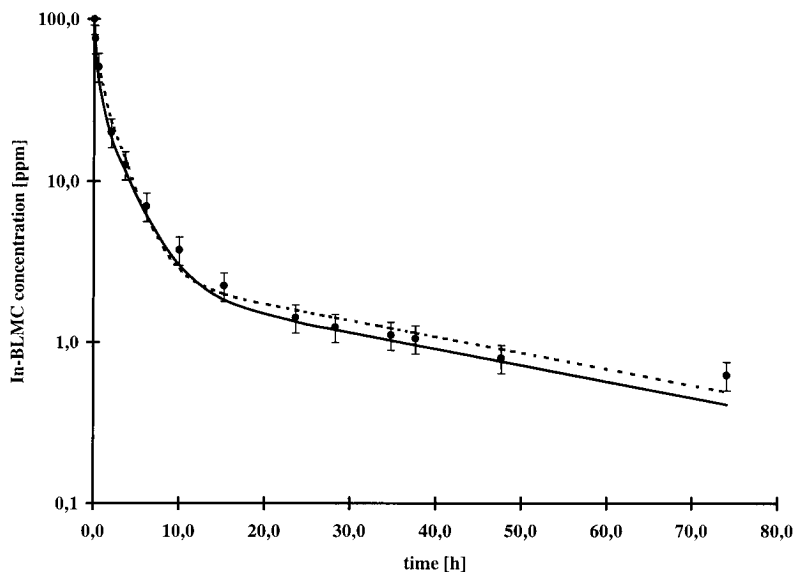
Fig. 5 Time-activity curve of ^{111}In-BLMC in plasma for one patient (No. 1) for the compartmental model (spot line) and exponential model (solid line). Single circles are observed values together with error estimates ± 10% of the detected values.

BLMC and observed values for one patient are shown in Figure 4. It is estimated that the error of the transfer rates is less than 15 percent for each patient based on the errors in data. The turnover time from the tumor is 4.5 ± 2.7 min and from depot 20 ± 8 h.

Correlation

The relationship between the three constants (A_1, A_2 and A_3) of the three-exponential curve and the equivalent constants derived from the compartmental is shown in Appendix 2. The r and p-values of the regression coefficients for the models were 0.88, ≤ 0.001 for A_1, 0.65, 0.02 for A_2 and 0.60, 0.04 for A_3, respectively. The time-activity curve of plasma for one patient derived from both compartmental and exponential models is shown together with the observed values in Figure 5.

DISCUSSION

In this study compartmental and non-compartmental models were applied for determinating the biodistribution of a labeled small-molecular tracer, indium-111 labeled bleomycin complex in humans. The models used have been formed with data from blood and tissue samples. In nuclear medicine, external detectors are frequently used to measure activity distributions. When using compartmental and non-compartmental models, it has been assumed that the labeled bleomycin is stable in *in vivo* conditions. It was also assumed that fluxes between compartments are linear and follow first-order kinetics and that the kinetic behavior of every compartment is distinct and homogeneous.

The kinetics of ^{111}In-BLMC is reported to be uniform in patients with normal cardiovascular and renal functions,[26,33] but our observations show it to be more complicated than has previously been reported, as a 3-exponential fit was needed to describe the data obtained from frequent blood sampling. The addition of a fourth exponential term did not significantly improve the square sum of error. The third exponent accounted for less than 5% of the elimination and might actually be derived from either free indium or tissue retention of ^{111}In-BLMC. In one case (No. 3) there was no significant difference between the 2- and 3-exponential fittings. The algorithms for the fitting programs are mostly some modifications of those by Marquardt.[34–38] In general, the number of exponentials of the function is related to error estimates and is not mathematically unique.[4,5] Background and noise (i.e. total error estimates) cannot be separated objectively in most studies, and thus the question of the number of exponentials in curves registered cannot be definitely solved. In addition, there are several problems in defining the optimal number of exponentials: exponents might be very close to each other, intensities possibly have different decades, there might be noise, potential non-linear curve parts or a suboptimal time grid.

In view of the data collected the best compartmental model to describe the kinetics of an indium-111 labeled bleomycin complex in humans has three compartments. The compartments are plasma, tumor and depot. Also two- and four-compartmental models were applied but, on the basis of the χ^2-tests, the open three compartmental model was found to be the one which most accurately described the distribution of ^{111}In-BLMC. Based on the models developed bleomycin is a tumor selective chemotherapeutic agent, which leaves the tumor more slowly

than it is cleared from the blood. The results of our model support the finding that there is a high uptake of ^{111}In-BLMC in high grade gliomas at 24 hours post injection, indicating a possible specific uptake in human gliomas.[27] Bleomycin both enters and leaves the undefined storage relatively slowly. In the applied four-compartmental model the kidneys were the fourth compartment. The problem of the complex correspondence between plasma clearance and urine excretion is known.[18] Urine samples cannot be utilized in a simple model because the transition of material from plasma to the kidneys is a complex non-linear dynamic process. Consequently, in this study there was no correlation with the half life of ^{111}In-BLMC in the urine and excretion transfer rate constant k_{EP}. Developing a more accurate model demands several samples from all the introduced compartments. The coefficients of transfer between compartments are sensitive parameters depending on the initial parameter values. Furthermore, if the value pairs of the test results received are fewer than the estimated parameters, then there will be an infinite number of solutions.[10] A tumor sample was not available for all patients. For patients without a tumor sample the initial transfer coefficients which are related to the tumor were calculated on the basis of the three patients for whom the tumor data were available. According to the results for these three patients, the material will enter the tumor faster than it leaves it. This can be perceived also in Figure 4. The turnover times determined on the basis of the transfer coefficients are reasonable. The turnover time from the depot was 20 ± 8 h. This is in good agreement with the result obtained with the non-compartmental model; the half-life of the slow component determined from the exponential fit was 18 ± 6 h and the mean transit time in the ^{111}In-BLMC total body pool was 13 ± 4 h.

The inlet-outlet theorem in non-compartmental modeling can be considered as a robust model for studying the biodistribution of any small molecule, e.g. ^{111}In-BLMC. Based on this model bleomycin is rapidly excreted from the plasma. The mean transit time in the total body was much longer, which probably means that bleomycin accumulates in some tissues and leaves them within a few hours. Both these findings were in good agreement with the results obtained from the compartmental models, as shown in Figure 5. Comparison of compartmental and non-compartmental models has been considered earlier.[12,39] Both these models are initially derived by using the same concepts; the mathematics behind these models is primarily similar but the difference in their interpretation leads to slightly different descriptions of the physiology, one in terms of transfer coefficients between a chosen set of compartments and the other in terms of the intercepts and decay constants in a multi-exponential equation. The difference between them is also in their ability to characterize modeling hypotheses accurately and quantitatively; and occasionally there are problems with their computability.[12] According to Gambhir et al.[39] it is pos-

sible to use both these methods, but when a system becomes more complicated, the correspondence of the models will weaken. In this study the two applied iterative and independent algorithms give similar results which correspond well with the test results.

The excretion rate (5 ml/min) obtained from the urine decay curve is in good agreement with the physiological findings. Plasma clearance of bleomycin is known to be rapid after i.v. administration.[40] Bleomycin is also rapidly excreted into urine. According to previous studies,[18] after injection about 10% of the injected activity is rapidly taken up by the kidneys, whereas the rest of the tracer is evenly distributed in the body so that a large fraction is excreted with a half-life of 10 h. This is in good agreement with the results obtained: the third mean transit time was 13 ± 4 h. Later, there is a secondary slow uptake in the liver, bone marrow and spleen, with a long retention of the activity before its final excretion in urine. This is presumably caused by the dissociation of the complex with the release of ionic indium.[18]

There is a desire to produce a simple and fault tolerant model. No model can be unique because it is always possible to create models which are more exact and more detailed.[7,12] The question still is what are the limits of the complexity of the model. The ability to make pathophysiological predictions is one of the goals in developing new models. It is essential to have some insight into the physiology of the system under study in order to obtain appropriate data and choose appropriate models. By these considerations one is able to make decisions regarding the ignorable effects of inaccessible data and the complexity of extraction and exchange routes.

It is concluded that both compartmental and non-compartmental modeling are sufficient to describe the kinetics of indium-111 labeled bleomycin complex. The non-compartmental model is more practical and to some extent more efficient in providing the needed information from the in vivo behavior of ^{111}In-BLMC than the compartmental model. The compartmental model used provides estimates of both extraction and excretion from the plasma and tumor.

APPENDIX 1

The detected time activity curve, $C_P(t)$, can be represented as the sum of exponential functions;

$$C_p(t) = \sum_i A_i e^{-g_i t}, \qquad i = 1, 2, 3 \qquad (A1)$$

Based on equation (A1) transit times can be written as[11];

$$t_1 = \frac{C_P(0)}{\dot{C}_P(0)} = \frac{\sum_i A_i}{\sum_i A_i g_i}, \qquad (A2)$$

$$t_2 = \frac{\int_0^\infty C_P(t)dt}{C_P(0)} = \frac{\sum_i A_i/g_i}{\sum_i A_i} \qquad (A3)$$

and

$$t_3 = \frac{\int_0^\infty tC_P(t)dt}{\int_0^\infty C_P(t)dt} = \frac{\sum_i A_i / g_i^2}{\sum_i A_i / g_i} . \qquad (A4)$$

APPENDIX 2

From equation (A1) in the case of a three-compartmental model one gets;

$$C_P(t)/I_P = A_1 e^{-g_1 t} + A_2 e^{-g_2 t} + A_3 e^{-g_3 t}, \qquad (A5)$$

where the activity in plasma is divided by the amount of tracer injected. A complete solution of a general three-compartmental model has been presented by Skinner et al.[41] Applying those results in the case of an open restricted three-compartmental model (Figure 1), one is able to derive a relationship between the transfer coefficients from the compartmental model and the coefficients and multiples from the exponential fit:

$$A_i = \frac{(g_i + k_{PT})(-g_i + k_{PD})}{(-g_i + g_j)(-g_i + g_k)}, \qquad (A6)$$

where one uses cyclic permutation ($ijk = 123$). In equation (A6) g_i and k_{lm} are derived from two independent algorithms.

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