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ORIGINAL ARTICLE

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The effect of malignant effusions on methotrexate disposition

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Abstract *Purpose:* The purpose of this study was to evaluate the effect of malignant effusions on the pharmacokinetics of methotrexate (MTX). *Methods:* Simulated drug concentrations in blood, tissues and effusion fluid spaces were generated using a previously published physiologically based pharmacokinetic (PBPK) model for MTX in humans. The model was expanded to incorporate effusion spaces with permeability rate-limited drug transport. The model was used first to simulate MTX plasma concentrations in patients without effusions. Then the effects of cardiac, peritoneal and pleural effusions on MTX plasma concentrations were investigated followed by an examination of the influence of effusion volume, binding in the effusate, and effusion space permeability clearance (PA) on MTX plasma pharmacokinetics. In addition, the effect of the disposition characteristics (e.g. volume of distribution) of the anticancer drug on the overall influence of an effusate was evaluated. Finally, the simulations were compared with MTX concentrations observed in the plasma and pleural fluid of a patient with a pleural effusion treated with MTX. *Results:* There was good agreement between the PBPK-simulated MTX plasma concentrations and observed values in patients without effusions. There was also a remarkable similarity between simulated and measured plasma and effusion MTX concentrations in a pediatric patient with a malignant pleural effusion. The physiological characteristics of an effusion, i.e. fluid volume, protein binding and membrane permeability clearance, modulate the influence of an effusion on the drug plasma concentration-time course. In general, effusions cause an increase in the steady-state volume of distribution but no change in the overall clearance of a drug. Malignant effusions were noticeable only in the disposition phase of MTX resulting in an apparent "third space." This was most prominent when the effusion fluid volume was large, the binding of MTX in the effusion fluid was greater than in plasma and the PA value was low. The percentage change in terminal half-life due to an effusion is significant for drugs with small volumes of distribution (332%) but not for those with large volumes of distribution (1.29%). In the case of MTX, and probably other anticancer drugs, the resulting increase in half-life may be associated with unanticipated toxicity.

Keywords Methotrexate · Malignant effusion · Physiologically based pharmacokinetic model

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Introduction

In advanced cancer, malignant cells may metastasize to serous body cavities such as the pleural, peritoneal and pericardial cavities. Once established, a significant fluid build-up can occur in these regions. This may be due to the increased vascular permeability characteristics of the malignant tissue in the cavity, obstruction of normal drainage mechanisms such as lymph vessels, or changes in the osmotic pressure of the fluid due to high protein content [1]. The normal volume of fluid in the pleural, peritoneal and pericardial spaces is several milliliters [1, 2, 3]. However, in patients with large fluid accumulation, these cavities may contain several liters [1, 2, 3]. Furthermore, the protein content may be similar to that found in the blood. These body cavities can therefore become regions for sequestering chemotherapeutic agents, thereby influencing plasma drug pharmacokinetics and earning the term "third space" [4]. Malignant effusions are usually detected in individuals with advanced metastatic disease, with almost 100,000 new cases of pleural effusions identified yearly in the United

States [1]. Although not as prevalent, pericardial and peritoneal effusions are also seen in patients with advanced cancer. Malignant effusions are often late complications of progressive cancer, and typically portend a poor prognosis.

The influence of these regions on anticancer drug pharmacokinetics has been noted by several investigators. Frei et al. in 1975 commented "...the dilution of MTX into a larger than normal volume in those patients with serosal effusions has been shown to result in prolonged plasma half-lives and to be associated with subsequent myelosuppression" [5]. Evans and Pratt likewise demonstrated the effect of a pleural effusion on the plasma MTX-time course in a pediatric patient with a pleural effusion [6]. The clinical significance of this phenomenon is further reinforced by two recent articles. Gandara et al. in a phase II trial of edatrexate and carboplatin found unexpectedly severe myelosuppression resulting in death from neutropenic sepsis in two patients with pleural effusions [7]. Similarly, a patient with non-Hodgkin's disease with bilateral pleural effusions experienced a normal course of treatment when fludarabine was administered shortly after drainage of pleural fluid. However, on a subsequent course, in which pleural drainage was not performed, the patient developed neutropenia and associated septicemia [8].

It is evident that malignant effusions can influence the pharmacokinetics of antineoplastic agents to the extent that they may be life-threatening. To date there has not been a rigorous systematic study of the effect of malignant effusions on the pharmacokinetics of anticancer drugs. The disposition of MTX has been shown to be influenced by malignant effusions [9]. Fortuitously, a detailed physiologically based pharmacokinetic (PBPK) model for MTX has been reported [10, 11, 12]. Furthermore, the disposition of the drug in the pleural, peritoneal and pericardial cavities has also been quantitatively described [13]. Using this information, the effect of malignant effusions on the pharmacokinetics of MTX can be critically examined.

Methods

Development of the PBPK model

The flow-limited PBPK model developed by Bischoff et al. and Dedrick et al. formed the basis of the model used to demonstrate the effects of malignant effusions on MTX pharmacokinetics [10, 11]. The model was modified according to the recommendation of Evans et al. [12]. In addition, compartments representing the lung and heart as well as the pleural, peritoneal, and pericardial cavities were added to the PBPK model as shown in Fig. 1. The resulting model was used to simulate MTX concentrations in blood, tissues, and effusion fluid spaces following intravenous infusion. Drug transport into and out of the effusion spaces was simulated using a permeability rate-limited model [14]. The volume terms and flow rates of the PBPK were chosen for a 70-kg individual. Mean permeability clearances (PA) as determined by Howell et al. [13] for each type of effusion were used (Appendix).

Simulation of the resulting PBPK model was performed using the commercial software package Berkeley Madonna (University of California, Department of Molecular and Cellular Biology, Berkeley) [15]. Equations used in the model are presented in the Appendix. The Runge-Kutta 4 algorithm was chosen for numerical integration.

Permeability rate-limited model for effusion space

The general kinetic features of a drug crossing a membrane and distributing into and out of an effusion space are as follows (Fig. 2). The anatomical compartments with the addition of the volume of effusion fluid (V_E) and the unbound fraction of drug (f_{UE}) in the effusion fluid represent tissues with an effusion space. Drug in tissues with anatomical volume (V), tissue blood flow (Q) and the unbound fraction of drug in the blood (f_U) distributes into fluid in the effusion space. C_P and C_E are the drug concentrations in the plasma and effusion fluid, respectively. The drug crosses the membrane of area (A) by a diffusive process characterized by permeability clearance (PA). This model implies that blood associated with the effusate is derived from blood perfusing the "host" tissue.

Mass balance equations describing each compartment associated with an effusion are:

$$V\frac{dC}{dt} = Q\left(C_P - \frac{C}{R}\right) + PA(f_{UE}C_E - f_U C_P) \quad (1)$$

$$V_E\frac{dC_E}{dt} = PA(f_U C_P - f_{UE}C_E) \quad (2)$$

where R represents the equilibrium distribution ratio (partition coefficient) of the drug between the tissue and plasma. Equations (1) and (2) express the drug concentration in the tissue and effusate as a function of time. There are two groups of parameters for the tissue. The first group, $Q\left(C_P - \frac{C}{R}\right)$, describes drug distribution into and out of the tissue under flow-limited conditions. The second group, $PA(f_{UE}C_E - f_U C_P)$, describes net movement of drug from the effusion space back to the plasma using the permeability rate-limited model. The assumptions for the permeability rate-limited model are: (1) entering drug is instantly and homogeneously distributed within each space, (2) binding of drug is instantaneously established. and (3) only unbound drug can cross the membrane.

Physiological parameters for the effusion spaces

PA is a function of both permeability (P) and area (A), and is expressed in milliliters per minute. Using PA as a measure of membrane transport, the efficiency of permeability can easily be compared with blood flow and elimination clearance to assess the relative contribution of these functions to drug transport between the effusion space and blood. Several physical and biological factors including molecular weight, hydrophobicity, blood and lymph flow, and the capacity of the capillary wall and intervening interstitium are incorporated into the PA parameter for transport across the peritoneal-blood barrier [16]. The same factors are assumed to likewise affect drug disposition in pleural and pericardial effusions. Howell et al. [13] determined PA values for all three malignant effusion sites by infusing MTX directly into each cavity until steady-state concentrations were achieved. Mean values of PA were 6.6 ml/min for the peritoneal cavity, 2.6 ml/min for the pleural cavity and 0.14 ml/min for the pericardial cavity.

The unbound fraction of MTX in plasma (f_U) and in effusion fluids (f_{UE}) may vary under certain clinical situations. The unbound fraction of a drug is dependent on the concentration of drug, the nature and concentration of the binding protein, as well as the binding association constant. Albumin is the major component of plasma proteins responsible for reversible drug binding in the blood. In the body, albumin is distributed in both the plasma and extracellular fluid. In a number of disease states, the concentration of protein may vary from that found in healthy individuals, potentially affecting the fraction of unbound drug. Thus the mean

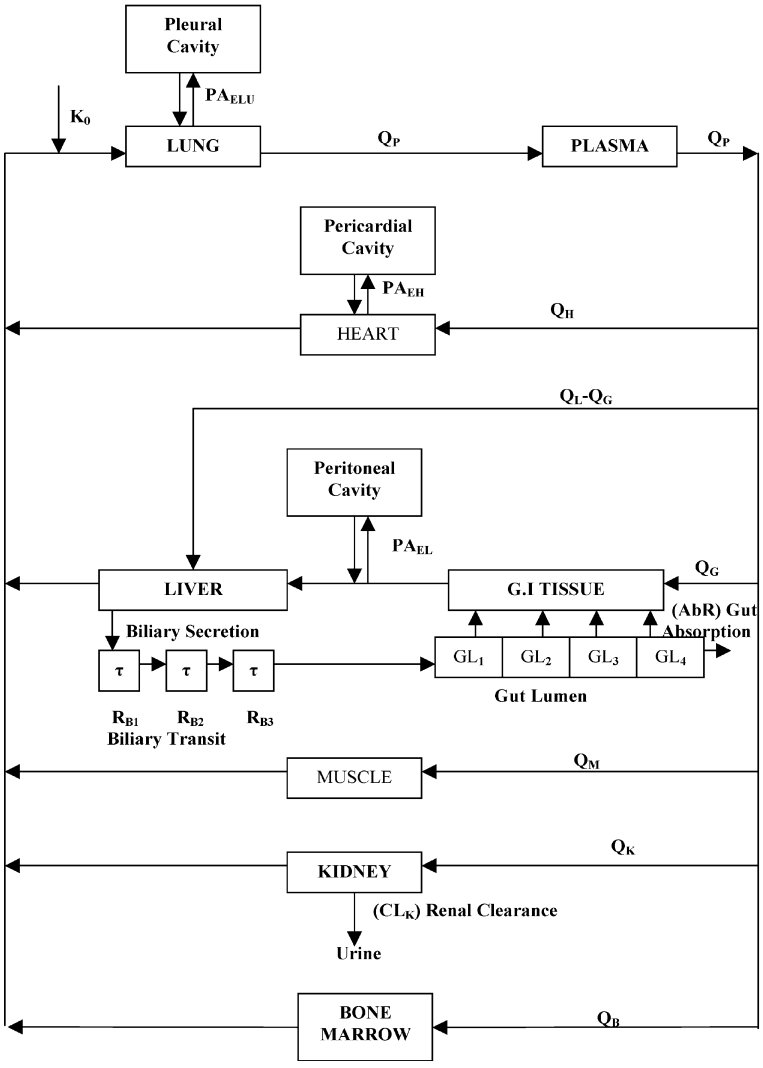


Fig. 1. Physiologically based pharmacokinetic model for methotrexate simulation with malignant effusions

pleural fluid protein concentration in healthy men is 1.77 g/100 ml (range 1.38 to 3.35 g/100 ml), whereas the corresponding mean plasma protein concentration is 4.25 g/100 ml (range 3.5 to 5 g/100 ml) [17]. In patients with malignant effusions, however, the protein concentration in the effusion fluid is frequently greater than that found in normal cavity fluid, with a typical value of 4 g/100 ml. In contrast, the plasma protein concentration in such patients is generally below normal levels with a typical value of 1.5 g/100 ml [18, 19, 20]. In agreement with these findings, clinical studies have shown that pleural fluid total MTX concentrations are consistently higher than the corresponding plasma concentration [6, 21].

Differences in both MTX and protein concentrations between effusion fluid and plasma may also influence the unbound fraction of drug. Skibinska et al. found that the percentage of MTX bound to plasma protein was $50.4 \pm 1.9\%$ in healthy subjects, but only $32.3 \pm 3.6\%$ in patients with cancer (breast carcinoma in most cases) [22]. Also, wide variation in drug binding to effusion fluid protein has been reported despite minimal variability in MTX plasma protein binding [23]. Nevertheless, when the protein concentration of effusion fluid is similar to that in the plasma, the unbound fraction of MTX in effusion fluid is similar to that in the plasma, with mean values around 0.5 [13]. In some disease situations, when the protein concentration in the effusion fluid increases, the binding of MTX to the protein will also increase, giving a lower unbound fraction of MTX.

Simulation studies

Simulations in patients without effusions: MTX plasma concentration-time curves were generated using normal fluid volumes in each effusion site. The resulting curve was compared with a range of values for MTX plasma concentrations determined in patients without effusions [6, 12].

The effect of the site of effusion on MTX disposition: To assess the influence of the different types of effusion (i.e. pleural, peritoneal and pericardial effusions) on MTX disposition, simulations of MTX plasma concentrations were performed using the same PBPK model parameters previously used in simulation studies [10, 11, 12]. Effusion site fluid volumes, both normal and malignant, were obtained from the literature [1, 2, 3]. The normal fluid volumes were 12 ml, 20 ml, and 40 ml, respectively [1, 2, 3]. In this simulation, a malignant effusion volume was set at 2000 ml for pleural, peritoneal and pericardial cavities [1, 2, 3]. This value was chosen to provide a significant but clinically realistic volume, although in the case of the pericardial sac it approaches a maximum value [3]. The mean PA values for MTX transport across the pleural, peritoneal and pericardial membranes determined by Howell et al. were 2.6, 6.6, and 0.14 ml/min, respectively, based on a 70-kg individual [13]. The unbound fraction of MTX in the plasma in cancer patients is 0.68 as reported by Skibinska et al. [22], and 0.5 in the effusion fluids [13]. Thus the protein concentration is similar between the plasma and effusion fluid.

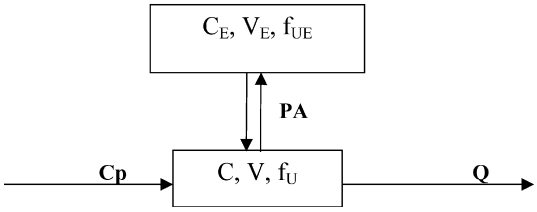


Fig. 2. Permeability rate-limited tissue model for drug transport into and out of the effusion cavities (V anatomical tissue volume, V_E volume of effusion fluid, f_U fraction unbound in the blood, f_{UE} fraction unbound in the effusion fluid, C total drug concentration in the tissue, C_E total drug concentration in the effusion fluid)

The effect of the physiological characteristics of effusion fluids on MTX disposition: A malignant effusion has several causes: pleural implantation, lymphatic obstruction, venous obstruction, and tumor cell suspensions. These interfere with fluid and protein reabsorption to differing degrees [1]. To assess the influence of effusion protein and the effusion volume on the plasma disposition kinetics of MTX, model simulations for patients with a malignant pleural effusion were performed by altering the unbound fraction of drug (f_{UE}) in the effusion fluid (e.g. f_{UE} 0.5, 0.4, 0.3, 0.2 and 0.1) and the volume in the pleural cavity (e.g. V_E 12, 100, 500, 1000, 1500, 2000, 2500, and 3000 ml). The unbound fraction of drug in the plasma remained constant at 0.68. All other model parameters were as described previously.

Each of the model simulations in (1) through (3) included a 6-h intravenous infusion of high-dose (5000 mg/m^2) MTX.

The effect of the disposition characteristics of anticancer drugs on the overall influence of an effusate: To investigate the effect of the disposition characteristics (e.g. volume of distribution) of the anticancer drug on the overall influence of an effusate, the partition coefficient of the muscle (Rm) was arbitrarily changed (0.15, 3, and 6) to represent different volumes of distribution of anticancer drugs. Model simulations for patients with and without malignant pleural effusions were made by altering the volume of a pleural effusion from 2000 ml to 12 ml. The unbound fraction of anticancer drugs in the plasma was held constant at 0.5. This figure was also used for binding in the effusion fluid, reflecting a similar protein concentration in the plasma and effusion fluid. The second simulation was performed to evaluate the effects of increased plasma protein binding. The unbound fraction was decreased to 0.1, 0.05, and 0.01 while leaving the fraction of unbound drug in the effusion at 0.5.

Comparison of the model-generated MTX plasma concentration-time curves with those observed in a pediatric patient: The patient described was a 12-year-old male with osteosarcoma of the left proximal tibia. Chest roentgenogram revealed a left pleural effusion and metastatic disease involving the left ribs, left lung, and left pleura. The fluid was characterized as an exudate. A 6-h 400-mg/kg constant intravenous infusion of MTX was administered. The effusion was characterized by reaccumulation of pleural fluid approximately 400 ml in volume at the time of administration of a second dose of MTX [6].

For comparison, simulations of MTX plasma and pleural fluid concentrations were made using the volume of pleural fluid of 400 ml as reported for the patient. The fraction of unbound drug was selected to be 0.2 in the effusion fluid, consistent with the exudate nature of the effusion fluid producing protein levels higher than those in plasma.

Pharmacokinetic analysis

The MTX plasma concentration-time profiles were generated using the Berkeley Madonna software package. Non-compartment pharmacokinetic methods were used to calculate mean residence time (MRT), steady-state volume of distribution (V_{SS}), total body clearance (CL), and terminal half-life ($t_{1/2}$). MRT was determined as the ratio AUMC/AUC and CL was calculated from the ratio Dose/AUC. V_{SS} was obtained from the product of CL and MRT. It is recognized that the parameter values are approximate since non-compartment analysis assumes linearity. Finally, AUC was determined using linear and log-linear trapezoidal numerical integration methods. The terminal slope of the methotrexate plasma concentration-time curve was estimated by a log-linear regression.

Results

The effect of the site of the malignant effusion

There was good agreement between simulated and measured plasma MTX concentrations in patients without effusions (Fig. 3). The same figure also includes simulations with large malignant effusions in pleural, peritoneal and pericardial cavities. These simulations demonstrate that an effusion has little influence on MTX

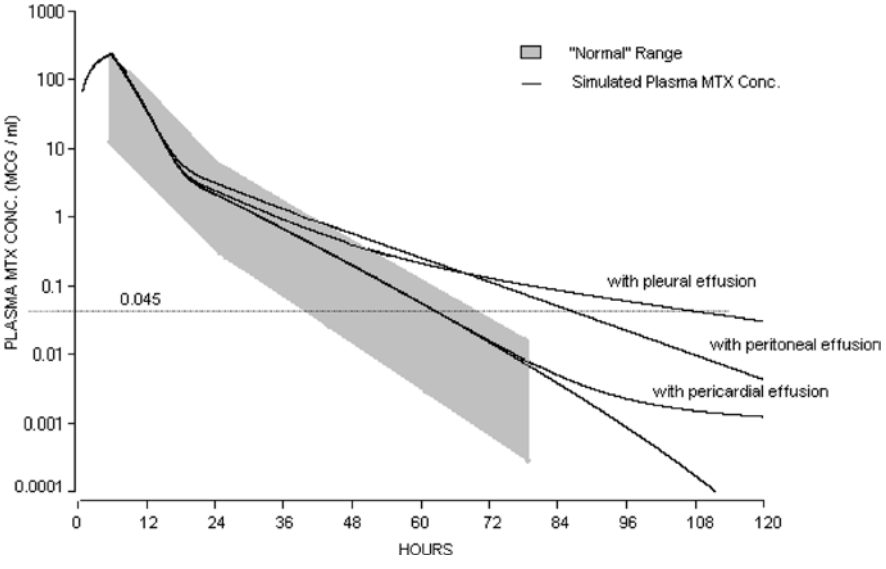


Fig. 3. Simulation of methotrexate plasma concentration-time profile when different types of effusion fluids were present ($V_E = 2$ l, $f_U = 0.68$, $f_{UE} = 0.5$). The *shaded area* represents the range of methotrexate plasma concentrations measured for the patients without effusions (from reference 12)

plasma concentrations during the initial decline of MTX concentration. That is, the presence of these effusions would not be detected shortly after drug administration. However, a marked decrease in the rate of decline of plasma concentrations was observed beginning 15 h after infusion in the presence of pleural effusions, 11 h after infusion with peritoneal effusions, and 60 h with pericardial effusion. This finding suggests that the drug initially rapidly entered the effusion spaces which were relatively small compared with the overall volume of distribution. Thus the distribution phase of the drug was relatively unaffected. However, protein binding in the effusion spaces coupled with low permeability of unbound drug contributed to a decrease in the rate of decline of the drug in the disposition phase.

Table 1 shows that when malignant effusions were present, MTX clearance did not change significantly, but the mean steady-state volume of distribution increased significantly compared with that measured in the absence of an effusion. The ratio PA to total body clearance ranged from 4.6% with peritoneal effusion to 0.09% with pericardial effusion (Table 1). With the pericardial effusion, the effect of the effusion was apparent much later in the MTX concentration time-course and the simulation showed a distinct triphasic decline in MTX plasma concentrations. The increase in the mean steady-state volume of distribution with a malignant effusion was 0.05 l/kg for pericardial effusion, 0.12 l/kg for pleural effusion and 0.14 l/kg for peritoneal effusion. These increases were greater than the estimated additional apparent volume of effusion fluid $\left(V_E \frac{f_U}{f_{UE}}\right)$ in the cavities of 0.039 l/kg (Table 1).

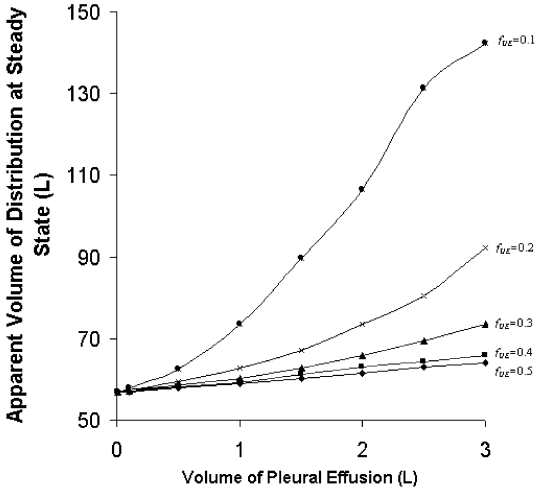


Fig. 4. The effects of physiological characteristics in the effusion spaces (fraction of unbound methotrexate in the effusion fluid and the volume of pleural effusion) on the apparent volume of effusion at steady state from simulation studies

Table 2. Methotrexate pharmacokinetic parameters calculated from simulated data influenced by the fraction unbound of methotrexate in pleural effusion fluid (f_{UE}) ($V_E = 2$ l, $f_U = 0.68$)

f_{UE}	CL (ml/min)	V_{SS} (l/kg)[a]	Terminal half-life (h)
0.5	145.32	0.88	25.47
0.4	145.43	0.90	31.52
0.3	145.56	0.94	42.35
0.2	145.72	1.05	63.81
0.1	145.96	1.52	127.0

[a]Calculated for a 70-kg individual

The effect of malignant effusion fluid characteristics

In Fig. 4, changes in either the unbound fraction of MTX in the effusion fluid (f_{UE}) or in the effusion volume in the pleural cavity (V_E) are seen to significantly affect MTX plasma disposition. When drug binding in the effusate or the effusion volume increased, the apparent steady-state volume of distribution (V_{SS}) and the terminal plasma half-life correspondingly increased. As seen in Table 2, with a pleural effusion volume of 2 l, and an increase in effusate binding of MTX, the apparent mean steady-state volume of distribution increased (from 0.88 l/kg to 1.52 l/kg) and the terminal plasma half-life was increased (from 25.47 to 127 h). However, the mean total body clearance (CL) of MTX did not change (145.32 ml/min vs 145.96 ml/min).

The effect of drug disposition characteristics on the overall influence of an effusate

The influence of an effusate on the disposition of a drug was found to be dependent on the pharmacokinetics of the drug. When the volume of distribution of MTX was

Table 1. Methotrexate pharmacokinetic parameters in different sites of malignant effusions calculated from simulated data ($V_E = 2$ l, $f_U = 0.68$, $f_{UE} = 0.5$)

Type of effusion	AUC (μg·min/ml)	C_{max} (μg/ml)	Terminal half-life (h)	CL (ml/min)	V_{SS} (l/kg)[a]	PA[b]/CL (%)	ΔV_{SS} (l/kg)[a,c]
Pleural	60,032	242.41	25.47	144.09	0.88	1.8	0.12
Peritoneal	59,700	238.73	13.18	144.89	0.90	4.6	0.14
Pericardial	59,544	245.57	285.86	145.27	0.81	0.09	0.05
Without effusion	59,746	245.61	5.89	144.78	0.76	–	–

[a]Calculated for a 70-kg individual
[b]Mean PA values measured by Howell et al. [13] from patients, 2.6 ml/min, 6.6 ml/min and 0.14 ml/min for pleural, peritoneal and pericardial cavities
[c]$\Delta V_{SS} = V_{SS}$(with effusion)–V_{SS}(without effusion), compared with the apparent volume of effusion fluid, $V_E \frac{f_U}{f_{UE}} = 0.039$L/kg

artificially elevated by increasing drug binding in the muscle tissue, the effect of a pleural effusion on the V_{SS} decreased from 15.8% to 0.89% and the change in half-life decreased from 332% to 1.29% (Table 3, Fig. 5). The effect of increasing drug plasma protein binding relative to binding in the effusate is a reduction in the fraction of the drug in the body residing in the effusate. This will diminish the effect of the effusion on plasma drug concentrations.

Comparison of simulation to a clinical case study

Figures 6 and 7 offer a comparison of the model-predicted MTX plasma and pleural effusion fluid concentrations with those obtained in a patient. With no alteration in the PBPK model parameters, it is evident that the model successfully predicted the effect of a pleural effusion on MTX pharmacokinetics in a patient with a pleural effusion. In both pleural effusate and plasma concentrations there was again little effect observed during the initial distribution phase of the plasma MTX concentration-time curve while substantial deviation was observed during the elimination or disposition phase.

Discussion

A previous clinical study demonstrated that a malignant effusion could result in a prolonged terminal plasma MTX half-life following administration of high-dose MTX [6]. Since prolongation of MTX increases the risk of severe toxicity, it is important to establish those clinical variables related to malignant effusions that alter MTX disposition [9]. Patients with malignant effusions should be considered "high-risk" patients, because their plasma MTX concentrations may remain above 0.1 μM (0.045 μg/ml) for longer than 72 h after leucovorin is discontinued [9]. Furthermore, administration of subsequent MTX doses, given the prolonged elimination, may further exacerbate the situation. Examination of Fig. 3

Table 3. The pharmacokinetic parameters of mean volume of distribution (V_{SS}) and terminal half-life with ($V_E = 2$ l) and without pleural effusion ($V_E = 12$ ml) calculated from simulated data influenced by Rm

Rm	V_{SS} (l/kg)[a]		Change (%)[b]	Terminal half-life (h)		Change (%)[b]
	With effusion	Without effusion		With effusion	Without effusion	
0.15	0.88	0.76	15.79	25.47	5.89	332.48
3	2.78	2.74	1.46	13.80	13.39	3.06
6	4.54	4.50	0.89	24.33	24.02	1.29

[a]Calculated for a 70-kg individual
[b]Change (%) = (with effusion–without effusion)/without effusion ×100%

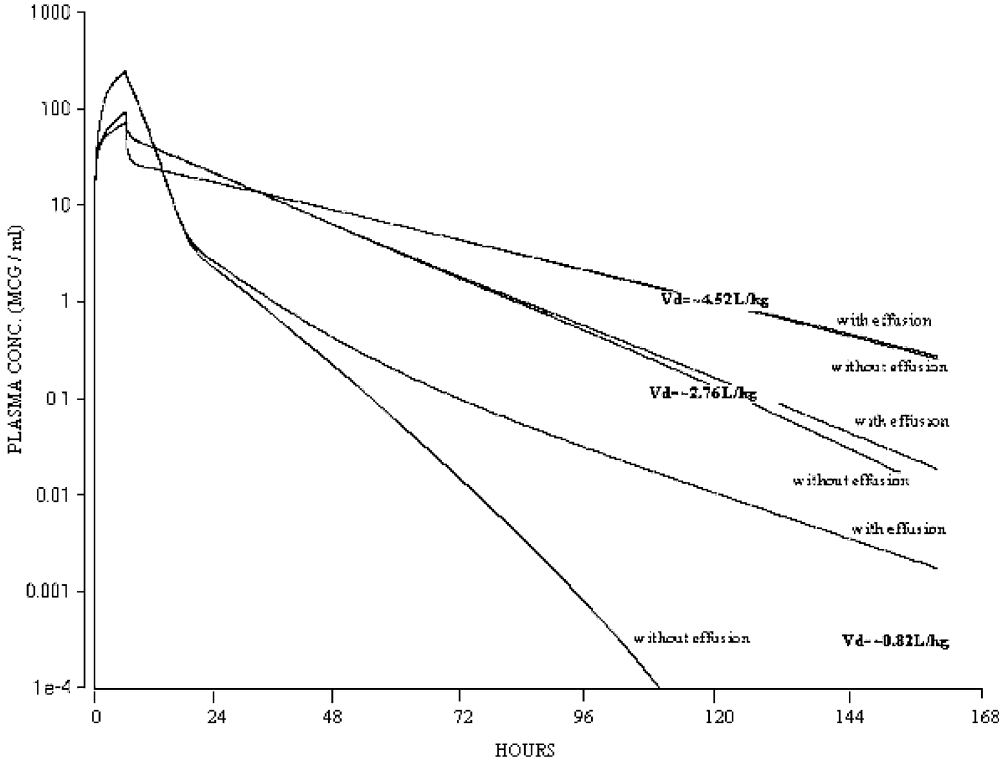


Fig. 5. Simulated plasma concentration-time profile of anticancer drugs with different volume of distribution in the presence and absence of pleural effusions

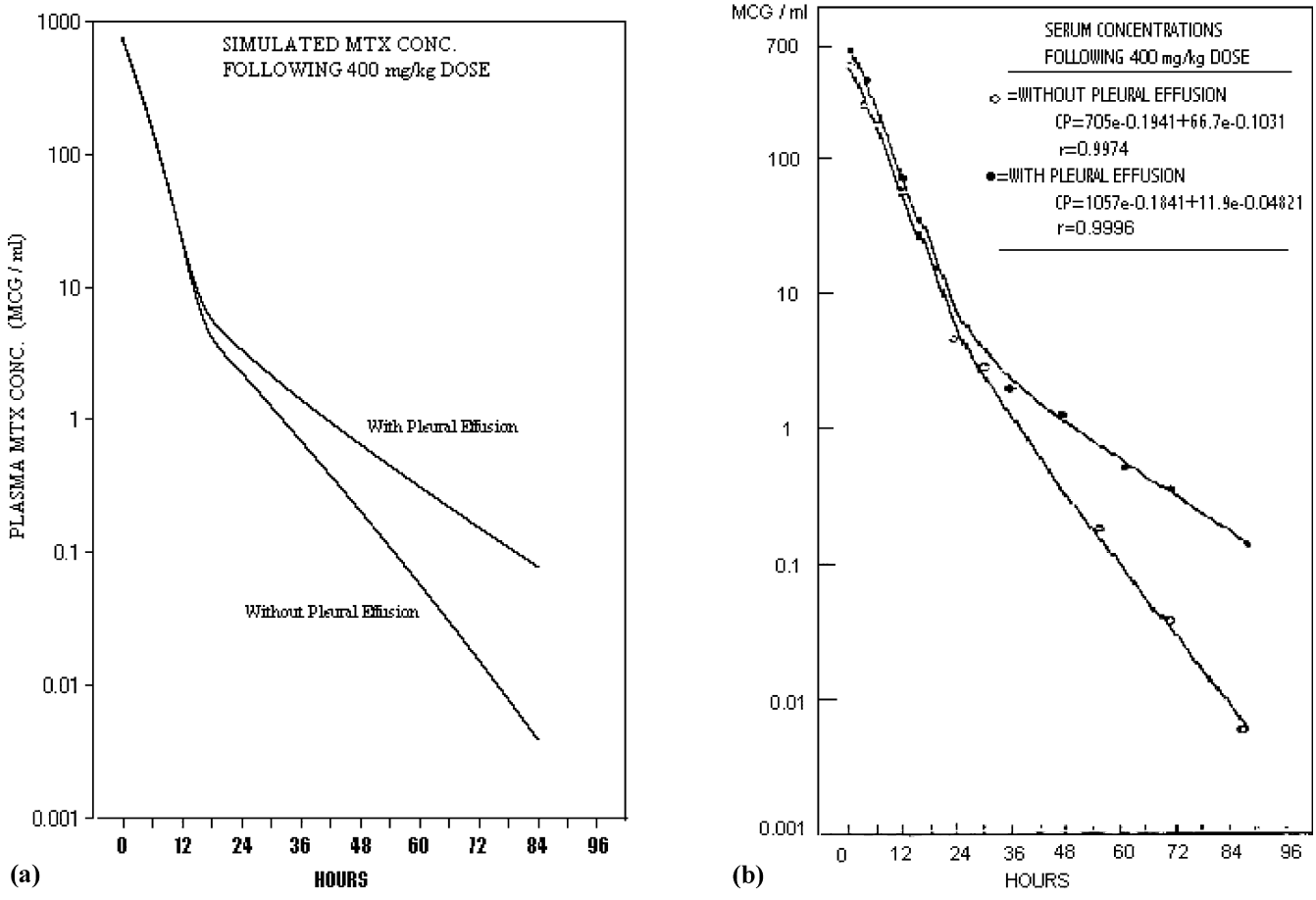


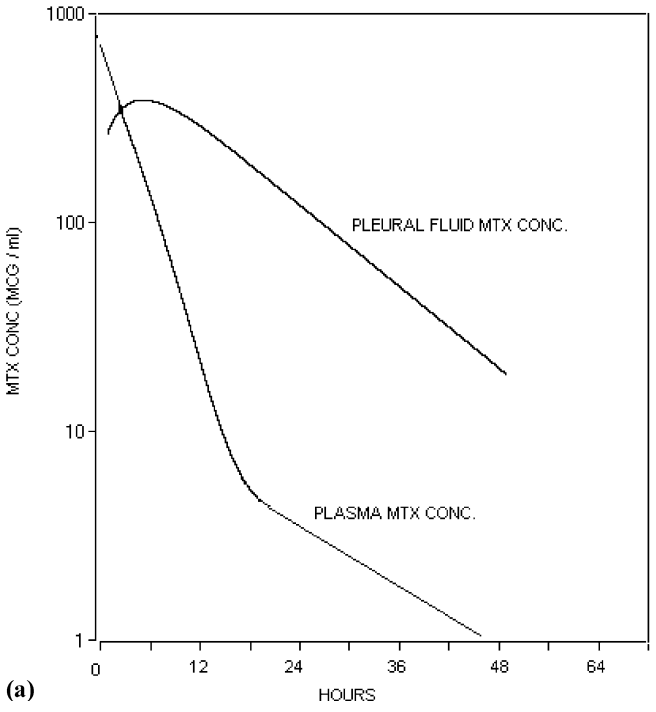
Fig. 6a, b. Comparison of model simulation and clinical observation of methotrexate plasma concentration in the patient with pleural effusion ($V_E = 400$ ml, $f_U = 0.68$, $f_{UE} = 0.2$). **a** Model simulation, **b** clinical measurement (from reference 6)

shows that for patients with pleural and peritoneal effusions, the MTX concentration may be sustained for about 90 h and about 100 h, respectively. It is also important to realize that at even higher MTX doses, e.g. 12,000 mg/m^2, it is conceivable that the MTX plasma concentration in a patient with cardiac effusion would be sustained at this level for exceedingly long time periods.

In the present study, a previously described PBPK model for MTX disposition was refined by the incorporation of effusion spaces. A permeability-rate limited model was used to describe drug transport into and out of the effusion spaces. Using model parameters from the original PBPK model and the specific transport parameters for the effusion spaces reported by Howell et al. [13], simulations were generated that reflected the influence of different sites of malignant effusions and changes in the characteristics of the effusion fluids. These simulations indicate that the volume of the effusate, drug binding in the effusate and the rate of transport into and out of the effusate space affect the extent to which a drug is sequestered in these regions. These factors in turn influence the volume of distribution and the terminal plasma MTX half-life. When these various parameters strongly favor accumulation of drug in the effusate, a characteristic "third space" becomes evident.

It has been postulated that the toxicity of MTX for normal tissue is more dependent upon the duration of exposure to the drug than upon the peak concentration achieved [9]. The increased risk of toxicity in patients with third-space fluid accumulation is well documented for several compounds, i.e. MTX [6] fludarabine [8], edatrexate and carboplatin [7]. For this reason, it is advisable to evacuate large effusions before administration of these agents. An additional pharmacokinetic characteristic that may influence the impact of an effusate on drug kinetics is the extent of distribution of the drug in normal tissues. Extensive tissue binding indicated by a large volume of distribution reduces the overall influence of an effusate on the disposition kinetics of a drug. This is consistent with recent observations that the pharmacokinetics of topotecan (V_{SS} about 130 l) is not affected by pleural or peritoneal effusions [24]. The disposition of drugs that are highly bound in the blood, such as teniposide, is unlikely to be substantially affected by the presence of an effusion.

The results of these simulation studies suggest a pharmacokinetic basis for the clinical observations that patients with malignant effusions being treated with anticancer drugs possessing relatively small volumes of distribution and low plasma protein binding may be at



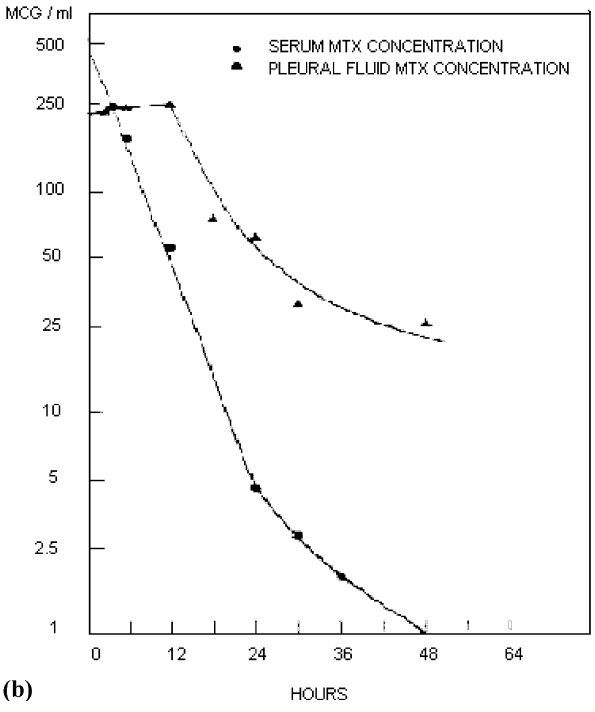


Fig. 7a, b. Comparison of model simulation and clinical observation of methotrexate effusion fluid concentration in the patient with pleural effusion ($V_E = 400$ ml, $f_U = 0.68$, $f_{UE} = 0.2$). **a** Model simulation, **b** clinical measurement (from reference 6)

particular risk of toxicity following high-dose chemotherapy due to an increased half-life.

Appendix

The differential equations for the PBPK

For lung:

$$V_{LU}\frac{dC_{LU}}{dt} = K_0(t) + Q_L\frac{C_L}{R_L} + Q_K\frac{C_K}{R_K} + Q_M\frac{C_M}{R_M} + Q_B\frac{C_B}{R_B} + Q_H\frac{C_H}{R_H} + PA_{LU}(f_{UELU}C_{ELU} - f_uC_P) - (Q_L + Q_K + Q_M + Q_B + Q_H)\frac{C_{LU}}{R_{LU}}$$

For pleural cavity:

$$V_{ELU}\frac{dC_{ELU}}{dt} = PA_{LU}(f_UC_P - f_{UELU}C_{ELU})$$

For heart:

$$V_H\frac{dC_H}{dt} = Q_P\left(C_P - \frac{C_H}{R_H}\right) + PA_H(f_{UEH}C_{EH} - f_UC_P)$$

For pericardial cavity:

$$V_{EH}\frac{dC_{EH}}{dt} = PA_H(f_UC_P - f_{UEH}C_{EH})$$

For plasma:

$$V_P\frac{dC_P}{dt} = (Q_H + Q_L + Q_K + Q_M + Q_B)\left(\frac{C_{LU}}{R_{LU}} - C_P\right)$$

For muscle:

$$V_M\frac{dC_M}{dt} = Q_M\left(C_P - \frac{C_M}{R_M}\right)$$

For kidneys:

$$V_K\frac{dC_K}{dt} = Q_K\left(C_P - \frac{C_K}{R_K}\right) - CL_K\frac{C_K}{R_K}$$

For liver:

$$V_L\frac{dC_L}{dt} = (Q_L - Q_G)\left(C_P - \frac{C_L}{R_L}\right) + Q_G\left(\frac{C_G}{R_G} - \frac{C_L}{R_L}\right) + PA_L(F_{UEL}C_{EL} - f_UC_P) - \frac{V_{MAXL}\ C_L/R_L}{K_{ML} + C_L/R_L}$$

For peritoneal cavity:

$$V_{EL}\frac{dC_{EL}}{dt} = PA_L(f_UC_P - f_{UEL}C_{EL})$$

For gastrointestinal tissue:

$$V_G\frac{dC_G}{dt} = Q_G\left(C_P - \frac{C_G}{R_G}\right) + AbR_{GL}$$

For bone marrow:

$$V_B\frac{dC_B}{dt} = Q_B\left(C_P - \frac{C_B}{R_B}\right)$$

For gut lumen:

$$V_{GL}\frac{dC_{GL1}}{dt} = 4rB_3 - \left(4K_f V_{GL} C_{GL1}\right) - AbR_{GL1}$$
$$V_{GL}\frac{dC_{GL2}}{dt} = 4K_f V_{GL}(C_{GL1} - C_{GL2}) - AbR_{GL2}$$
$$V_{GL}\frac{dC_{GL3}}{dt} = 4K_f V_{GL}(C_{GL2} - C_{GL3}) - AbR_{GL3}$$
$$V_{GL}\frac{dC_{GL4}}{dt} = 4K_f V_{GL}(C_{GL3} - C_{GL4}) - AbR_{GL4}$$

The gut absorption rate is given by:

$$AbR_{GLi} = \frac{V_{MAXGL}\, C_{GLi}}{K_{MGL} + C_{GLi}} \quad i = 1, \ldots, 4$$
$$AbR_{GL} = \frac{AbR_{GL1} + AbR_{GL2} + AbR_{GL3} + AbR_{GL4}}{4}$$

The biliary transit rate is given by:

$$\frac{drB_1}{dt} = \frac{\frac{V_{MAXL}\, C_L/R_L}{K_{ML} + C_L/R_L} - rB_1}{\tau}$$
$$\frac{drB_2}{dt} = \frac{rB_1 - rB_2}{\tau}$$
$$\frac{drB_3}{dt} = \frac{rB_2 - rB_3}{\tau}$$

Renal clearance is given by:

$$CL_k = BSA\ 92.0 - (13.8)(LnCp)$$

Nomenclature

- AbR absorption rate, micrograms per minute
- R strong specific binding, micrograms per gram
- C concentration, micrograms per milliliter
- CL_k renal clearance, milliliters per minute
- K_f Michaelis-Menten constant, microgram per milliliter
- $K_{0(t)}$ drug infusion rate, micrograms per minute
- Q plasma flow rate, milliliters per minute
- R tissue-to-plasma equilibrium distribution ratio for linear binding
- r drug transport rate in bile, micrograms per minute
- t time, minutes
- V volume, milliliters
- V_{MAX} maximum rate of saturable process, micrograms per minute
- Wt body weight, kilograms
- ρ nominal residence time in bile transit subcompartments, minutes
- PA permeability area product, milliliters per minute

Subscripts

- G gastrointestinal tissue
- GL gut lumen
- K kidney
- L liver
- M muscle
- P plasma
- B bone marrow
- *1, 2, 3, 4* gut lumen or bile subcompartments
- ELU effusion in the pleural cavity
- EH effusion in the pericardial cavity
- EL effusion in the peritoneal cavity

Model parameters for a 70-kg individual

- $V_{MAXL} = 1000$ μg/min
- $K_{ML} = 5$ μg/ml
- $V_{MAXGL} = 1900$ μg/min
- $K_{MGL} = 200$ μg/ml
- $\rho = 10$
- $R_K = 3.0 + 0.3/\mathrm{C_p}$
- $R_G = 1.0 + 0.1/\mathrm{C_p}$
- $R_L = 3.0 + 0.4/\mathrm{C_p}$
- $K_f = 0.001\ \mathrm{min^{-1}}$ (normal value)
- $R_{LU} = 1.0 + 0.1/\mathrm{C_P}$
- $R_H = 1.0 + 0.1/\mathrm{C_P}$
- $R_B = 1.0 + 0.2/\ \mathrm{CP}$
- $R_M = 0.15$

Volume equal:

- $V_p = 3000$ (plasma)
- $V_K = 280$ (kidney)
- $V_L = 1350$ (liver)
- $V_G = 2100$ (gastrointestinal tissue)
- $V_{GL} = 2100$ (gastrointestinal lumen)
- $V_M = 30{,}000$ (muscle)
- $V_{LU} = 600$ (lung)
- $V_H = 300$ (heart)
- $V_B = 1400$ (bone marrow)
- $V_{ELU} = 12$ ml (normal value)
- $V_{EH} = 40$ ml (normal value)
- $V_{EL} = 20$ ml (normal value)
- $f_U = 0.68$

Organ plasma flow equal:

- $Q_k = 700$ (kidneys)
- $Q_L = 800$ (liver)
- $Q_G = 700$ (gastrointestinal)
- $Q_M = 420$ (muscle)
- $Q = 240$ (heart)
- $Q_B = 72$ (bone marrow)

where Q is in milliliters per minute and V is in milliliters

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