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PharmCalc: Program for the calculation of clinical pharmacokinetic parameters of methotrexate

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Summary. A new program package (PharmCalc) has been developed for the calculation of basic pharmacokinetic parameters (half-time, systemic clearance, renal clearance, AUC, volume of distribution, CSF/serum distribution ratio) of methotrexate (MTX). The program helps in the early recognition of patients at risk for toxicity and calculates the dosage of folinic acid rescue adjusted to the serum levels of MTX. The program offers a standardized and automated evaluation procedure for MTX pharmacokinetics and provides an easy-to-use tool for further research in this field. The concept and routines of the program are described.

Introduction

The applications of different computer programs are becoming increasingly widespread in clinical pharmacology and cancer chemotherapy. However, most of the software developed for such purposes is rather sophisticated, requiring that the user have basic knowledge of clinical pharmacology and experience with computers. The main use of such programs in the retrospective or concurrent analysis of clinical pharmacological data. Such programs as are available commercially are rather expensive, and therefore only major centers can afford them. Nonetheless, these programs, e.g. KINPAK, NONLIN 84/PCNONLIN, AUC-RPP, offer a full palette of clinical-pharmacological analysis and data handling [4, 6, 10], and no doubt they are essential for at least the phase I clinical trials.

Methotrexate is currently the only cytostatic drug for which serum concentrations are monitored routinely, whenever the drug is administered in a dose higher than 1000 mg/m^2. The pharmacokinetic properties of the drug have been widely discussed in the literature (a Medline search under the keywords Methotrexate and Pharmacodynamics in association provided 1883 titles for the period 1966–1986). However, these studies were performed on various bases and with different calculation methods, so that comparison of the results is often difficult. In spite of the numerous examinations, there are still a number of unanswered questions in this field. Although there seems to be general agreement on the critical concentrations in the serum at different times, clinical pharmacological parameters are not directly used in the care of the patient, except in a few places [2]. This could be because the calculations involved in the conventional methods are rather time-consuming and therefore not compatible with daily work on the busy oncology wards. Many oncologists, unless they have a special interest in the subject, are not sufficiently experienced in clinical pharmacokinetics to be fully aware of the importance of these in treatment with high or massive doses of MTX.

The basic motivation for the development of the PharmCalc program was the perceived need for a standardized, automated calculation and evaluation procedure for data obtained after MTX infusions. The main aim of the program is to provide a bedside help for those staff members who are involved in chemotherapy with MTX. Another aim is to provide a research tool, as its output is a standardized, basic set of pharmacokinetic parameters calculated by the use of generally acceptable methods. The projected distribution of the program free of charge by the copyright owner (major drug companies[1]) means that it can be available without extra costs in most places where MTX therapy is performed. This may result in a large body of comparable clinical and pharmacokinetic data as a source for further evaluations.

Methods

The PharmCalc program is written in GWBasic, and this or a compatible BASIC version is available on most personal computers. The options offered in the menu to the program are: calculation of half-life in the postdistributional phase, calculation of systemic clearance, renal clearance, area under the curve/area under the data-curve, apparent volume of distribution, cerebrospinal fluid/serum distribution ratio, and possible modification of the dosage for folinic acid rescue. Data analysis is not based on compartmental model assumptions, but does also allow 2- or 3-compartment model analysis by the use of least-square algorithms.

The menu organization of the program allows calculation of the different parameters separately in time. A number of clinical remarks and recommendations have been built in, according to the actual result and the current time from the end of the MTX infusion.

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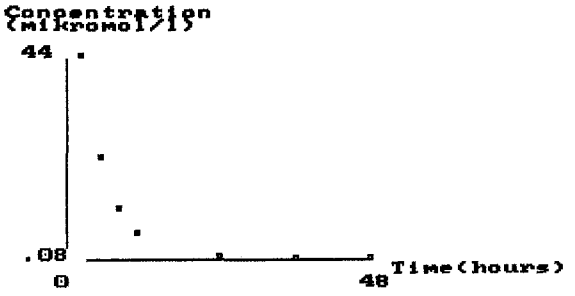
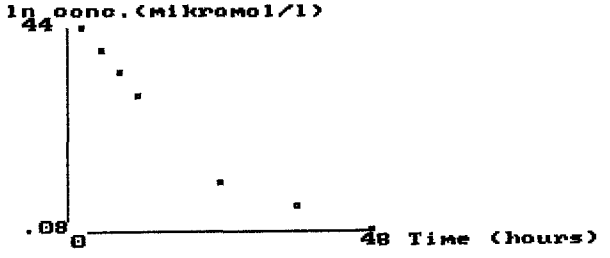
PRINTOUT of Concentration-time input data

Pair #	Concentration data (mikromol/l)	Time data(hours)
1	44.000	2.00
2	22.000	5.00
3	11.000	8.00
4	5.500	11.00
5	0.350	24.00
6	0.170	36.00
7	0.000	48.00





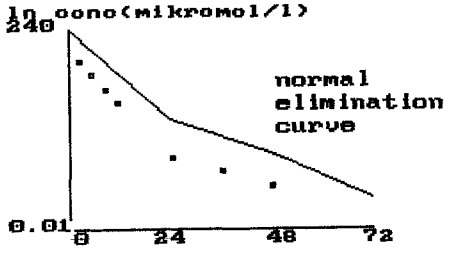


Fig. 1. Graphic printouts of PharmCalc. *Y axis:* concentration or ln concentration of MTX; *X axis:* time (h) from the end of the MTX infusion

Display of the input data on the screen, correction facility and hard copy printout of the input data and the results are standard options in each module of the program. Confidence limits for the input data are built in to decrease the likelihood of incorrect entries. Concentration data can be entered in any of the most commonly used units (mol/l, µmol/l, µg/ml).

The half-life in the postdistributional phase is calculated according to the equation: $t\frac{1}{2} = LN\ 2/Kd$, where Kd is the elimination rate constant of the drug and is calculated as the negative slope of the least-squares regression line of time against the natural logarithm of concentration data.

Calculation of the elimination half-life is possible for all combinations of concentration-time data pairs, as well as a graphic printout and a semilogarithmic plot of the input data (Fig. 1). In versions developed for the pilot study in Norway on childhood acute lymphoblastic leukemia (ALL) and for the BFM-86 protocol for ALL in children, a graph comparing the patient's data and the 90th percentile of the normal elimination curve is included.

The systemic clearance of MTX is calculted according to the equation: R/Css, where R is the zero-order infusion-rate constant and Css is the concentration at steady state.

The program includes two alternative options for calculation of the renal clearance of MTX. If the MTX concentration has been determined solely from the total volume of collected urine and the serum concentrations at the beginning and at the end of the urine collection period are known, the following equation is used: Cl(r) = U*V/dP, where U is the concentration in the urine, V is the urine flow, and dP is the difference between the serum concentrations at the start and at the end of the urine collection period. When the concentration of MTX has been measured in multiple serum and urine samples during the collection period, then the equation Cl(r) = Ump*V/Pmp is used, where Ump and Pmp are the MTX concentrations in the urine and serum, respectively, at the midpoint of the urine collection period. Both values are calculated by the least-squares regression method.

The area under the data curve is calculated by the trapezoidal method: AUC/t(n)-t(n-1)/= Summa/t(n)-t(n-1)/*/C(n)+C(n-1)/:2, where t is the time of sampling and C is the concentration of the drug in the n-th sample. The value of AUC can be calculated and displayed throughout the MTX infusion and for all the combinations of intervals delimited by the samples. Total AUC is also displayed.

The apparent volume of distribution is given by the equation Vd = A(b)/C, where C is the concentration and A(b) is the absolute amount of drug in the body. A(b) at the end of the infusion is calculated according to the equation: $A(b) = (R/Kd)*(1-(0.5)^n)$, where R is the zero-order infusion rate constant, Kd is the elimination-rate constant and n is the duration of the infusion expressed in number of half-lifes.

For the post-infusion period the following equations are applied: if dosage, half-life and AUC are known, then: Vd = Dosage*Half-life/AUC*ln2 or Vd = (R/C)*half-life/ln2, where R is the rate of elimintion, and C is the actual concentration of the drug in the serum. R is calculated as follows: R = Kd*A(b), where Kd is the elimination-rate constant and A(b) is the absolute amount of the drug in the body at the time of the examination.

$A(b) = A(0)*e^{(-Kd*t)}$, where A(0) is the absolute amount of drug in the body at the end of the infusion and t is time since the end of the infusion. The CSF/serum distribution ratio is simply the quotient of the concentrations of MTX in the CSF and serum samples taken at the same time.

The use of all the above equations is based on modern handbooks of clinical pharmacology [5, 7, 8].

Modification of the dosage of folinic acid rescue is based on the equation: 10*C*0.76*bw, where C is the MTX concentration in mg/l [9].

The program compares the input concentration and time data with the 90th percentile of the normal elimination curve and recommends a change to the regular rescue schedule only if the concentration value is higher than acceptable. The rescue modification program has been developed for the doses of 8 g/m^2 and 5 g/m^2 used in the Norwegian pilot study and for the BFM-86 protocol for the treatment of ALL in children, respectively.

Results

Some printouts produced with PharmCalc are reproduced here as examples.

Example 1. A 10-year-old boy received treatment with infusion of 8000 mg/m^2 methotrexate over 24 h as a part of the therapy protocol for ALL. The following data were available in connection with the treatment:

Total dose: 8000 mg/m^2 (1600 mg/m^2 during 1 h to 6400 mg/m^2 over 23 h). Steady-state concentration in serum: 1.3e−4 mol/l. CSF concentration at the end of the infusion: 1.4e−6 mol/l. Serum concentration 24 h after the end of the infusion: 2.1e−6 mol/l. Serum concentration 48 h after the end of the infusion: 3.5e−7 mol/l. Urine was collected for 24 h from the end of the MTX infusion. Total volume of collected urine: 3200 ml. MTX concentration in the collected urine: 3.1e−3 mol/l. MTX concentration in the urine sample taken 1 h after the start of the urine collection: 8.8e−3 mol/l; 8 h after: 5.4e−4 mol/l; 22 h after: 4.1e−6 mol/l. Body surface area of the patient: 1.25 m^2, weight: 35 kg. The PharmCalc program was used for calculation of different pharmacokinetic parameters of the above treatment, and the following results and printouts were obtained:

PharmCalc Prg.:Calculation of Half-time of Methotrexate in serum

# #

Patient: HL
Date of treatment: 16. 10. 86.
Comments: ALL in remission. Normal course.

PRINTOUT of Concentration-time input data

Pair #	Concentration data (mol/l)	Time data (hours)
1	0.000130000	0.00
2	0.000002100	24.00
3	0.000000350	48.00

# #

Half time of MTX for the period between samples No. 1−2: 4.03 hours.

# #

# #

Half time of MTX for the period between samples No. 2−3: 9.28 hours.

# #

PharmCalc Prg.Calculation of systemic clearence of Methotrexate

# #

Patient: HL
Date of treatment: 16. 10. 86.
Comments: No comments.

# #

Systemic clearence of MTX is 78.50 ml/min/sqmeter

# #

PharmCalc Prg.Calculation of renal clearence of MTX

# #

Patient: HL
Date of treatment: 16. 10. 86.
Comments: Fluid intake 3000 ml/sqmeter. Urine ph > 7.5

PRINTOUT of the data # # # # # # #

Body surface area: 1.25 sqmeter
Duration of the urine collection: 24 hours
Total volume of the collected urine: 3200 ml
MTX concentration in the collected urine: .0031 mol/l
Serum MTX conc. at the beginning of urine collection: .00013 mol/l
Serum MTX conc. at the end of the urine collection: .0000021 mol/l

# #

# #

Renal clearence of MTX: 43.08922 ml/min/sqmeter

# #

PharmCalc Prg.Calculation of renal clearence of MTX

# #

Patient: HL
Date of treatment: 16. 10. 86.
Comments: No comments.

PRINTOUT of the input data # # # # # # #

Body surface area (sqmeter): 1.25
Duration of the urine collection (hours): 24
Volume of the collected urine (ml): 3200

(u) concentration-time pair #	concentration (mol/l)	Time (hours)
1	0.00880000	1.00
2	0.00054000	8.00
3	0.00000410	22.00

(s) concentration-time pair #	concentration (mol/l)	Time (hours)
1	0.00013000	0.00
2	0.00000210	24.00

# #

Renal clearence of MTX is 48.62886 ml/min/sqmeter for the examined period

# #

PharmCalc Prg. Calculation of Area Under the Curve for MTX infusions

# #

Patient: HL
Date of treatment: 16. 10. 86.
Comments: No comments

# #

Area Under the Curve during the infusion of MTX is 85.07117 mg/ml * min.

Area Under the Curve between the end of the MTX infusion and the first sampling is 43.2227 mg/ml * min.

Area under the curve for the period between 24−48 hours after the end of MTX infusion is: .8016322 mg/ml * min.

Area Under the Curve from the start of the infusion to 48 hours after the end of the infusion is 129.0955 mg/ml * min.

PharmCalc Prg.Calculation of Apparent Volume of Distribution of MTX

# #

No comments.
Patient: HL
Date of treatment: 16. 10. 86.
Comments: No comments.

# #

Apparent Volume of steady-state distribution is: 26.86648 l/sqmeter.

Coefficient of Vd is .9595169 l/kg.

Absolute amount of MIX in the body at the end of the infusion is 1587.196 mg/sqmeter.

# #

PharmCalc Prg.Calculation of Apparent Volume of Distribution of MTX
# #
No comments.
Patient: HL
Date of treatment: 16. 10. 86.
Comments: No comments.
# #

Volume of distribution of MTX 24 hours after the end of the infusion is 26.83904 l/sqmeter
Coeff.Vd is .9585371 l/kg

Absolute amount of MTX in the body at the end of the infusion was 1587.196 mg/sqmeter.

Absolute amount of MTX in the body 24 hours after the end of the infusion is 25.61314 mg/sqmeter.

# #
# #

Volume of distribution of MTX 48 hours after the end of the infusion is 26.84256 l/sqmeter
Coeff.Vd is .9586626 l/kg

Absolute amount of MTX in the body at the end of the infusion was 1587.196 mg/sqmeter.

Absolute amount of MTX in the body 48 hours after the end of the infusion is 4.269416 mg/sqmeter.

# #

PharmCalc Prg. Calculation of CSF/serum distribution ratio of MTX
# #
Patient: HL
Date of treatment: 16. 10. 86.
Comments: No comments.
# #
0.011
is the CSF/serum distribution ratio 24
hours after the start of the MTX infusion
# #

Example 2. Each option of the menu of PharmCalc versions 1.1 and 1.2 (developed for the Norwegian pilot study and for the BFM-86 study) contains notes to call attention to delayed drug elimination or risk of toxicity. The following example demonstrates the kind of printout produced when systemic clearance is less than 30 ml min^{-1} m^{-2}.

PharmCalc Prg.Calculation of systemic clearance of methotrexate
# #
Patient: GG
Date of treatment: XX
Comments: vomiting during the infusion
PRINTOUT of the INPUT DATA # # # # # #
Steady state concentration: .00026 mol/l
MTX Dose: 5000 mg/sqmeter
Duration of the MTX infusion: 23 hours
A loading dose of 500 mg/sqmeter was given
# #
Systemic clearance of MTX is 27.60 ml/min/sqmeter.
The patient is at high risk for delayed drug elimination! Consider the following measures:

1. Control renal function!
2. Control previous hydration (volume and pH of the urine). Continue i.v. hydration (3000 ml/sqmeter).
3. Check: Was the serum sample taken appropriately?
4. Check: Was the determination of the concentration correct?
5. Take a serum sample 4 hours later and:
6. Calculate half-time from the values. If it is longer than 3.5 hours, consider the modification of the rescue dose!
7. Observe the patient carefully in the following 120 hours, even if no obvious toxicity would be manifested!

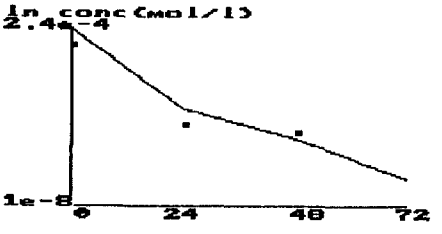
# #

There are three different types of printout when the dosage of folinic acid is calculated, depending on the time the sample has been taken.

Example 3. This example demonstrates that the calculation of half-time with PharmCalc can predict increased risk for toxicity at least 24 h earlier than if one considers only the serum levels.

PRINTOUT of Concentration-time input data

Pair #	Concentration data (mol/l)	Time data(hours)
1	0.000090000	0.00
2	0.000000950	24.00
3	0.000000600	48.00



# #
Half time of MTX for the period between samples No. 1–2: 3.65 hours.
# #

The patient is at high risk for delayed drug elimination!
Check MTX levels and renal function more frequently in the following period!
# #

# #
Half time of MTX for the period between samples No. 2–3: 36.19 hours.
# #

The patient is at high risk for delayed drug elimination!
Control laboratory parameters and MTX levels frequently! Consider the modification of the rescue dose!
# #

Example 4. At 44 h after the end of an MTX infusion (dose: 5000 mg/m^2 per 24 h) to a child with ALL (BSA 1.25 m^2, BW 35 kg) an MTX concentration of 3e–7 mol/l was found in serum (this value is in the normal range of disappearance). The following printout was obtained:

# #

Continue the regular schedule of rescue until serum MTX concentration falls below 5e-8 mol/l.

# #

Example 5: At 28 h after the end of a MTX infusion (dose: 5000 mg/m^2 per 24 h) to a child with ALL (BSA 1.25 m^2, BW 35 kg) the serum MTX concentration was measured as 2e−6 mol/l. The following printout was given by PharmCalc:

PharmCalc: Rescue modification program
# #
Patient: NN
Date: 12. 12. 86.
Time: 18 pm
Comments: 4 vomiting during the last 6 hours!
# #
Recommended daily dose of folinic acid: 967.0 mg.
(773.6 mg/sqmeter/die.)
Give 120.9 mg i.v. in every third hour.
(96.7 mg/sqmeter)
Check MTX concentration in 6 hours. Then, if it is within the normal range of disappearance, return to the regular schedule of folinic acid administration, and continue until MTX level falls below 5e-8 mol/l.
If MTX concentration is elevated in 6 hours too, calculate the dosage of the rescue again!
# #
NOTE: This is NOT a VALID document without the signature of the responsible physician!

Example 6. At 8 h after the end of a MTX infusion (5000 mg/m^2 per 24 h) the serum MTX concentration was 5e−5 mol/l. The following recommendation was given by the program:

# #
Such a high MTX concentration can be rescued (if it can be at all) only by very high doses of folinic acid (theoretic dose: 302.2 mg every third hour).
Control renal function. If it is normal, continue overhydration and alkalinisation of urine. Control MTX concentration again in 4 hours, and calculate the dose of rescue then too.
If renal function is impaired, start with the above dose immediately!
# #

Discussion

The PharmCalc program is different from other available packages because it was developed to focus on the pharmacokinetics of MTX. This allows a large number of relevant clinical data and recommendations. It takes account of the routine of sampling in the practice and the information it provides is less sophisticated than that obtained with other programs but still acceptable in view of the relatively small samples. The documentation provided by the hard copy printouts of the program could be a useful reference source in comparative pharmacokinetic studies of MTX. Individual pharmacokinetic parameters have been shown to have prognostic importance in childhood ALL. Further confirmation of these results [1, 3] requires the analysis of data on a widespread basis. The implications of such observations for treatment may result in an important new field of application for the program.

With PharmCalc it becomes obvious that in some cases the use of pharmacokinetic parameters makes it possible to predict increased risk of delayed drug elimination or toxicity earlier than consideration of the concentration data alone.

The structure of the program, with separate files for each parameter – while it reduces the performance speed – could help to make the calculations clearer. (However, a program module for the quick calculation of the parameters is also included, to ease the use of the program for retrospective analysis). Even the act of listing the data necessary for calculation of the different parameters may help in the planning of studies on the pharmacokinetics of MTX.

The program can be run in demonstrations for educational purposes, showing the effect of alterations of the input data on the results. The program is supplemented with a Manual, which provides detailed information on the use of the program and a list of the definitions and equations applied. The planned distribution free of charge means that even small departments can have the benefit of the program.

The authors are convinced that the individual pharmacokinetics of the cytostatic drugs must be considered more thoroughly in the planning and implementation of cancer treatment programs. The availability of pharmacological data on MTX at the bedside with the help of a user-friendly computer program is believed to be a step in this direction.

References

1. Borsi JD, Revesz T, Schuler D (1987) Prognostic importance of systemic clearence of methotrexate in childhood acute lymphoblastic leukemia. Cancer Chemother Pharmacol 19: 261
2. Evans WE, Stewart CF, Chen CH, Crom WR, Bowman WP, Abramowitch M, Simone JV (1979) Pharmacokinetic monitoring of high-dose MTX. Early recognition of high-risk patients. Cancer Chemother Pharmacol 3: 161
3. Evans WE, Pratt CB, Taylor RH (1984) Methotrexate systemic clearance influences probability of relapse in children with standard risk acute lymphocytic leukemia. Lancet I: 359
4. Kaufman B (1986) KINPAK: a program for standardized pharmacokinetic analysis. Methods Find Exp Clin Pharmacol 8: 615
5. Melmon KL, Morelli HF (1978) Clinical pharmacology: basic principles in therapeutics, 2nd edn. Macmillan, New York
6. Ritschel WA (1986) AUC-RPP: BASIC computer program for compartment model-independent pharmacokinetic analysis. Methods Find Exp Clin Pharmacol 8: 633
7. Ritschel WA (1983) Graphic approach to clinical pharmacokinetics. Prous, Barcelona
8. Rowland M, Tozer TN (1980) Clinical pharmacokinetics: concepts and applications. Lea and Febiger, Philadelphia
9. Sauer HJ, Schalhorn A, Wilmans W (1980) Rationale Grundlagen und Praxis des Citrovorumfactor-Schutzes nach hochdosierter Methotrexate-Therapie. Onkologie 3: 64
10. Weiner DL (1986) NONLIN84/PCNONLIN: software for the statistical analysis of nonlinear models. Methods Find Exp Clin Pharmacol 8: 625

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