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Computer-assisted Customized Antimicrobial Dosages

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The use of a computer-based consultation program to customize dosage regimens of antimicrobials for patients with meningitis or bacteremia is described.

Using clinical and laboratory information entered by the user, the program determines causative organisms, recommends therapeutic regimens, and generates a graph depicting the expected blood level of each drug as a function of time. During therapy selection, the program considers the site of infection, the susceptibility of the organism to antibiotics, and the patient's clinical status and drug history.

Individualized pharmacokinetic values allow for dosage adjustments in renal failure and estimation of blood levels. If renal impairment is present, dosage regimens for drugs excreted by the kidneys are adjusted to assure the desired steady-state blood levels. To help in selection of the optimal regimen, estimated blood levels for each regimen are graphed along with the minimum inhibitory concentration for the organism and the toxic level of the drug.

A built-in knowledge base in conjunction with patient-specific information enables the computer program to determine appropriate treatment specific to a patient's age, renal function, and prior drug reactions.

Index terms: Antibiotics; Anti-infectives; Automation, data processing, computers; Blood levels; Dosage schedules; Methodology; Pharmacokinetics; Rational therapy; Resistance

This report describes the use of a computer-based consultation program, called Mycin, to customize dosage regimens of antimicrobials for patients with meningitis or bacteremia. The Mycin program, which is operational within a research setting, makes therapeutic decisions using its built-in knowledge about infectious diseases together with clinical and laboratory data about a patient.[a] The program's diagnostic capabilities, design, and decision-making mechanism have been described in detail elsewhere.[1,2]

The processes that the program uses in its selection of antimicrobials and subsequent dosage calculations have been refined to take into account more patient- and drug-specific factors. In the past, all dosage recommendations were based on normal adult doses. Now, the program is able to recommend optimal therapy by considering information about the patient, such as age and renal function, as well as pharmacokinetic variables of drugs. The addition of the ability to customize doses as described herein expands the capabilities of the consultation program.

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Antimicrobial Selection

In response to questions generated by the program, the health care professional who is seeking a consultation provides Mycin with clinical and laboratory data about the patient. Mycin uses this information to establish the presence of an infection and the identity of the infecting organism(s) (Figure 1). If positive laboratory identification is not available, Mycin ranks possible pathogens in order of likelihood. Antimicrobials are then chosen that will effectively treat all likely organisms.

To select drugs to which the organisms are usually sensitive, Mycin uses susceptibility data from the Stanford bacteriology laboratory. The program also considers the fact that the patient's previous antimicrobial treatment may influence an organism's susceptibility. Mycin will disfavor a drug that the patient was receiving at the time a positive culture was taken.

Drug-specific factors are considered before therapy is chosen. Some drugs, such as the cephalosporins, are not recommended for patients with meningitis because they do not adequately cross the blood-brain barrier and they may

Figure 1. Consultation. Mycin makes a diagnosis using a built-in knowledge base and clinical and laboratory data about the patient. Each infection is listed followed by the possible causative organisms in order of likelihood. The health professional's responses are in upper-case letters and follow a double asterisk (**); all other text is generated by the computer.

```
Please enter information about the patient.
     Name              Age      Sex      Race
1) ** JOHN JONES       34       MALE     CAUCASIAN
     .
     .
     .
Please enter the results of pending cultures in the following table.
     site              date          smear
                       collected     examined?
6) ** CSF              9-NOV-79      YES
     stain of          morphology
     smear
7) ** GRAMNEG          ROD
     .
     .
     .
25) Is John Jones immunosuppressed (e.g., corticosteroid therapy, cytotoxic
     drug therapy, radiation therapy, leukemia, lymphoma)?
** YES
26) Has John Jones received corticosteroids just prior to or during this in-
     fection?
** NO
     .
     .
     .
My therapy recommendations will be designed to treat for organisms that
either are very likely or, although less likely, would have a significant effect on
therapy selection if they were present. It is important to cover for the following
probable infection(s) and associated organism(s):

INFECTION-1 is MENINGITIS

  (ITEM-1) E.COLI [ORGANISM-1]
  (ITEM-2) PSEUDOMONAS-AERUGINOSA [ORGANISM-1]
  (ITEM-3) KLEBSIELLA-PNEUMONIAE [ORGANISM-1]
     .
     .
     .
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lead to the development of resistance.[3] One antimicrobial may be selected over another similar drug because it causes fewer or less severe side effects. For example, nafcillin sodium is often preferred over methicillin sodium for treatment of staphylococcal infections because of the reported interstitial nephritis associated with methicillin.[4] Mycin's knowledge base is continually updated to include new indications or adverse reactions as they are reported in the medical literature.

Several patient-specific factors may further limit the list of acceptable antimicrobials. Tetracycline, for example, is not recommended for children,[5] or pregnant[6] or breast-feeding[7] women. Also, prior adverse reactions to antimicrobials are extremely important considerations that are not overlooked by Mycin.

Customizing Doses

Efficacious treatment of infectious diseases begins with selection of the antimicrobial; however, it is likely that the patient will not be cured unless the dose and the route of administration of the drug are appropriate. Mycin takes into account the site of the infection, the age of the patient, and the patient's renal status in determining the dose regimen for each drug.

The age of the patient is an important consideration when selecting the dose of an antimicrobial. The half-life of some drugs may be longer in neonates than in adults because of the immaturity of their microsomal enzyme system and kidneys.[8] Therefore, the dose of these drugs, in milligram-per-kilogram amounts, should be lower in neonates than in adults. On the other hand, some antimicrobials, such as gentamicin sulfate, may require a higher dose in children than in adults, possibly because of a larger volume of distribution.[9] When appropriate, therefore, Mycin uses different calculations for determining doses for neonates, infants, children, and adults.

Most antimicrobials are fully or partially excreted by the kidneys; for this reason, it is necessary to consider the patient's renal function to determine a safe and effective dosage regimen. The program uses the patient's creatinine clearance as an indicator of the degree of renal impairment. Doses are adjusted in patients over six months of age if the creatinine clearance falls below 80 ml/min/1.73 m^2 and if over 15% of the drug is excreted unchanged in the urine. In children between one week and six months of age, the dose is changed if the creatinine clearance is less than 60 ml/min/1.73 m^2. A creatinine clearance of 30 ml/min/1.73 m^2 indicates renal impairment in infants[b] between one day and one week old.[10] Because of the passage of maternal creatinine into the infant serum at birth, no estimate of renal function is attempted if the newborn is less than one day old. For infants aged less than six months, Mycin warns the user of the large degree of possible error in the estimated doses because of the changing renal function and the poor relationship between glomerular filtration rate and body surface area.[11]

When the creatinine clearance of an adult patient is not known, it is estimated from the age, sex, weight, and serum creatinine.[12] For children less then 12 years of age, the height and serum creatinine are used to estimate the creatinine clearance.[13] If two consecutive serum creatinines indicate rapidly changing renal function a printed warning recommends repeating the assessment of the degree of impairment before an accurate dosage regimen can be determined. The creatinine clearance is adjusted to average body surface area before the program calculates a dose[14] (Figure 2).

Should the creatinine clearance indicate renal failure, Mycin will calculate doses based on the first-order pharmacokinetic properties of the antimicrobials (see Table 1) and the patient's creatinine clearance. A description of the formulas used can be found in the Appendix.

The program provides three different methods of adjusting antimicrobial dose. One method changes the dose, another alters the dosing interval, while the third calculates a new dose given any interval. This last option allows the health professional to select an interval that is convenient for the nurses to follow and a dose of the drug that is a reasonable volume to administer. A loading dose is calculated for each regimen so an effective blood level can be reached as soon as possible. The dose is provided both in a milligram-per-kilogram amount and as the number of milliliters, capsules, or tablets required (Figure 3).

Figure 2. Renal function. The patient's creatinine clearance is used as an indicator of the degree of renal function. When the creatinine clearance is not known, it is estimated from the age, sex, weight, and serum creatinine of the patient and adjusted to average body surface area before the dose is calculated.

```
•
•
•
47) Does John Jones have a clinically significant allergic reaction to any
    antimicrobial agent?
** NO
48) Do you have reason to suspect that John Jones may have impaired renal
    function?
** YES
49) What is the most recent creatinine clearance in ml/min which you feel
    is a true representation of John Jones's renal function?
** UNKNOWN
50) What is the most recent serum creatinine of John Jones (in mg/100
    ml)?
** 1.9
51) What is the previous serum creatinine of John Jones (in mg/100 ml)?
** 1.8
52) Number of days between John Jones's two most recent serum creati-
    nines:
** 2
53) John Jones's weight in kilograms (or (number) POUNDS):
** 70
54) John Jones's height in centimeters (or (number) INCHES):
** 175
Estimated body surface area is 1.9 sq. meters.
Dosage adjustments will be based on the calculated creatinine clearance of 42.7
    ml/min/1.73 sq. meters (adjusted to average body surface area.)
•
•
•
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Table 1. Antimicrobials Recommended by Mycin and the Pharmacokinetic Variables of the Drugs Whose Doses Are Adjusted in Renal Failure

Drug Name	Route of Administration	"a" Nonrenal Elimination Rate Fraction (hr^{-1})	"b" Slope of K vs. CCl	"1e" Urinary Elimination Fraction (24 hr)	Volume of Distribution[a] (% kg bodyweight)	
Amikacin[21-23] [b]	IM	0.057	0.0031	0.94	21	(50 for age 4 days)
Amphotericin B			Not adjusted			
Ampicillin[24]	IV	0.059	0.014	0.92	26	
Carbenicillin[25,26]	IV	0.06	0.005	0.99	18.4	
Cefazolin[27-29]	IV	0.022	0.0028	0.95	13.5	(16.5 for CCr 25 ml/min)
Cephalothin[30,31]	IV	0.40	0.0097	0.69 (in 6 hr)	26	
Chloramphenicol			Not adjusted			
Clindamycin			Not adjusted			
Doxycycline			Not adjusted			
Erythromycin			Not adjusted			
Ethambutal[32]	PO			0.61		
Flucytosine[33,34] [c]	PO	0.0067	0.0026	0.90	88	
Gentamicin[9,35]	IM/IV	0.007	0.0022	0.96	28	(42 for age 5 yr)
Isoniazid[36,37]			Not adjusted			
Kanamycin[38-40] [c]	IM	0.020	0.0029	0.94	22	(50 for age 6 mo)
Methicillin[41]	IV			0.88	43	
Nafcillin[42]	IV	0.058	0.005	0.38	38	
Penicillin G[42-44] [c]	IV	0.12	0.0087	0.80	16	
Rifampin[45]	PO			0.19		
Streptomycin[46,47]	IV	0.059	0.9924	0.80	26	
Tetracycline			Not recommended in renal failure			
Ticarcillin[26,48] [c]	IV	0.04	0.0054	0.86	20	
Tobramycin[49-51]	IV	0.028	0.0025	0.90	31	(24 for age 5 yr)
Vancomycin[52,53] [c]	IV	0.0046	0.001	0.90	47	

[a] Steady-state values, when available (assuming average body weight of 70 kg).
[b] Superscript numbers refer to reference list.
[c] Values for columns marked a and b are estimated from half-life information.

Figure 3. Dose regimens. Mycin provides three different dose regimens for each antimicrobial whose dose must be adjusted in renal failure. One method changes the dose, another alters the interval, while the third calculates a new dose given any interval.

[REC-1] My preferred therapy recommendation is:
Give the following in combination:
1) CHLORAMPHENICOL
Give: 1.75 g (17.6 ml) q6h IV [calculated on basis of 25 mg/kg]
2) GENTAMICIN
After a loading dose of: 112 mg (2.8 ml, 80 mg/2 ml ampule) IV [calculated on basis of 1.6 mg/kg],
give: 70 mg (1.8 ml, 80 mg/2 ml ampule) q8h IV [calculated on basis of 1.0 mg/kg] plus consider giving 5 mg q24h intrathecal
Or, after a loading dose of: 140 mg (3.6 ml, 80 mg/2 ml ampule) IV [calculated on basis of 2.0 mg/kg],
give: 119 mg (3.0 ml, 80 mg/2 ml ampule) q14h IV [calculated on basis of 1.7 mg/kg] plus consider giving 5 mg q24h intrathecal.
[normal dose is 1.7 mg/kg q8h IV]

Would you like to enter a new dosing interval?
** YES

Please enter the number of hours.
** 12

After a loading dose of: 133 mg (3.4 ml, 80 mg/2 ml ampule) IV [calculated on basis of 1.9 mg/kg],
give: 105 mg (2.6 ml, 80 mg/2 ml ampule) q12h IV [calculated on basis of 1.4 mg/kg] plus consider giving 5 mg q24h intrathecal

If a patient's renal function changes during therapy, the prescriber can obtain a new dosage recommendation without repeating the entire infectious disease consultation. A shortened version of the consultation will recalculate the doses on the basis of the patient's current renal function. The program will request only that information necessary for determining the new doses, such as the most recent creatinine clearance (or serum creatinine).

Selection of Dosage Regimen

Although it is widely debated which dosage regimen is best, it is generally recognized that the blood level of antimicrobials used to treat bacteremias should exceed the minimum inhibitory concentration (MIC) while remaining below toxic levels. The health professional must decide between allowing the drug level to fluctuate above and below the MIC or maintaining the drug level above the MIC through more frequent dosing. This decision is based on a variety of factors including the organism's identity and the drug under consideration. To aid the prescriber in selecting the most appropriate regimen, Mycin generates a graph for

each regimen showing the steady-state blood levels over time (Figure 4). The MIC of the organism and the toxic level of the drug (when they are available) are also included on the graph. The graph provides a rough estimate of the blood levels and the time of peak concentration in the patient.

The blood level at time t is calculated from the equation[15]

$$\text{Blood Level} = \frac{FDk_a}{Vd(k_a - K)}\left(\frac{e^{-Kt}}{1 - e^{-K\tau}} - \frac{e^{-k_a t}}{e^{-k_a \tau}}\right)$$

The dose (D) and the dosing interval (τ) vary for each regimen. The fraction of the dose absorbed (F) depends on the route of drug administration. The elimination rate constant (K) of the drug is determined based on the degree of renal impairment in the patient. Since recent studies have shown that the volume of distribution (Vd) of some drugs depends on the age or renal status of the patient, Mycin considers these factors, as well as weight, when calculating the volume of distribution. Information about absorption rate constants (k_a) for most drugs is limited; therefore, the absorption rate was estimated from a nomogram using the time of peak concentration and the elimination rate of the drug in patients with normal renal function.[16]

The graph is provided for the prescriber to improve the initial selection of a drug regimen. It is not designed to replace the practice of measuring blood levels in the patient; monitoring blood levels whenever they are available is strongly recommended.

Explanation of Recommendations

At the conclusion of the consultation, the health professional can ask Mycin simple questions to obtain assurance that the diagnosis and treatment are reasonable. These questions may be specific, about the current consultation, or they may be general, regarding any of the system's knowledge. A justification for the therapy selection is provided that includes the reasons for selecting one particular antimicrobial instead of another. Also available is an explanation of the calculations used to decide on a dose (Figure 5). The health professional can ask to see relevant parts of

Figure 4. Graph. To aid the prescriber in the selection of the most appropriate regimen, Mycin generates a graph showing the estimated steady-state blood levels over time for each regimen. The graph is presented exactly as it is printed by the computer.

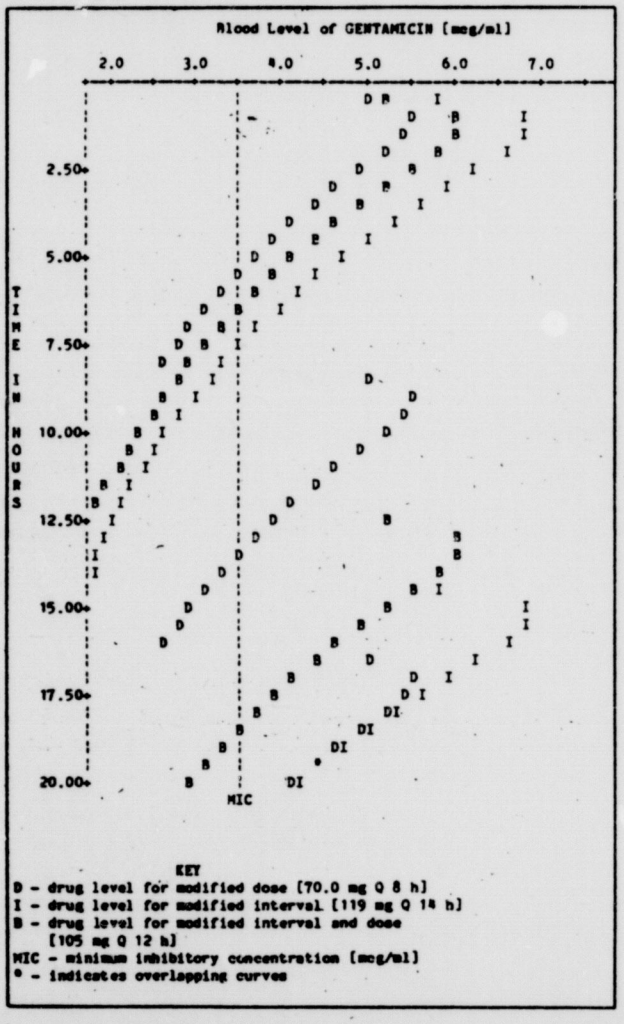

Figure 5. Explanation. The health professional can ask Mycin questions to obtain assurance that the diagnosis, treatment, and dose are reasonable.

** HOW DID YOU CALCULATE THE DOSE FOR GENTAMICIN?

When GENTAMICIN is given for MENINGITIS, the recommended dosage is: if age is >2 yrs then 1.7 mg/kg q8h IV plus consider giving 5 mg q24h IT, else 2.3 mg/kg q8h IV plus consider giving 2.5–4 mg/day IT.

The normal dose for John Jones is: 119 mg (3.0 ml, 80 mg/2 ml ampule) q8h IV [calculated on the basis of 1.7 mg/kg] plus consider giving 5 mg q24h IT

GENTAMICIN is excreted by the kidneys, so its dosage must be modified in renal failure.

The following table shows how the patient's renal function was determined:

Identifier	Value	Definition
SCR1	1.9	The most recent serum creatinine (mg/100 ml)
SCR2	1.8	The previous serum creatinine (mg/100 ml)
CCr(f)	42.7	Estimated creatinine clearance, adjusted for normal body surface area (ml/min/1.73 sq. meters)
CCr(n)	100	The average normal creatinine clearance for John Jones's age group
CCr-(min)	80	The minimum normal creatinine clearance for John Jones's age group

Since CCr(f) < CCr(min), John Jones has renal impairment.

To modify the dosage of GENTAMICIN, the following pharmacokinetic parameters were used:

Identifier	Value	Definition
a	.007	The fraction hourly loss of a drug due to non-renal processes
b	.0022	The slope of the plot of the elimination rate constant of a drug versus the patient's creatinine clearance
Q	.57	The drug's elimination rate fraction: elimination rate of the drug as a fraction of the drug's 'normal' elimination rate.

Q was calculated using the formula:

$$Q = [a + b * CCr(f)]/[a + b * CCr(n)]$$

My first dosage recommendation decreased the amount of GENTAMICIN and left the dosing interval unchanged. The new amount was calculated by multiplying the old amount by Q.

The second recommendation increased the dosing interval and left the amount of GENTAMICIN unchanged. The new interval was calculated by dividing the old interval by Q.

Mycin's knowledge base, including justification and literature references (Figure 6).

Summary

Mycin is able to customize therapy recommendations by using its built-in knowledge base in conjunction with patient-specific information. The large knowledge base contains facts about organism susceptibilities to drugs, epidemiology of infectious diseases, and pharmacokinetics and toxicity of various antimicrobials. This knowledge enables the program to determine appropriate treatment that is specific to a patient's age, renal function, and prior drug reactions.

Mycin's explanation capability allows health care professionals to analyze the process by which the program arrived at a therapy recommendation. This capability also may play an educational role by reminding the health professional of critical factors to consider when prescribing therapy for other patients.

The accuracy of Mycin's diagnosis and antimicrobial selection has been formally evaluated[17,18] and its recommendations have been shown to be comparable to those of infectious disease experts. The dosage calculations described in this report remain to be evaluated thoroughly before the program can be used widely outside a research setting.

Conclusion

Increasing evidence of inappropriate antimicrobial therapy indicates a need for assistance in the expanding area of infectious disease therapy selection.[19,20] There is a recognized need for continuing education as well as for computational assistance with dosage adjustments in renal failure. This is not surprising when one recognizes all of the factors that must be considered in a therapy decision. One response to the problem of antimicrobial misuse is to increase the availability of infectious diseases expert consultations. A consultation not only provides assistance in determining the appropriate therapy for the patient under consideration but also is an educational experience for the health professional requesting the consultation. Computer-based consultation programs, such as Mycin, can provide medical professionals with clinical advice and educational information when human consultants are not available.

Figure 6. Justification. The person obtaining a Mycin consultation can see the decision rules that the program uses, including justification and literature references.

```
** HOW DO YOU DETERMINE BODY SURFACE AREA?
RULE 104
[This rule applies to any patient, and is tried in order to find out about the patient's
    estimated body surface area]
If: 1) The weight of the patient is known, and 2) The height of the patient is
    known
Then: Use Boyd's algorithm to calculate body surface area from weight and height
    [Boyd, E. The Growth of the Surface Area of the Human Body, 1935 pp
    1-133.]
Author: Wraith
Justification: A comparative evaluation with statistical analysis of the Boyd
    method with the DuBois formula demonstrated that the Boyd formula is
    more accurate for abnormal body types. [Sendray J et al., Determination
    of human body surface area from height and weight, Applied Physiology,
    7(1):1-12, July 1954.]
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[a] Mycin is written in the Interlisp language and runs on a DEC PDP-10 computer. The program uses techniques from the branch of computer science known as Artificial Intelligence to perform the complex reasoning tasks that are involved in medical diagnosis.

[b] The creatinine clearance in infants is less than that in adults because of lower glomerular membrane permeability, smaller glomerular filtering surface, lower perfusion pressure, and lower renal plasma flow.

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Appendix

Equations for Calculating Dosage Regimens

Adjustments to antimicrobial doses are directly related to the elimination rate fraction, which describes the elimination rate of the drug in a patient as a fraction of its 'normal' elimination rate constant.

The following abbreviations are used in the equations for calculation of the dose regimens:

- Q = Elimination rate fraction;
- K(f) = Fraction of the drug eliminated per hour in the patient with renal failure;
- K(n) = Fraction of the drug eliminated per hour in 'normal' subjects;
- CCr(f) = Creatinine clearance in the patient with renal failure (ml/min/1.73 m^2);
- CCr(n) = Age-related creatinine clearance in 'normal' subjects. If age is >6 months old, value is 100 ml/min/1.73 m^2; 1 week < age < 6 months, 80 ml/min/1.73 m^2; 1 day < age < 1 week, 45 ml/min/1.73 m^2;
- a = Fraction of the drug eliminated per hour by nonrenal means;
- b = Slope of K vs. CCr line;
- fe = Fraction excreted unchanged in the urine;
- D(f) = Maintenance dose of the drug for the patient in renal failure;
- D(n) = Maintenance dose of the drug in 'normal' subjects;
- LD = Loading dose;
- τ(f) = Dosing interval for the patient in renal failure;
- τ(n) = Dosing interval in patients with normal renal function;
- τ(s) = Selected dosing interval.

The elimination rate of the drug is linearly related to the endogenous creatinine clearance as shown in the following formula.[15,54,55]

$$Q = K(f)/K(n) = (a + b\ CCr(f))/(a + b\ CCr(n))$$

The pharmacokinetic variables used in the formula above were extracted from literature references.[21–53] For some antimicrobials, it was necessary to estimate the values of variables a, b, and K(n) from half-life information. This was done using the relationship that exists between K and the creatinine clearance, based upon normal and anuric half-life values.[54]

The following formula is used to determine Q for drugs for which the values of a or b could not be determined[56,57]:

$$Q = K(f)/K(n) = 1 - fe[1 - (CCr(f)/CCr(n))]$$

Using the elimination rate fraction, the dosage regimen is adjusted in three ways:

(1) the dose (D) can be decreased while the dosing interval (τ) remains the same

$$D(f) = D(n) \times Q;$$

(2) The dosing interval can increase while the dose remains the same

$$\tau(f) = \tau(n)/Q; \text{ or}$$

(3) The user can select a more convenient dosing interval

$$D(f) = D(n) \times Q \times (\tau(s)/\tau(n))$$

Finally, the loading dose is calculated depending on the dose regimen, in the following ways[56,58]:

(1) If the dose is changed,

$$LD = D(f)/(1 - e^{-K(f)\tau(n)})$$

(2) If the dosing interval is changed,

$$LD = D(n)/(1 - e^{-K(f)\tau(f)})$$

(3) If both the dose and the interval are changed,

$$LD = D(f)/(1 - e^{-K(f)\tau(f)})$$

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Individualizing Phenytoin Dosage Regimens Using a Programmable Calculator

Philip K. Ng

A programmable calculator procedure for the determination of individualized phenytoin dosage regimens is described.

The calculator is programmed based on a one-compartment, open model using the Michaelis-Menten equation. A detailed description of the programs and user instructions are presented. The programs allow calculation of oral dosage regimens and steady-state phenytoin levels. The first two programs require a given dose and one corresponding steady-state minimum concentration point to estimate a dosage regimen and steady-state serum level. The second two programs, which provide a more accurate prediction of dosage regimen and steady-state serum levels, require two dose and steady-state minimum concentration points.

The calculator programs provide a rapid and reliable means of estimating a patient's phenytoin dosage regimens and steady-state serum levels.

Index terms: Anticonvulsants; Automation, data processing; Blood levels; Calculators; Dosage schedules; Methodology; Phenytoin

Phenytoin is a useful drug in the management of epilepsy. It is now clear that phenytoin follows Michaelis-Menten kinetics in humans[1–8] with an optimal therapeutic range of 10–20 mg/liter.[9,10] Because of its unique pharmacokinetic property, a nonlinear relationship between steady-state serum concentration and the dosage of phenytoin exists. A change in phenytoin dose can cause a disproportionately large change in serum concentration. It has been found that patients treated with phenytoin often have nonoptimal (i.e., <10 mg/liter or >20 mg/liter) serum levels.[1,2,10–12] Achieving therapeutic levels of phenytoin in patients is difficult, partly because of the saturable (Michaelis-Menten) pharmacokinetics of this drug.

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A patient's Michaelis-Menten constants for phenytoin may be estimated by means of a proper linear transformation of the Michaelis-Menten equation and at least two known dose and steady-state serum concentration points. The individual Michaelis-Menten constants obtained can then be substituted in the Michaelis-Menten equation to predict the steady-state serum levels corresponding to any dose. Recently, various workers[5,6,8,13,14] have used different linear transformations of the Michaelis-Menten equation for individualizing dosage regimens and determining Michaelis-Menten constants of phenytoin. The above methods require use of graphic determination or of a computer program based on the direct linear plot.

This article reports the use of a programmable calculator to individualize phenytoin dosage regimens when one, or preferably two, dosage regimens and the corresponding steady-state minimum serum concentration(s) of phenytoin for the patient are known.

Theoretical

The pharmacokinetics of phenytoin can be adequately described by an open, one-compartment model with a single saturable route of elimination.[8,11] Equation 1 applies to the steady state for a one-compartment, open model, with constant rate of administration and Michaelis-Menten elimination kinetics:

$$R = (V_m\overline{C_{ss}})/(K_m + \overline{C_{ss}}) \quad (1)$$

where R is the constant rate of administration (mass/time), V_m is the maximal rate (mass/time) at which phenytoin can be metabolized, K_m is the Michaelis constant (mass/volume) of phenytoin, which can be viewed as the concentration at which the enzyme is half saturated, and $\overline{C_{ss}}$ is the average steady-state serum phenytoin concentration (mass/volume). At steady state, the rate of administration (R) equals the rate of elimination.

When R of equation 1 is replaced by the "dose rate" (D/τ), with bioavailability assumed to be unity,[8] equation 2 is obtained:

$$D/\tau = (V_m\overline{C_{ss}})/(K_m + \overline{C_{ss}}) \quad (2)$$

where D is the dose (mass) and τ is the dosing interval

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(time). Equation 2 can be rearranged to express $\overline{C_{ss}}$ as a function of the "dose rate":

$$\overline{C_{ss}} = [K_m(D/\tau)]/[V_m - (D/\tau)] \quad (3)$$

The average serum phenytoin concentration at steady state ($\overline{C_{ss}}$) during any given dosing interval cannot be readily measured since it requires several blood samples. But the minimum concentrations at steady state (C_{ss}^{min}) are easily obtained in therapeutic drug monitoring. Hence equation 3 is rewritten to give equation 4:

$$C_{ss}^{min} = [K_m^{app}(D/\tau)]/[V_m^{app} - (D/\tau)] \quad (4)[15]$$

where K_m^{app} is apparent Michaelis constant (mass/volume) of phenytoin, and V_m^{app} is apparent maximal rate (mass/time) at which phenytoin can be metabolized. Both K_m^{app} and V_m^{app} are operationally useful variables, but are not the same as the actual K_m and V_m.

It is extremely difficult to predict the average or minimum steady-state serum phenytoin level in an individual for any given dose by means of equation 3 or 4 and the average K_m (or K_m^{app}) and V_m (or V_m^{app}) from the literature. This is because intersubject variability of the Michaelis-Menten variables (K_m or K_m^{app} and V_m or V_m^{app}) is very large.[3,7,8,11,16] Houghton and coworkers[17] found that the genetic differences and the effect of saturation kinetics have more influence on the steady-state serum phenytoin levels than do age, height, weight, and sex.

If a given dosage regimen and the corresponding minimum phenytoin concentration at steady state (C_{ss}^{min}) in a patient are known, then the following equation can be written:

$$C_{ss1}^{min} = [K_m^{app}(D_1/\tau_1)]/[V_m^{app} - (D_1/\tau_1)] \quad (5)$$

where D_1 and τ_1 are the dosage and dosing interval, respectively, of a given dosage regimen with C_{ss1}^{min} being the corresponding minimum concentration at steady state. It is impossible to solve for the two unknowns (i.e., K_m^{app} and V_m^{app}) in equation 5 with only one known dose and steady-state minimum concentration point. Since the nature of the hydroxylase enzyme system responsible for phenytoin metabolism is likely to be less variable than is the amount of the enzyme in most patients,[4] the apparent Michaelis constant (K_m^{app}) is assumed to be the same in all patients. Thus, the V_m^{app} can be calculated for each patient. Various investigators have made this assumption when constructing nomograms to predict phenytoin dosage in patients when only one dose and steady-state concentration point were known.[4,16] Assuming K_m^{app} or K_m (average = 11.5 mg/liter)[8] is the same in all patients, then V_m^{app} or V_m can be solved by rearranging equation 5:

$$V_m^{app} = [(K_m^{app} D_1)/(C_{ss1}^{min}\tau_1)] + (D_1/\tau_1) \quad (6)$$

Once the V_m^{app} of phenytoin is calculated for a patient it is possible to predict the patient's corresponding C_{ss}^{min} for any dosage regimen (i.e., D and τ) by using the V_m^{app} obtained, average K_m^{app}, and solving for C_{ss}^{min} in equation 4. Depending on the desirable C_{ss}^{min} chosen, the dosage regimen can be adjusted accordingly. This method can be used for an initial adjustment of phenytoin dosage, if only one known dose and steady-state serum concentration point is available. This estimation of V_m^{app} for a given patient by assuming a constant K_m^{app} in all patients serves as a very crude approximation. It has been shown that large intersubject variation of both K_m (or K_m^{app}) and V_m (or V_m^{app}) occurs.[3,7,8,11,16] Therefore, this estimation can only be used as an initial guide to dosage adjustment of phenytoin.

If two dosage regimens and the corresponding minimum serum phenytoin levels at steady state (C_{ss}^{min}) in the same patient are known, the following two equations can be obtained:

$$C_{ss1}^{min} = [K_m^{app}(D_1/\tau_1)]/[V_m^{app} - (D_1/\tau_1)] \quad (7)$$

$$C_{ss2}^{min} = [K_m^{app}(D_2/\tau_2)]/[V_m^{app} - (D_2/\tau_2)] \quad (8)$$

where D_1 and τ_1 are the first set of dosage and dosing interval with C_{ss1}^{min} being the corresponding minimum level at steady state, D_2 and τ_2 are the second set of dosage and dosing interval with C_{ss2}^{min} being the corresponding minimum level at steady state.

Since there are two unknowns (i.e., K_m^{app} and V_m^{app}) in equations 7 and 8, the values of K_m^{app} and V_m^{app} can be obtained by solving both equations:

$$K_m^{app} = [(D_1/\tau_1) - (D_2/\tau_2)]/[(D_2/C_{ss2}^{min}\tau_2) - (D_1/C_{ss1}^{min}\tau_1)] \quad (9)$$

$$V_m^{app} = [(K_m^{app} D_2)/(C_{ss2}^{min}\tau_2)] + (D_2/\tau_2) \quad (10)$$

Once the values of K_m^{app} and V_m^{app} of phenytoin in a given patient are obtained, it is possible to predict the corresponding C_{ss}^{min} of any phenytoin dosage regimen (D and τ) by employing known K_m^{app} and V_m^{app} in equation 4 and solving for C_{ss}^{min}.

Program Procedure

Four programs are stored on one magnetic card. The procedure for the solution of equations 4, 6, 9, and 10, by means of the Hewlett-Packard Model 97 programmable calculator (Hewlett-Packard (Canada) Ltd., Mississauga, Ontario, Canada, L4V 1L9) is embodied in the four programs. Programs 1 (equation 6) and 2 (equation 4), which operate in sequence, are presented in Figure 1. A given dosage regimen and one corresponding steady-state minimum level (C_{ss}^{min}) of phenytoin are needed as input for both programs. Program 1 estimates V_m^{app} for phenytoin, assuming a constant K_m (11.5 mg/liter)[8] in all patients. Program 2 then predicts the steady-state minimum concentration (C_{ss}^{min}) of phenytoin for any given dose. User instructions and output of programs 1 and 2 are outlined in Figure 2.

To illustrate the use of both programs, the data for ten patients, as reported by Richens,[16] were used. Table 1 shows the observed steady-state concentrations for each patient at two different daily doses of phenytoin, and the program-predicted phenytoin concentration for each patient, given only one dose and steady-state concentration point.

Programs 3 (equations 9 and 10) and 4 (equation 4), which operate in sequence, are presented in Figure 3. Two known dose and steady-state minimum concentration points are needed as input for both programs. Program 3 estimates K_m^{app} and V_m^{app} of phenytoin for individual patients. Program 4 then predicts the steady-state minimum concentration (C_{ss}^{min}) of phenytoin for any given dose. User instructions and out-

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