Computerized Approach to Monitoring Aminoglycosides

Teresinha Leal, Jean-Jacques Parez, Roger Vanbinst, and Pierre E. Wallemacq

Aminoglycosides are still used extensively in the treatment of nosocomial infections with Gram-negative bacteria. However, the treatment is associated with several adverse effects. Aminoglycosides monitoring is therefore essential to prevent toxic accumulations and to reach therapeutic concentrations. A computer program, PHARMONITOR, has been developed to optimize aminoglycosides monitoring, responding to the demands of most clinical daily situations. This program, based on a one-component open pharmacokinetic model, is developed for IBM PC-compatible computers, using D-Base III+. It can calculate \( t_{1/2} \), \( V_c \), \( C_{\text{drug}} \), \( C_{\text{max}} \) and the theoretical optimal dose and interval and also evaluates the creatinine clearance. The program has been conceived to allow maximal speed, flexibility, and reliability by the use of (e.g.) a linear least-squares analysis, the possible reference to previous protocols, the extensive use of keywords to classify and recall patients according to their pathologies, the development of messages recommending maximal dose or minimal dosing interval, and increasing the safety of the analysis. We consider the program a valuable tool for adjusting aminoglycoside dosage in individuals.

Additional Keyphrases: therapeutic drug monitoring · pharmacokinetics

Since the discovery of streptomycin more than 40 years ago, aminoglycosides continue to be used extensively in the treatment of severe Gram-negative bacterial infections, particularly those acquired in the hospital. The synergistic effects of using these drugs with beta-lactams and the relatively low and reversible bacterial resistance to aminoglycosides contributed to the success of the treatment. The therapeutic activity seems to be directly dose-dependent and related to the ratio of peak serum concentration to minimal inhibitory concentration (MIC).

However, aminoglycosides are associated with severe adverse effects. Primarily, nephrotoxicity and irreversible ototoxicity are described as accompanying high...
program, which performs the following operations:
- routinely optimizes aminoglycosides dosing regimens, with the greatest possible flexibility, rapidity, and caution
- creates a database of patients' details, results, and protocols
- allows retrospective population studies with keywords
- prints summarized or full protocol reports in the language of choice (English, French, or Dutch)
- provides a valuable didactic tool for clinical pharmacokinetics

Materials and Methods
Because the program is to be used in routine TDM, we gave priority to optimal data handling. PHARMONITOR, a single computer-screen program, has been particularly conceived for rapid monitoring (<6 min for a patient's analysis). The program has been developed on an IBM PC-compatible computer, with use of D-Base III+, which allows the integration of pharmacokinetic calculations with data management. The pharmacokinetic calculation is based on the one-compartment model equations first suggested by Sawchuk and Zaske (7), which allows linear least-squares analysis. In steady-state, this model should approximate sufficiently the elimination phase of aminoglycosides and allow quick routine evaluations of the amount of drug and dosing interval needed to obtain target concentrations. As many as five serum drug concentrations can be analyzed. From the equations listed in Table 1, the program calculates $t_{1/2}$, $V_d$, and $Cl_{drug}$ (equations 1–4); the optimal theoretical dose and interval (equations 5 and 6); and the predicted peak and trough drug concentrations corresponding to the dosage regimen selected (equations 7 and 8). Moreover, it evaluates the creatinine clearance from the formula of Cockcroft-Gault (equation 9), and Schwartz (equation 10) for adults and children (<18 years old), respectively. [The equation of Cockcroft-Gault will be corrected by the body surface area, unless the patient's height is unknown; the body surface area is evaluated from the formula of Boyd (equation 11) (8).] The program also calculates the peak concentration (extrapolated at the end of the infusion = $t_0$) and the correlation coefficient for the linear-regression equation.

Figure 1 displays the data management diagram, from the new clinical and laboratory data, up to the final dosage regimen selected. Owing to the flexibility of the program, not all clinical variables are absolutely necessary to perform the dosing calculation. However, the more of these variables that can be included (e.g., body weight, height, creatinine concentration in serum), undoubtedly the more reliable the calculated protocol will be. The program allows the suppression of a concentration from the calculation, if necessary (still keeping track of it in the final report), or the saving of data, even when incomplete (without known dose, timing, etc.). All patients' data are recorded and can easily be recalled later, at any stage of a new analysis. Such reference is
usually of great help to determine the best dosage regimen. Recalculation of the data can be performed easily. Furthermore, retrospective population studies are possible by using diagnosis keywords characterizing each patient (patient populations could be assembled for statistical purposes: e.g., renal insufficient, premature). Users are free to create or modify their own database or keywords dictionary, concerning (e.g.) diagnoses, peak or trough target values, protocol comments, and the language of the printed reports. They can also add any other drug, as long as the target peak and trough concentrations are known.

In addition to the pharmacokinetic calculations described above, special messages prompt minimal recommended dosing interval and maximal dose, based respectively on the creatinine concentration in serum and the patient’s weight. The minimal dosing interval message is based on a population study (n = 641), describing the relationship between creatinine clearance and elimination of the drug. The population studied included patients with different pathologies, of various ages and both sexes, with all patients being in steady-state regarding renal function (variations of serum creatinine >20% were excluded) and the aminoglycoside regimen (measurements after at least three infusions). Indeed, according to pharmacokinetic principles, a linear regression generally describes the relationship at steady-state between the elimination rate constant (k_e) and the creatinine clearance. However, after stratifying our data, we observed an optimal linear regression correlating the drug half-life with the logarithm of the creatinine clearance, as presented in Table 2 for different aminoglycosides. Such a relationship, therefore, yields recommended intervals corresponding to the creatinine clearance ranges and to the drug involved.

The maximal recommended dose (which can be modified by the user) is obtained from the medical literature, taking into account the patient’s body weight and the frequency of drug administration (e.g., 20 mg/kg of

### Table 1. Pharmacokinetic and Biological Equations Used in the PHARMONITOR Program

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
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<tbody>
<tr>
<td>( k_e = -\text{slope} \times 2.303 )</td>
<td>(1) Terminal rate constant for elimination (h(^{-1}))</td>
</tr>
<tr>
<td>( t_{1/2} = 0.693/k_e )</td>
<td>(2) Elimination half-life (h)</td>
</tr>
<tr>
<td>( V_d = K/\left( k_e \times C_{\text{max}} - C_{\text{min}} \times e^{-k_e \times t} \right) )</td>
<td>(3) Distribution volume</td>
</tr>
<tr>
<td>( C_{\text{max}} = K \times V_d \times k_e \times (1 - e^{-k_e \times t})/(1 - e^{-k_e \times t}) )</td>
<td>(4) Maximum concentration</td>
</tr>
<tr>
<td>( C_{\text{min}} = C_{\text{max}} \times e^{-k_e \times (t_{\text{desired}} - t)} )</td>
<td>(5) Minimum concentration</td>
</tr>
<tr>
<td>( t = -\ln \left( \frac{C_{\text{min}}}{C_{\text{max}}} \right) \times t_{\text{desired}} )</td>
<td>(6) Time to reach desired concentration</td>
</tr>
<tr>
<td>( K = \frac{K_{\text{desired}}}{V_d \times k_e \times (1 - e^{-k_e \times t})} )</td>
<td>(7)比例常数</td>
</tr>
<tr>
<td>( C_{\text{max}} = \frac{K_{\text{desired}}}{V_d \times k_e \times (1 - e^{-k_e \times t})} )</td>
<td>(8) Maximum concentration</td>
</tr>
<tr>
<td>( C_{\text{min}} = \frac{K_{\text{desired}}}{V_d \times k_e \times (1 - e^{-k_e \times t})} )</td>
<td>(9) Minimum concentration</td>
</tr>
<tr>
<td>( F = \frac{140 - \text{age} \times \text{wt}}{7.2 \times S_G} \times 1.73 \times \text{BSA} \times 10^{-4} \times \left(\frac{\text{wt}}{1000}\right)^{0.7235} - 0.1088 \times \log(\text{wt} \times 1000) )</td>
<td>(10) Body weight formula</td>
</tr>
</tbody>
</table>

### Table 2. Linear-Regression Analyses for \( k_e \) (h\(^{-1}\)) or \( t_{1/2} \) (h) vs \( C_{\text{min}} \) (mL/min) or \( \ln C_{\text{min}} \) for Various Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amikacin (n = 303)</th>
<th>Vancomycin (n = 280)</th>
<th>Gentamicin (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r )</td>
<td>0.962</td>
<td>0.958</td>
<td>0.910</td>
</tr>
<tr>
<td>Slope (SD)</td>
<td>-4.9 (0.3)</td>
<td>2.6 (0.3)</td>
<td>-2.5 (0.2)</td>
</tr>
<tr>
<td>Intercept (SD)</td>
<td>26.3 (1.3)</td>
<td>0.05 (0.02)</td>
<td>14.7 (1.1)</td>
</tr>
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</table>

* y vs x. Values were stratified in 17-20 data.

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Fig. 1. Data management diagram used in the PHARMONITOR program.
body weight per day administered once or twice a day).

The aim of such messages is to emphasize some usual limits, and hence to help the user avoid aberrant drug regimen calculations (possibly resulting from errors of dosing or sampling). Therefore, this program should increase the safety of the analysis substantially. For instance, a satisfactory agreement between the two intervals—that from a population study and that from the individual kinetic calculation—should reinforce the choice of the dosage regimen. On the other hand, a great disparity between both values should warn the user of a possible mistake in the sampling or in the evaluation of the creatinine clearance.

Results and Discussion

The reliability of the pharmacokinetic model used in the PHARMONITOR program has been assessed by comparing the peak and trough concentrations predicted by the program (equations 7 and 8), before any dosage modification, with the corresponding serum concentrations observed a few days after the proposed modification. This study has been performed in a routine TDM environment, according to the following criteria:

- Measurements were performed in steady-state (after at least the third infusion), with complete patients' data (creatinine, weight, timing, etc.).
- Patients with unstable renal function (serum creatinine variations >20%) were rejected from the study.
- Patients maintained under the same dosage regimen, or patients whose calculated proposed treatment was not followed by the physician, were also rejected.
- Patients younger than one year were excluded from this study.
- Analyses of patients' samples always included two to four serum samples (drawn just before the infusion, and at least 1 h after the end of the infusion) and resulted in plausible kinetics; data presenting a great disparity between recommendation messages and individual kinetic calculations were excluded.
- Predicted and observed trough and peak drug concentrations were evaluated just before and just after infusion (t₀). Peaks were extrapolated back to the end of the infusion by using the slope calculated from the post-infusion concentrations.

The results presented in Table 3 demonstrate the usefulness of such calculations in predicting the optimal dosage regimen, and appear satisfactory in a TDM context. The slightly but statistically significant (P <0.05) higher values measured could be explained by a progressive accumulation of the drug in the deep compartment after several days of treatment. Indeed, the use of one-compartment equations tends to underestimate aminoglycoside concentrations, particularly trough concentrations.

Because the correlation does not always accurately reflect the presence of a bias in the predicted values, the performance of this forecasting method has been further evaluated by calculating the bias and precision according to Sheiner and Beal (9). For a population of 144 serum concentrations ranging from 0 to 35 mg/L, including different aminoglycosides, the mean squared prediction error, a measure of precision, is here 6.55 (95% confidence interval, 3.33 to 9.76). The mean prediction error, a convenient measure of bias, is -0.81 (95% confidence interval, -1.28 to -0.33).

The limitations of such a pharmacokinetic model are well recognized. Because steady-state is necessary to reach accurate evaluation, one must wait until the third infusion after the onset of the treatment, or after any modification of the dosage regimen, before measuring serum concentrations and performing such pharmacokinetic monitoring. Peak and trough concentrations are generally satisfactory for monitoring patients in steady-state. However, to improve the accuracy of the evaluation, or at the early stage of the treatment, we recommend measuring three postinfusion concentrations distributed in the time according to the renal function. Aminoglycoside pharmacokinetics may change with time and clinical status. Therefore, even in absence of any dosage regimen modification, aminoglycoside monitoring should be performed at least once every three days.

Patients with unstable renal function may present erroneous estimates of creatinine clearance, and of pharmacokinetics. Adequate aminoglycoside regimens should therefore be obtained by referring to the physician and considering the PHARMONITOR program only as a guideline. Vigilance and further measurements of serum drug concentrations will be necessary during the course of therapy.

To avoid any interference with the distribution phase (which could result in nonlinear kinetics), we strongly suggest collecting blood specimens at least 1 and 2 h after the end of the infusion for aminoglycosides and vancomycin, respectively. The success of such monitoring involves of course the compliance of the medical staff and nursing staff, who are asked to fill out a request form with the minimal biometric characteristics of the patient (weight, height, and age); the main biological

<table>
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<tr>
<th>Table 3. Linear-Regression Analyses between Predicted (x) and Observed (y) Serum Concentrations (mg/L) of Various Antibiotics</th>
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<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>n</td>
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<tr>
<td>r</td>
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<tr>
<td>Slope (SD)</td>
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<tr>
<td>Intercept (SD)</td>
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Values predicted by the PHARMONITOR program were compared with values measured a few days after adjusting the dosage.
data, including the pathology and the serum creatinine concentration; and finally the current dosage regimen with the accurate time schedule of the infusion and blood sampling. Obtaining such information may require frequent clinical seminars to emphasize the usefulness of a correct monitoring and consequently of the fundamental considerations involved.

Aminoglycosides monitoring has been successfully performed in our hospital for more than 10 years. The PHARMONIT program has been routinely used since August 1989 to monitor >7000 patients' analyses, with a daily average of 25 patients.

In conclusion, once the limitations inherent in the pharmacokinetic model are well understood, this computer program is a useful tool for individual adjustment of aminoglycosides in a clinical environment, but obviously should not substitute for the clinician's judgment in the final decision, especially for critically ill and unstable patients. This program is designed to optimize the well-known method of pharmacokinetic forecasting of Sawchuk and Zaake (7), by adapting this to the computer and by enhancing its safety by including recommendation messages based on population statistics. Both the kinetic model selected and the data-handling contribute to the speed and reliability of the analysis. We expect that the PHARMONIT program could be used as the basic framework for other drug monitoring developments.

References

CLIN. CHEM. 37/8, 1419–1423 (1991)

Serum Lactate Dehydrogenase Isoenzyme 4/5 Ratio Discriminates between Hepatocarcinoma and Secondary Liver Neoplasia

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Total lactate dehydrogenase (LD; EC 1.1.1.27) and its five isoenzymes were determined in sera from (a) 98 cases of cirrhosis at various stages classified according to Child and Turcotte; (b) 37 cases of hepatocarcinoma (HC) at different stages of the Okuda classification; (c) 17 patients with secondary liver neoplasia (SLN), mainly from an abdominal primary site; and (d) 19 cases of abdominal neoplasia without liver metastasis, in an attempt to contribute to the differential diagnosis between these conditions. LD-4 was enhanced in SLN and LD-5 in HC, thus indicating the LD-4/LD-5 ratio as a potential index with which to differentiate between HC and SLN patients. At a cutoff value of 1.05, 91% of these patients were correctly classified (82% for SLN and 95% for HC). Consequently, this biochemical index appears to be an efficient and rapid indicator to distinguish HC from SLN. On the other hand, the LD isoenzymes are unable to discriminate between HC and cirrhosis or between abdominal neoplasia with and without liver metastases.

Additional Keyphrases: cancer • cirrhosis • hepatobiliary disease

Recent studies in clinical enzymology have improved the capacity to differentiate among various chronic liver diseases, including neoplasia (1–6). We have previously focused our attention on discriminating between hepatocarcinoma (HC) and cirrhosis (4–6), which is one of the most frequently encountered differential diagnoses in the field of hepatobiliary diseases.4 Various patterns of serum γ-glutamyltransferase isofoms have been proposed as specific indicators of these diseases; in addition, a faster anodic γ-glutamyltransferase isofom has been identified as a specific serum signal of HC.

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Received November 27, 1990; accepted June 7, 1991.

4 Nonstandard abbreviations: HC, hepatocarcinoma; SLN, secondary liver neoplasia; AN, abdominal neoplasia; ANOVA, analysis of variance; and ROC, receiver operating characteristic.