ANALYZING CONCENTRATIONS IN SPHERICAL DIFFUSION MODELS: ANALYSIS OF ENDOCARDIAL VEGETATIONS AND OF POST-ANTIBIOTIC EFFECT

Jelliffe R[1], Barbaut X[2], Maire P[2], El Brouzi A[3], and Vergnaud JM[3].
1 - USC School of Medicine, Los Angeles, USA, 2 - ADCAPT, Hospices Civils de Lyon, France, and 3 - Faculty of Sciences, St. Etienne, France.

Introduction

A problem in the treatment of patients with infectious endocarditis is that it is difficult to estimate if the drug is able to kill the organisms in the center of a vegetation. Because of this, a diffusion model was made of this process.

A spherical shape was assumed for the vegetation, as shown in Figure 1, and it was modeled having several concentric layers, with diffusion taking place from layer to layer. The sphere was assumed to be homogeneous, isotropic, and as having constant diffusivity. The diffusion was assumed to be dependent on the concentration of drug in the surrounding medium, such as the serum concentration, and its time course. The diameter of endocardial vegetations can be measured by transesophageal echocardiography.

The following equation was used to model the diffusion:

$$\frac{\partial C}{\partial t} = \frac{1}{r^2} \cdot \frac{\partial}{\partial r} \left[D \cdot r^2 \cdot \frac{\partial C}{\partial r} \right]$$

where C represents the concentration in the sphere at time t, at a distance r from the center of the sphere, and D represents the coefficient of diffusion in the sphere.

When D is assumed constant, the equation becomes

$$\frac{\partial C}{\partial t} = D \cdot \left[\frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \cdot \frac{\partial C}{\partial r} \right]$$

The vegetation is assumed to be continuously immersed in the surrounding medium, and the drug concentration in that medium is assumed to attain a value which results in equilibrium with the very outer layer of the sphere. The medium then undergoes the changes in concentration with time that constitute the serum level time course. This time course is thus presented as the input to the spherical model [1].

The diffusion coefficient found by Bayer, Crowell, et al. for aminoglycosides in experimental endocarditis [2,3] was used. The model has become part of the USC*PACK clinical programs for individualizing drug dosage regimens [4]. The model can also be used to simulate behavior inside an abscess, and, by appropriate choice of sphere diameter and diffusion coefficient, to simulate the post-antibiotic effect of a certain desired duration.

Examples: Simulated Endocardial Vegetations of Various Diameters

Suppose one were to develop an amikacin dosage regimen for a hypothetical 65 year old man, 70 in tall, weighing 70 kg, with a serum creatinine of 1.0 mg/dL. Let us assume that he has a vegetation seen by echocardiography on his aortic valve that might be either 0.5, 1.0, or 2.0 cm in diameter. We wish to examine the ability of an amikacin regimen designed to achieve serum peaks of 45 ug/ml and troughs of about 5.0 ug/ml to reach effective concentrations within the vegetation in these three cases. Let us apply the findings of Bayer et el [2,3] to compute the time course of probable amikacin concentrations in the center of these three vegetations of different diameters, to examine their possible ability to kill an organism having an estimated minimum inhibitory concentration (MIC) of 8.0 ug/ml, for example.

Using the Amikacin program in the USC*PACK collection [4], let us estimate, from the patient's age, gender, height, weight, and serum creatinine concentration, that his creatinine clearance (CCr) is about 69 ml/min/1.73M^2. This method of estimating CCr is discussed in detail in another paper in this symposium. We enter the target goal for the peak serum concentration of 45 ug/ml and an initial trough concentration of about 5.0 ug/ml. The ideal dose interval to achieve that peak and trough exactly, adjusted for the patient's renal function, employing a planned duration of the IV infusion of 0.5 hr, turns out to be 10.231 hrs. Let us approximate this in a practical manner by choosing a dose interval of 12 hrs. The dosage regimen to achieve the peak goal with such a dose interval is, when revised to practical amounts, 850 mg for the first dose, followed by 750 mg every 12 hrs thereafter.

On this regimen, predicted serum concentrations are 43 ug/ml for the peak and 3.2 ug/ml for the trough, possibly a bit low at the trough. The peak is 542 % of the stated MIC, and serum levels are predicted to be at least the MIC for 66 % of each dose interval. The AUC/MIC ratio for the first 24 hours is 48.8. The plot of these predicted serum concentrations is shown in Figure 2.

The question now is whether or not this predicted serum concentration profile will result in adequate penetration of the vegetation in each of the three cases, and whether or not the regimen will kill effectively there, as well as in the central (serum level) compartment.

Figure 3 shows the predicted amikacin concentrations in the center of the vegetation having a diameter of 0.5 cm. As shown, concentrations rise rapidly above the MIC and stay there, suggesting that the above regimen should probably be able to kill organisms having an MIC of about 8.0 ug/ml fairly promptly in the center of the vegetation. The time lag of concentrations in the center of the sphere is modest, about 3-4 hrs, behind the serum concentrations.

On the other hand, if the vegetation were 1.0 cm in diameter instead, the drug would take longer to diffuse to the center, and the rise and fall of drug concentrations would be more damped, as shown in Figure 4.

Further, if the diameter of the vegetation were 2.0 cm, all this would take still longer, and the time course of the computed concentrations in the center would be as shown in Figure 5. The drug would take considerably longer to diffuse to the center of the vegetation, and significant growth of organisms might well take place before the concentrations reach and exceed the MIC.

For every doubling of the diameter of the sphere, the equations show that it will take 4 times as long (the square of the ratio of the diameters) to reach an equal concentration in the center of the sphere.

Another Example: Simulating an Abscess or a Post-Antibiotic Effect.

Another use for such a spherical model might, of course, be an abscess. If we could know the diffusion coefficient into abscesses of different sizes we could similarly begin to model and compute the concentrations of drug into the abscess. There might well be different diffusion coefficients through the wall, into the bulk of the abscess, and into the center. All this is theoretically capable of being determined. Effects of oxygen tension and pH upon bacterial growth and response to drugs can also be determined by careful needle aspiration done at carefully documented times just prior to incision and drainage of them, with careful cultures and determination of pH, pO2, viable organisms, and rates of growth and kill from different parts of the abscesses.

Figure 6 shows simulated concentrations in the center of a small sphere simulating a microorganism having a diameter of 0.1 micron, 3 simulated layers of diffusion, and a diffusion coefficient of 1.5×10^{-14}. This particular sphere has the property that in its center, the concentrations of drug fall below the MIC about 6 hrs after the serum levels do, thus simulating (without making any suggestions or conclusions about mechanism of action) a post-antibiotic effect of about 6.0 hrs, as the organisms will not begin to grow again for about 6 hrs after the serum concentrations fall below the MIC.

All the effects of these computed concentrations in the center of these spheres will be discussed in another paper devoted specifically to modeling bacterial growth and kill. We see here that diffusion into and out of spherical porous objects can be modeled. The equations describing this process are the same as those for release of drug from a sustained-release preparation formulation.

References.

1.   Maire P, Barbaut X, Vergnaud JM, El Brouzi M, Confesson M, Pivot C, Chuzeville M, Ivanoff N, Brazier J, and Jelliffe R: Computation of Drug Concentrations in Endocardial Vegetations in Patients during Antibiotic Therapy. Int. J. Bio-Med. Comput., 36: 77-85, 1994.

2.   Bayer A, Crowell D, Yih J, Bradley D, and Norman D: Comparative Pharmacokinetics and Pharmacodynamics of Amikacin and Ceftazidime in Tricuspid and Aortic Vegetations in Experimental *Pseudomonas* Endocarditis. J. Infect. Dis., 158: 355-359, 1988.

3.   Bayer A, Crowell D, Nast C, Norman D, and Borelli R: Intravegetation Antimicrobial Distribution in Aortic Endocarditis Analyzed by Computer-Generated Model: Implications for Treatment. Chest, 97: 611-617, 1990.

4.   Jelliffe R, Schumitzky A, Van Guilder M, and Jiang F: User Manual for version 10.7 of the USC*PACK Collection of PC Programs, USC Laboratory of Applied Pharmacokinetics, December 1, 1995.
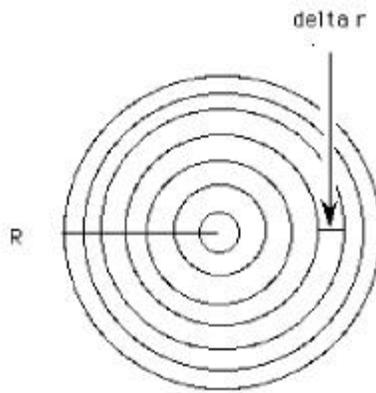
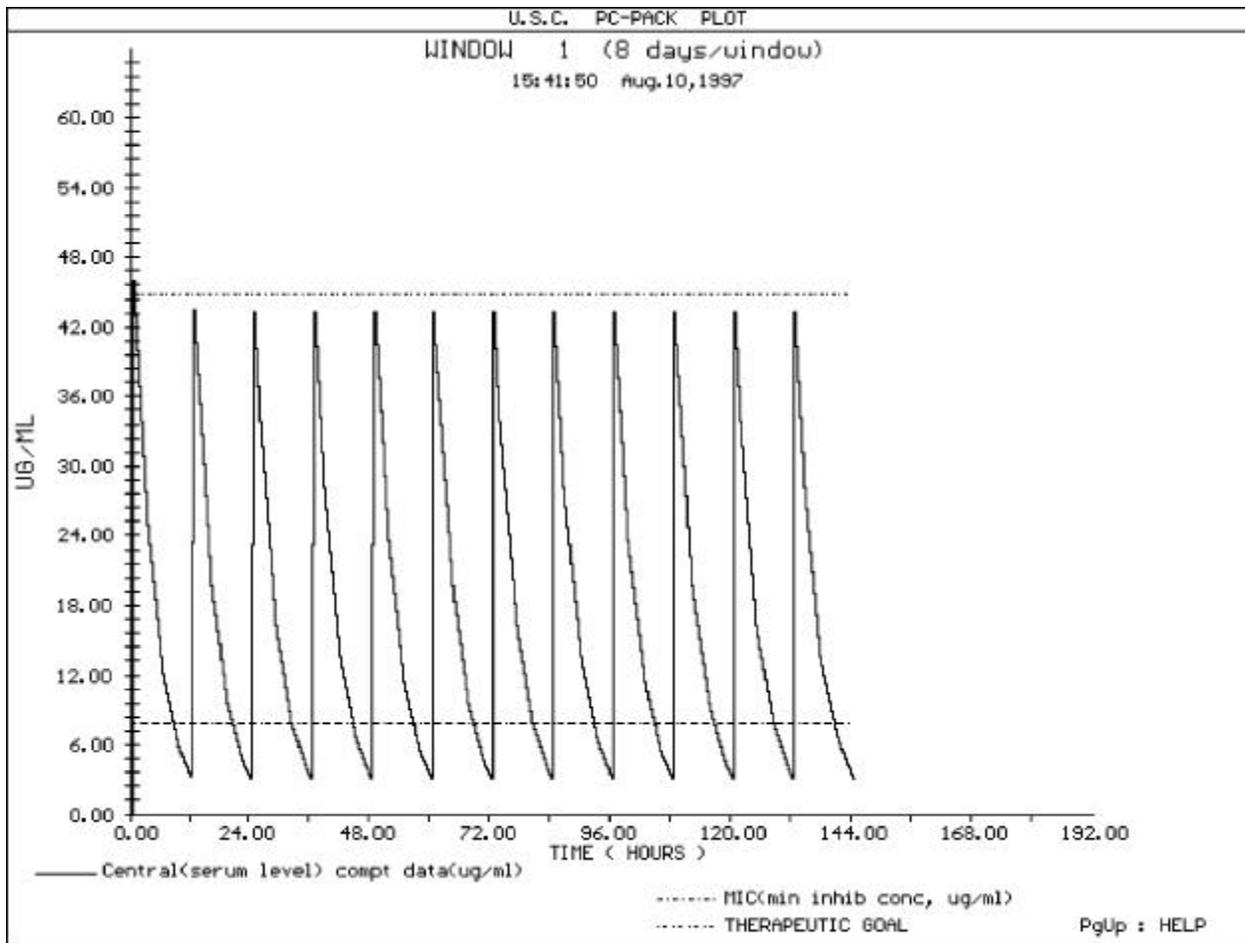Figure 1. Diagram of the concentric layers of the spherical model of the endocardial vegetation.

Figure 2. Predicted time course (the first 6 days) of serum Amikacin concentrations for the patient described. Upper horizontal dotted line - initial stated target peak serum concentration of 45 ug/ml. Lower horizontal dashed line - the estimated organism MIC of 8.0 ug/ml.
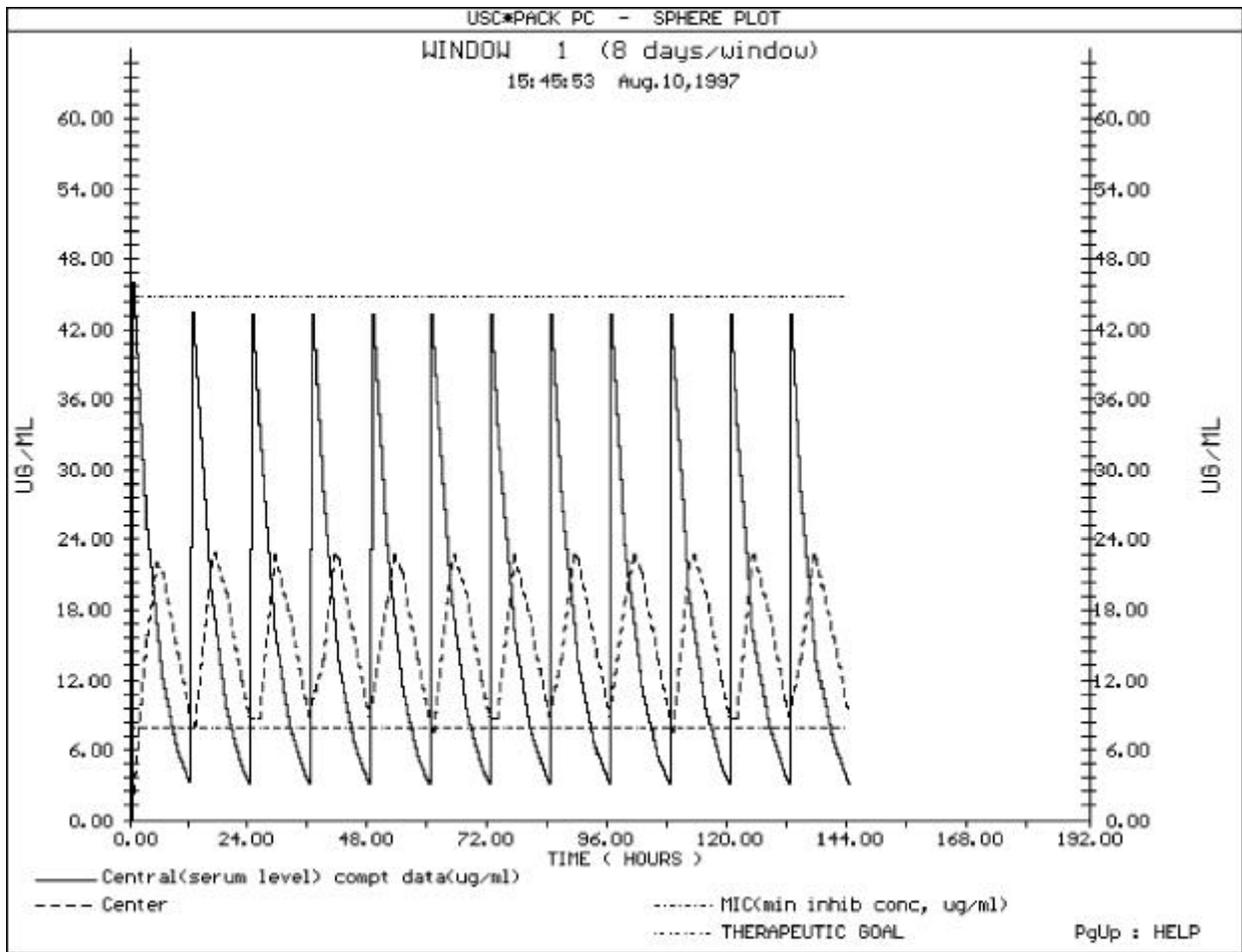
Figure 3. Predicted time course (the first 6 days) of Amikacin concentrations (dashed line) in the center of a simulated endocardial vegetation of 0.5 cm. Solid line - Predicted serum concentrations, and other lines and symbols as in Figure 2. The predicted endocardial concentrations rise promptly, and are consistently above the estimated MIC of 8.0 ug/ml.
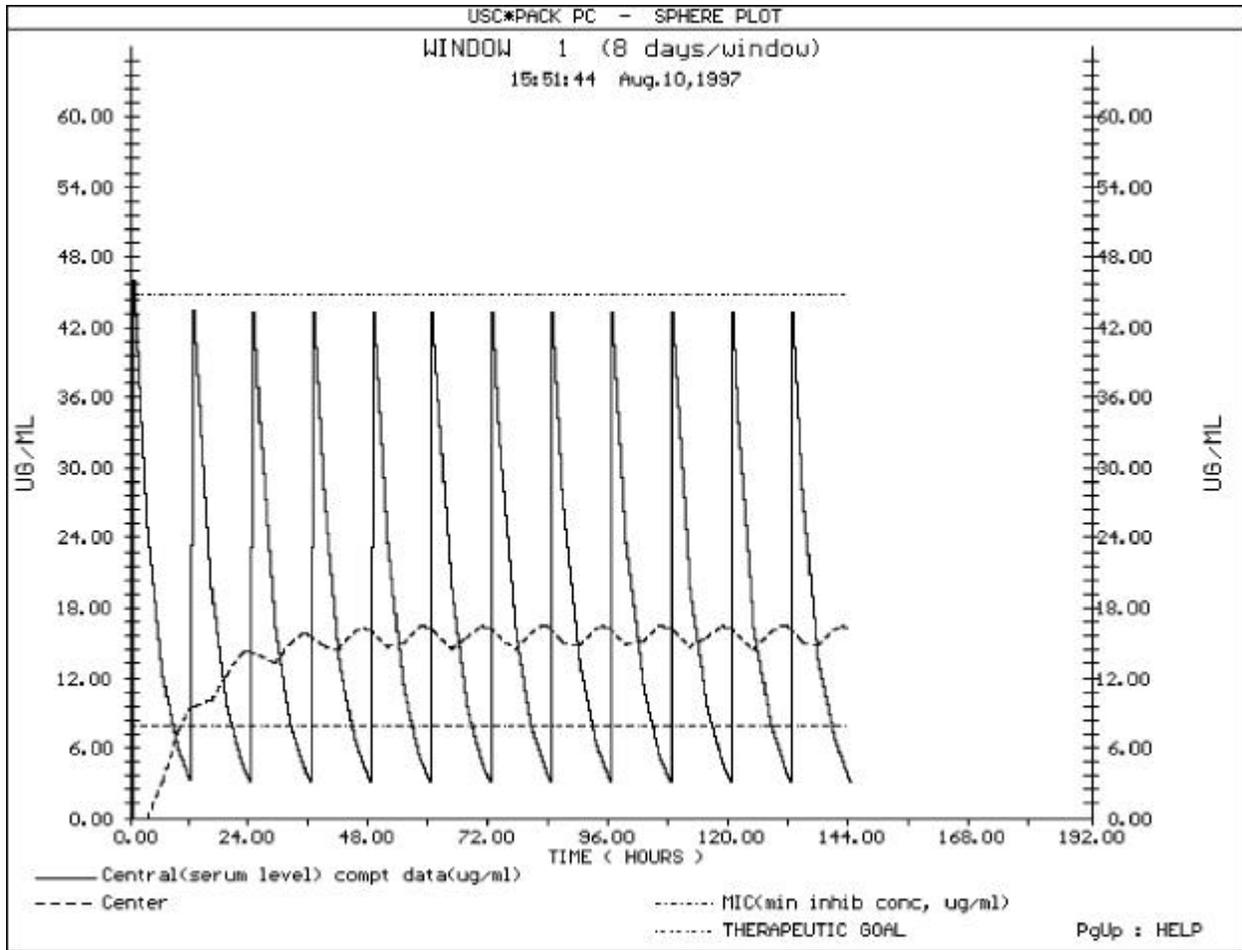
Figure 4. Predicted time course (the first 6 days) of Amikacin concentrations (dashed line) in the center of a simulated endocardial vegetation of 1.0 cm. Solid line - Predicted serum concentrations, and other lines and symbols as in Figure 2. The predicted endocardial concentrations rise more slowly, are more damped, with smaller oscillations from peak to trough, but once the estimated MIC is reached, are consistently above 8.0 ug/ml.
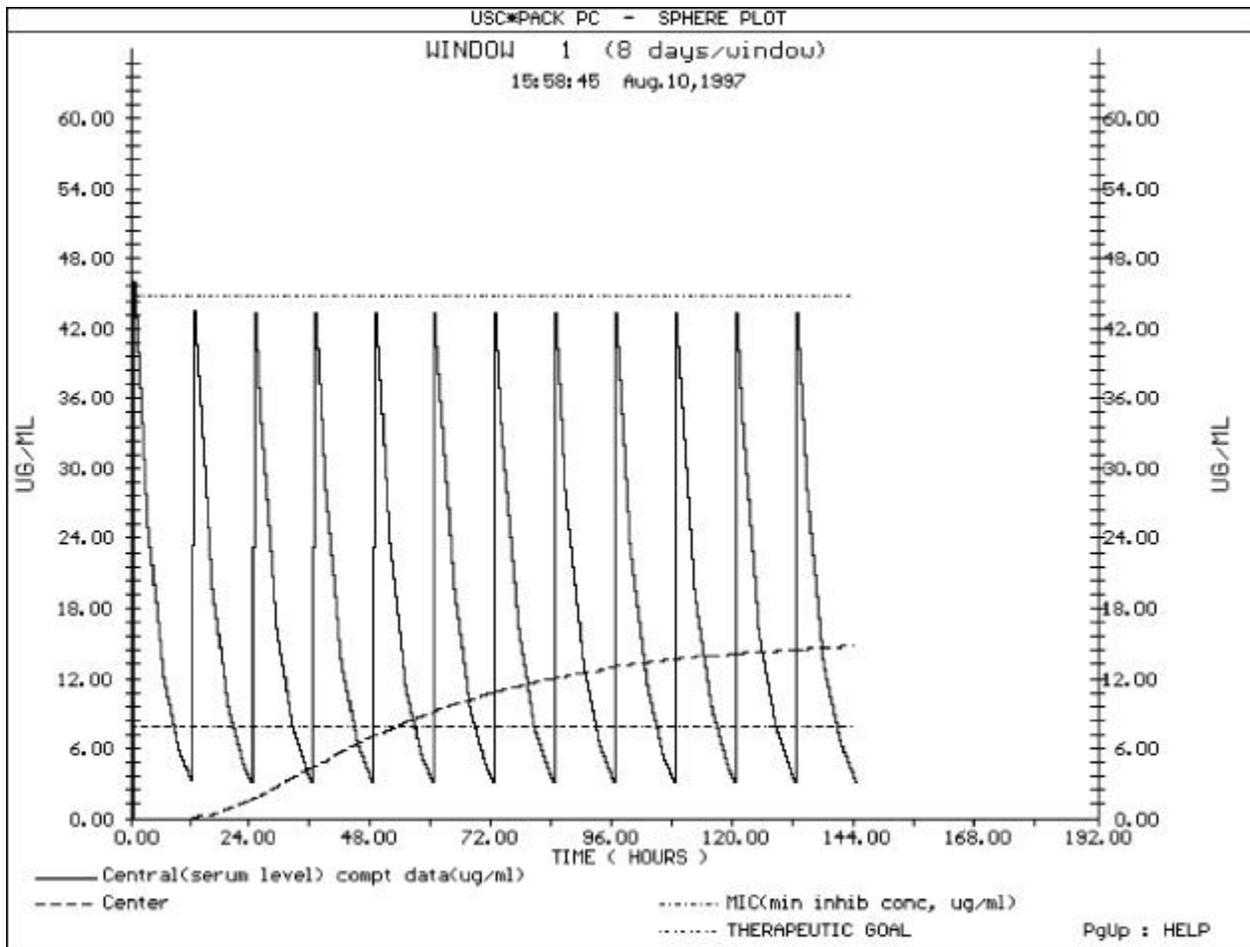
Figure 5. Predicted time course (the first 6 days) of Amikacin concentrations (dashed line) in the center of a simulated endocardial vegetation of 2.0 cm. Solid line - Predicted serum concentrations, and other lines and symbols as in Figure 2. The predicted endocardial concentrations rise much more slowly and are much more damped, with essentially no oscillations from peak to trough. Once the estimated MIC is reached, the concentrations are consistently above 8.0 ug/ml, but two full days are required before the MIC is reached.
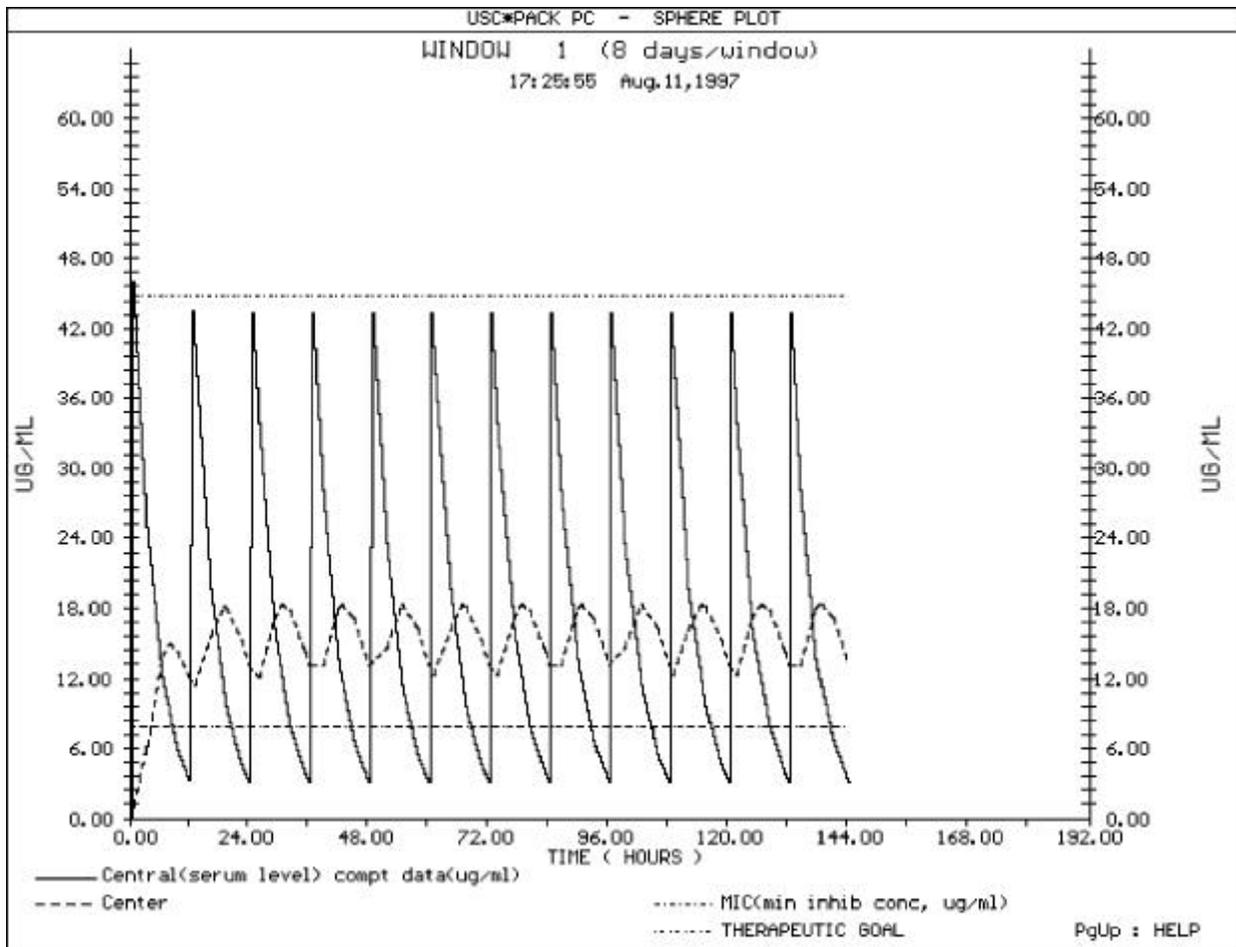
Figure 6. Plot of computed amikacin concentrations (the first 6 days) in the center of a simulated microorganism. Parameters in the sphere diffusion model are adjusted so that concentrations in the center of the organism lag behind the serum concentrations and, if they fall below the MIC, would do so approximately 6 hrs after the serum concentrations do, thus simulating a post-antibiotic effect of about 6 hrs.