

INITIAL CONDITIONS AND THEIR USE IN THERAPEUTICS: AN AMINOGLYCOSIDE AND A DIGOXIN PATIENT WITH RAPID CHANGES IN MODEL PARAMETER VALUES.

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Most pharmacokinetic analyses deal with patients, and their pharmacokinetic models, who have stable values for their various parameters such as volume of distribution, rate constants, clearances, etc.. However, this is not always so, even though one can express a rate constant as an intercept plus a slope times a descriptor of elimination such as creatinine clearance or cardiac output [1], so that renal function can change from dose to dose during therapy, and the patient's drug model can keep up with these changes as they take place.

Probably the most serious problem in analyzing pharmacokinetic data in patients is caused by sudden significant changes in a patient's volume of distribution (Vd) of the central (serum concentration) compartment. It is generally known, for example, that patients in an ICU setting have larger values for the Vd of gentamicin and other aminoglycosides than do general medical patients. Indeed, young very healthy people who suddenly require an aminoglycoside for a perforated or gangrenous appendix often have even smaller values for Vd [2]. It is interesting that each patient, himself, also goes through such transitions as his clinical status changes.

AN AMINOGLYCOSIDE PATIENT WITH SUDDEN CHANGE IN STATUS

An interesting example of such an individual change was a 54 year old man in Christchurch, New Zealand, seen through the courtesy of Dr. Evan Begg. He was 69 in tall, weighed 80 kg, and his serum creatinine on admission was 0.7 mg/dL. He had a pyelonephritis, was receiving tobramycin 80 mg approximately every 8 hours. He had a measured peak serum concentration of 4.6 and a trough of 0.4 ug/ml respectively, and had been felt by all to be having a satisfactory clinical response. During this time, his Vd was 0.18 l/kg, based on those two serum samples. However, on about the 6th day, he suddenly and unexpectedly relapsed and went into clear-cut septic shock. This patient's antibiotic therapy was discussed in the two previous papers. The present paper concerns how the analysis was able to proceed from one population model to the other, switching from that of a general medical patient at first to that of an ICU patient, and finally back to that of a general medical patient again.

Following this initial phase and his relapse from therapy, he was aggressively treated with much larger doses. He received 300 mg every 12 hours during this time. His serum concentrations rose to peaks of 10.1 ug/ml. During this period of sudden septic shock, his serum creatinine rose from 0.7 to 3.7 and his CCr fell to about 18 ml/min/1.73m². After about another 10 days he improved. At that time his serum concentrations rose to a peak of 16, and it was necessary to sharply reduce his dose to 140 mg about every 12 to 24 hours. His serum creatinine fell to 1.1 to 1.3 mg/dL, and his CCr rose to 57 ml/min/1.73m².

When one tries retrospectively to fit the entire data set, it was simply not possible to get a good fit to all the serum data. Most data points were obtained during the second, his sickest

phase, and they dominated the fit. The ones at the beginning, prior to his sepsis, and at the end, after his recovery from it, were not at all well fitted.

Because of this, the data was divided into three parts - an initial one before his relapse into sepsis, a second one when he was septic, and a third one following his recovery, but before it was felt safe to discontinue his therapy. Each data set was fitted separately, using the USC*PACK programs [2].

During the first data set, the first 6 days, when his behavior was that of a general medical patient, not seriously ill, his V_d was 0.18 L/kg as described above. The problem then was to pass on the ending values of his serum concentrations, and those in his peripheral, nonserum compartment, as initial conditions to the second data set. This was done.

A major change in his V_d was then seen during his septic phase. It rose from 0.18 in his previous phase to 0.51 L/kg, and his K_{slope} , the increment of elimination rate constant per unit of CCr , fell to zero. However, his K_{cp} , the rate constant from serum to peripheral compartment, rose to 0.255 hr^{-1} , suggesting that he was "third-spacing" his tobramycin somewhere. The ending concentrations in his central (serum) compartment for this data set were 2.09 ug/ml, and for his peripheral compartment were a very high 44.1 ug/kg.

These ending values were then passed on to the third part of his data set, that of his recovery. During this time his peaks were 16 and 12 ug/ml, and his dose was reduced to 140 mg every 12-24 hours. His V_d during this third phase, that of recovery, when he was no longer seriously ill, had fallen greatly to 0.15 L/kg, close to his previous value as a general medical patient.

The use of initial conditions permitted the intelligent analysis of this patient's data, especially as quite significant concentrations were present not only in his central (serum) compartment, but also in his peripheral compartment, during the transition from his second to his third phase.

At the Cleveland Clinic, Drs Peter Slugg and Marcus Haug spoke of " V_d collapse", as the V_d would drop from a larger to a smaller value, as described it as an indicator of incipient recovery of the patient. The present patient not only demonstrated such V_d collapse, but also showed its opposite, V_d expansion, as he made the transition from being a general medical patient with a pyelonephritis to a seriously ill ICU patient in septic shock. Thus not only do different populations of patients have different values of V_d , but each individual patient goes through these transitions, as demonstrated by this patient. The analysis of this patient's data was greatly facilitated, and indeed was only possible, by breaking his dosage history up into several parts. Each part was then analyzed, and the ending concentrations from one part were passed on to the next data set as initial conditions or concentrations of drug present prior to the first dose given in the next data set.

A PATIENT ON DIGOXIN AND QUINIDINE

Another example of the utility of using initial conditions is the example, provided through the courtesy of Dr. Marcus Haug, of a 72 year old woman, 4 ft 10 in tall, weighing only 75

pounds. She was admitted to a hospital with congestive heart failure and atrial fibrillation. Her creatinine clearance (CCr) was 38 ml/min/1.73m², falling to 23 after admission. She had been receiving 0.25 mg of digoxin daily. This was continued after admission to the hospital. A serum digoxin level was 1.8 ng/ml on admission.

Following this, her serum creatinine rose to 1.8 mg/dL, and her digoxin level after 5 days rose to 2.5 ng/ml. Her digoxin was stopped, even though she had no clinical manifestations of toxicity. The next day her serum level had fallen to 2.0, and the next day it was down to 1.4 ng/ml.

At this point her ventricular rate with her atrial fibrillation had risen beyond a reasonable resting rate, and she was begun again on digoxin, again at 0.25 mg/day, to control it. However, quinidine was now also added to her regimen. Her CCr was 22 ml/min/1.73m². Five days later her serum digoxin level was measured and found to be 7.6 ng/ml for a trough and 10.0 ng/ml two hours after the next dose was given.

What was going on here? She again had no clinical evidence of toxicity. Was all of this due to the digoxin - quinidine reaction? Was it a problem of digoxin - like material appearing in the assay as a result of her poor renal function? Was there something else in addition?

The clinical problem was analyzed as follows. First, her original dosage history on digoxin alone was fitted to her serum levels, using the 2-compartment population model for digoxin made from the work of Reuning, Sams, and Notari [3]. This included the three measured serum levels. At the end of that part of her history, just before her first dose of quinidine was added, her fitted and predicted central compartment (serum) concentration was 1.19 ng/ml, and her peripheral (nonserum) compartment concentration was 7.58 ug/kg. These relationships are shown in Figure 1.

These two ending values from this first phase of her analysis were passed on as initial concentrations of drug already present in those compartments of her pharmacokinetic model at the time her digoxin was restarted, but now with quinidine as well. The population model for digoxin with quinidine [2] was used. This model was not fitted to her subsequent serum levels, but merely used to supply predictions of those high measured levels. If the prediction was good, the interpretation would be that the interaction would quantitatively account for the measured levels found. If not, then another explanation would have to be devised.

As shown in Figure 2, the predicted concentration of 7.2 ng/ml closely matched the measured one of 7.6 ng/ml. In addition, the measured level of 10.0 ng/ml was predicted as 9.9 ng/ml. Because of these good predictions, it was felt that the digoxin-quinidine interaction explained the measured levels well, and that no other alternative explanation was needed. This is a good example of how pharmacokinetic analyses can be used to evaluate experiences with drugs, and can provide strong evidence for or against a particular question or issue, much more than a clinical opinion made without the aid of such a model. The use of initial conditions was the key to being able to change from one population model to another in the middle of a patient's history. In the same way, one can make the transition from regular theophylline to long-acting preparation, for example. With the use of initial conditions, one can thus follow the patient as he goes from one situation to another, passing on the data from one set to another.

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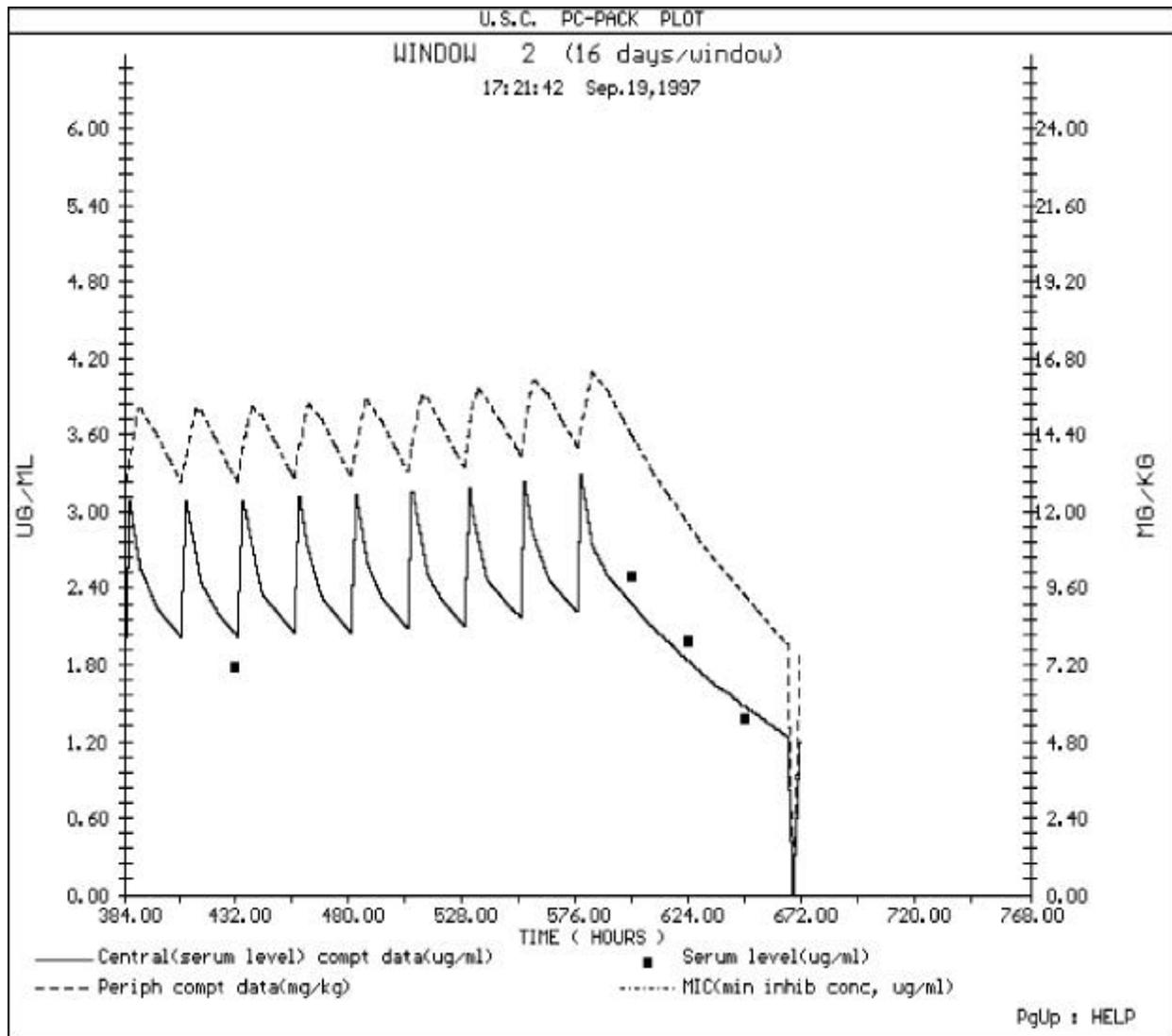


Figure 1. Plot of serum and peripheral compartment digoxin concentrations of patient admitted receiving digoxin. She was receiving 0.25 mg of digoxin daily, and weighed only 75 lb. Solid rectangles - measured serum levels. Solid line and left hand scale - digoxin serum concentrations. Dashed line and right hand scale - digoxin peripheral (nonserum) compartment concentrations. Using the Bayesian approach, the population model for digoxin was fitted to the patient's data of doses and serum levels. Serum levels rose as her renal function worsened. Digoxin was stopped after the serum level of 2.5 ng/ml was obtained, after which her serum levels fell to 1.4, and, in the fitted model, finally to 1.19ng/ml at the end of this plot, when digoxin was begun again, but along with quinidine.

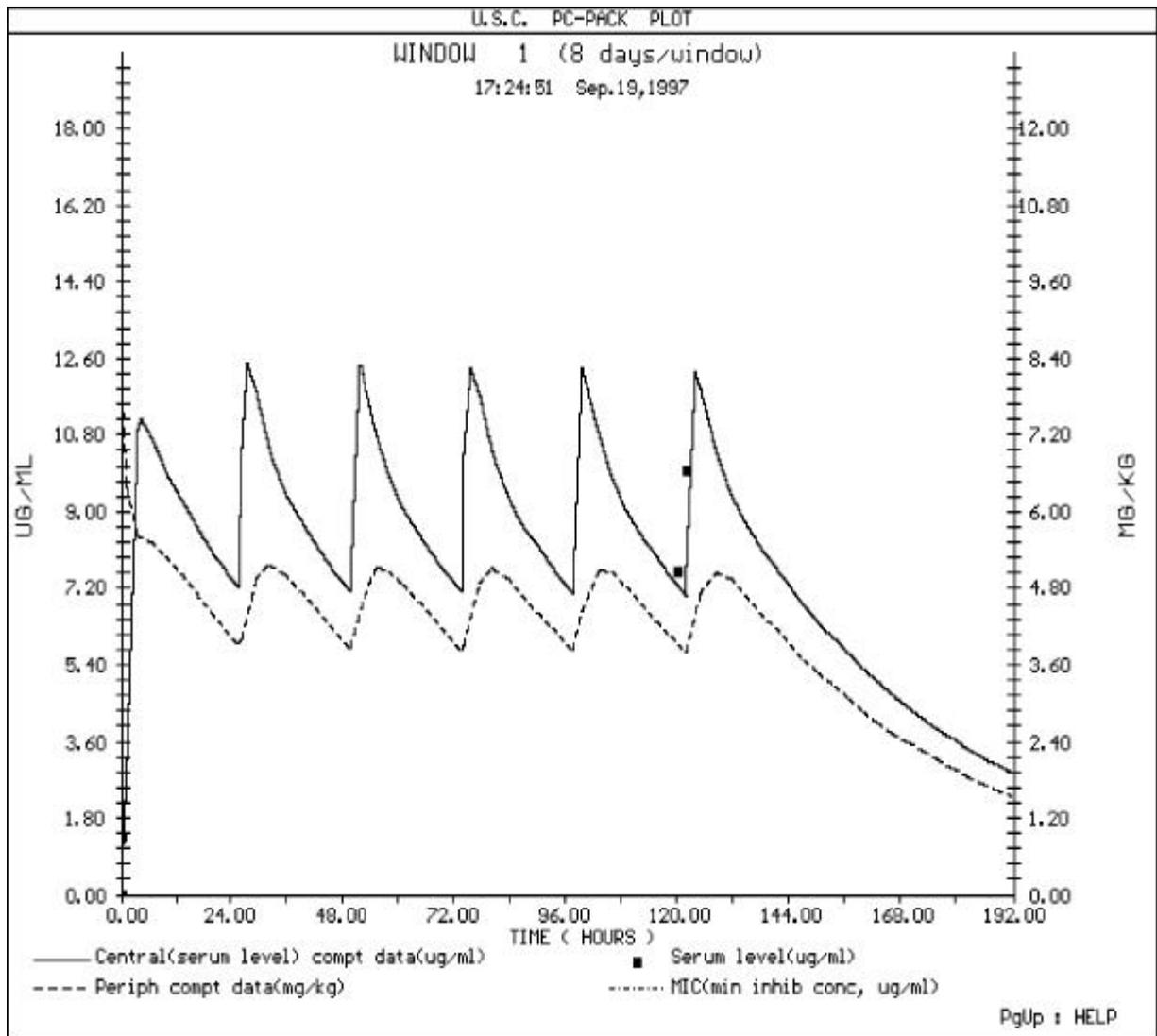


Figure 2. Plot of serum and peripheral compartment digoxin concentrations of patient admitted receiving digoxin. In this plot, digoxin was restarted at 0.25 mg/day, but along with quinidine. Solid rectangles - measured serum levels. Solid line and left hand scale - digoxin serum concentrations predicted using the population model for digoxin with quinidine [2]. Dashed line and right hand scale - predicted digoxin peripheral (nonserum) compartment concentrations. This plot begins with initial conditions equal to the final concentrations found at the end of the plot in Figure 1.