

VADS SYSTEM: CREATING VIRTUAL ANIMALS AND BACTERIA

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ACVIM Forum
May 23, 2001

Now I am going to talk about my portion of what we have been working on and I call it creating virtual animals and virtual bacteria.

VADS PK Modeling

- ◆ Want to extrapolate to population and estimate the applicability of a regimen to the population

Most of the pharmacokinetic data are based on a small number of animals, and so what we would like to be able to do is extrapolate to a population of animals and to try to make some kind of estimation of how applicable a particular regimen is to that population.

Virtual animals

- ◆ Our approach:
 - ▼ Create virtual animals via Monte Carlo simulations (using @Risk software)
- ◆ The software selects random values from a defined distribution multiple times, which values may then be used in other calculations

So, our approach is to create virtual animals and the way we are doing this is using Monte Carlo simulations, and the software we are using is actually a risk assessment software system. And essentially what the software does is it selects random values from a defined distribution as many times as you tell it to. Then those values can be used in other calculations, and that is what we're doing.

Case 1

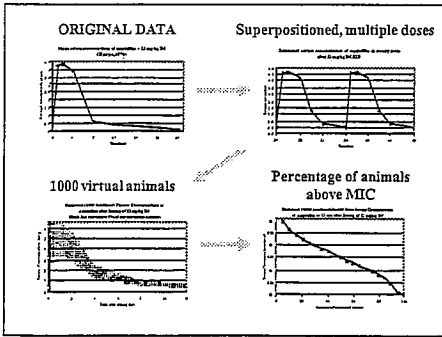
Available data are single dose mean serum concentrations (and SD)

Steps:

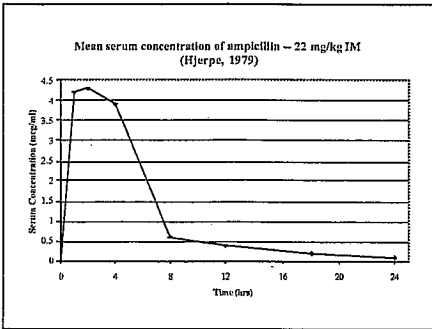
1. Model multiple doses via superpositioning
2. Simulate superpositioned data multiple times
3. View cumulative percentage of animals at a given concentration (corresponding to an MIC)

So let me just go through a couple of cases or examples. Dr. Langston talked about how we have two different types of data, particularly with ampicillin. In the first case, the data that we have available are single dose data, mean serum concentrations with an estimate of standard deviation. And so the steps that we are going through are to first model multiple doses, as Dr. Langston just talked about, using superpositioning. Then, what I do is simulate that superpositioned data multiple times, up to a thousand times or fifteen hundred times. And then we look at that to view a cumulative percentage of animals that are at a given concentration, that corresponds to MIC. The assumptions that we are making at this point are that we would like the serum concentration to remain higher

than the MIC for 100% of the dosing interval. And we realize that is relatively conservative, but it makes the modeling fairly straightforward.



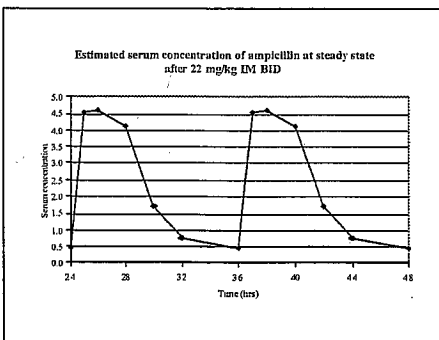
I have a flow chart here. So this is an example of single dose data, 22 mg/kg, IM



And this is what the mean serum concentrations look like over time. So that is what was available in the literature, and standard deviations were also reported for each time point.

hours	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Sum
0	0					0.00
1	4.2					4.20
2	4.3					4.30
4	3.9					3.90
8	0.59					0.59
12	0.35	0				0.35
13	0.323627	4.2				4.52
14	0.290928	4.3				4.59
16	0.235109	3.9				4.14
18	0.18158905	0.59				1.77
20	0.148111	0.35				0.74
24	0.09	0.35	0			0.45
25	0	0.323627	4.2			4.52
26	0	0.290928	4.3			4.59
28	0	0.235109	3.9			4.14
30	0	0.18158905	0.59			1.77
32	0	0.148111	0.35			0.74
36	0	0.09	0.35	0		0.45
37	0	0	0.323627	4.2		4.52

So our first step is just what Dr. Langston just showed you, the superpositioning. Here is dose 1, dose 2, dose 3, and so on, and you add them across to get the multiple dose concentration.

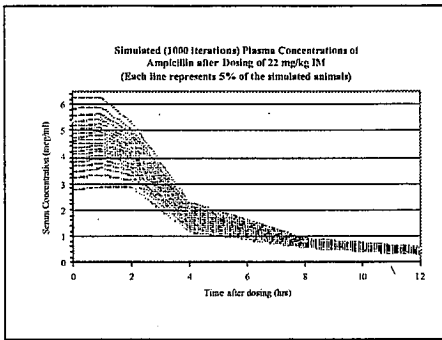


And then this is essentially the graph that he showed you, with the superpositioned, steady-state data.

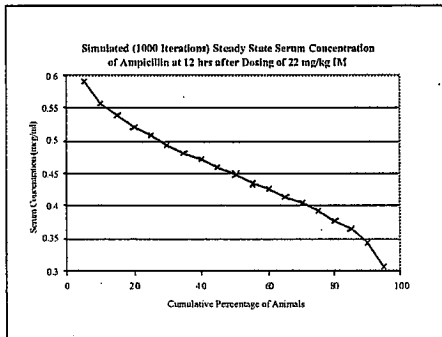
Hours	Mean	SD	
1	4.2	1.08	4.2
2	4.3	1.07	4.3
4	3.9	0.76	3.9
8	0.59	0.1	0.59
12	0.36	0.07	0.36
18	0.19	0.05	0.19
24	0.09	0.05	0.09
12 + 24 hr concentration			0.45

and then tell it to add across, so that is what this is right here. Adding 12 hour plus 24 hour concentrations.

I have used that data and plugged it into the At Risk software, the Monte Carlo simulation software, which is kind of built onto Microsoft Excel. So we built it into a spreadsheet. So here is the original data, and here are the mean concentrations and the standard deviations. And then at each time point I've shown, I don't actually utilize all of these time points, but at each time point, this is how I tell the simulation to select. This is the distribution that I would like the software to select for each simulation, so the mean is 4.2 and the standard deviation is 1.08. In this case, based on superpositioning, we found that 12 hour and 24 hour concentrations are all that we needed to add in order to get that 12 hour concentration trough. And so all I did was tell it to select from these two distributions



And I did this without the times, and these are actually each fifth percentile, so each line represents 5% of the simulated animals, so this is what the curve looks like. You could essentially superimpose that mean superpositioned data down the middle here, but this gives us a much better idea of the spread of the population.



So what we have done is take that information and the percentile information and draw this curve with the X-axis here is cumulative percentage of animals, and then serum concentration. So this is at 12 hours, so immediately prior to the next dose, what is the trough of these thousand virtual animals after 22mg/kg IM at steady state? And so what we would be presenting to the VADS user would be a graph similar to this and probably some information like; we estimate that 75% of the animals remain above a trough of 0.4 for a large percentage of the dosing interval. And so the regimen would be 22 mg/kg IM, q 12 hours, if you have an MIC of 0.4 or less, something along those lines.

Assumptions in Case 1

- ◆ Superpositioning assumes linearity
- ◆ To date, assume normal distribution of serum concentrations at a given time point
- ◆ Assume that serum concentration must remain above MIC for entire dosing interval for most drugs in the food animal repertoire
 - ▼ conservative

So some of the assumptions that we made as Dr. Langston talked about, like assuming linearity of our dosing, serum concentration and elimination. We also have assumed a normal distribution of serum concentrations at any given time point; that may or may not be the case. That is certainly in the @Risk software; you tell it to select what type of distribution to select from, and I have told it to select from a normal distribution. There are some opportunities to do other things with that, but at this point, that is what we have been doing. And then like I said, we are assuming that the serum concentration needs to be above the MIC for the entire dosing interval. And as we have said, anywhere from 50% to 90% depending on whether it is a Gram (-) or Gram (+) organism; that may in

fact be the case. But we are certainly trying to be conservative, at least at this point.

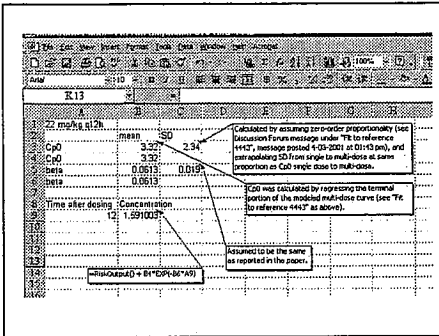
Case 2

Available data are calculated parameters

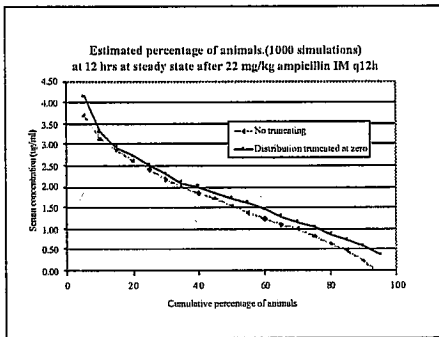
Steps:

1. Depending on data, may need to model for other parameters (e.g., Cp_0), or at other doses.
2. Simulate modeled equation multiple times.
3. View cumulative percentage of animals at a given concentration (corresponding to an MIC)

So what if we have calculated parameters? Mean and standard deviations for calculated parameters for modeled data. So, depending on the data, as Dr. Langston pointed out, sometimes we need to model further parameters, or model further doses. And then essentially do the same thing, but we have an equation for the model instead of just superpositioning. And then we look at that cumulative percentage of animals.



So, here is my @Risk model, if I am going to use an equation. So, the time we are looking at is 12 hours, immediately prior to the next dose. And I am modeling the concentration at that time based on a standard pharmacokinetic equation where the concentration at time, t = the y intercept times E to the $(-)$ Kt , Kb or β , being the elimination constant. And so here is Cp_0 , the Y intercept that has been modeled, regressed, based on the multi-dose curve. And the β is assumed to be the same, even though we have changed the dose.

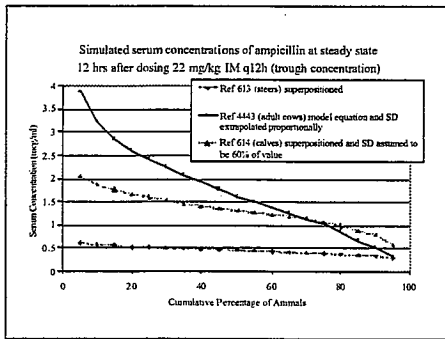


The problem that we have at this point is: what are we using for standard deviation, if we change the dose, we've gone from the dose used in that paper which was 7 mg/kg, and now we are going up to 22 mg/kg. We can extrapolate that mean, but what is the standard deviation. Standard deviations aren't exactly linear. So this is a big problem that we are having is how to estimate the variability of a modeled constant, or a modeled parameter, when we don't have any individual animal data. In order to do a simulation, we need to have some estimate as to what the variability is. In any case, I performed a thousand simulations, you can tell the @Risk software to truncate at zero or truncate at a particular point. And so I looked at it to see how much difference there was if I told it not to select anything below zero. And you can see that there are some differences in the distribution, but these are some of the things we are going to have to be looking at.

Questions

- ◆ How to reconcile data from different papers, and using different modeling techniques

So one of our big questions is how are we going to reconcile data from different papers? Dr. Langston alluded to that with the heterogeneous data, and how do we reconcile data using different modeling techniques? Superpositioning versus model equations.



There are three different references that were all modeled to the same dose, 22 mg/kg, IM, q 12 h. Steady-state concentration immediately prior to the next dose.

Techniques

- ◆ Acquire individual animal data to compare methods of population estimates
 - ▼ Mean serum concentrations
 - ▼ Modeled parameters

Steers in one paper, adult dairy cows in another, and calves in another, with different types of modeling. We are not so much concerned about what the actual serum concentration is at this point, but the difference between the fifth percentile and the eightieth percentile of animals, and how much difference is that going to make in our estimate of population. So see, these are some of the questions that we are wrestling with.

Questions

- ◆ How to reconcile data from different papers, and using different modeling techniques
- ◆ How to extrapolate variance when dose required is not as reported or if time points must be extrapolated to fit the superpositioning data

So what we would like to do, and we are in the process of doing is trying to acquire the individual animal data, the original data to compare methods of estimating these populations of animals. If we just go with mean serum concentrations and standard deviations, how does that look as compared to model parameters? Because in those previous papers, those are two different sets of data. So, we have no way, necessarily, of knowing what the differences really were in the outcome. And the other question, how do we extrapolate variance? When we are modeling for different dose, or if we have to extrapolate between time points, as we have to do occasionally with superpositioned data. How are we going to estimate what the standard deviation or the variance is, in order to come up with our Monte Carlo simulation?

Variance

- ◆ Must know in order to perform simulations
 - ▼ Need distribution characteristics
- ◆ When 2 values are added in superpositioning, the SD is the square root of the 2 squared SD's
- ◆ In other cases, have assumed SD is a constant proportion of the value and used that proportion to calculate SD of extrapolated values.
 - ▼ Invalid but easy

What we have done until now is assume that standard deviation is a constant proportionate of the mean value, and that is not really valid, but it is certainly easy. And what I have done in some cases is use a high estimate for standard deviation, just in order to come up with something. Recognizing that it is conservative, but that we don't have anything else to go on.

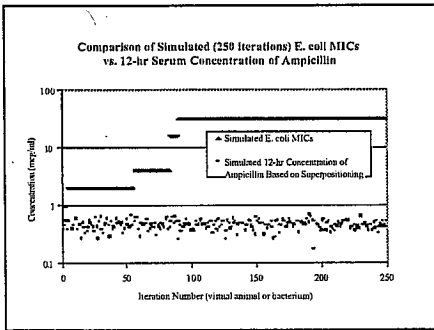
Unknown MIC

- ◆ What about modeling for empirical therapy?
 - ▼ Published and diagnostic laboratory susceptibility data will be used to construct a projected distribution of pathogen MICs.
 - ▼ The virtual animals will now be exposed to virtual pathogens.

So, what if we don't know what the MIC is? What if we don't have any culture and sensitivity results? All we have is modeling for, essentially, empirical therapy? So, what we are going to do is look at published data, and/or diagnostic laboratory susceptibility data, to construct what we think the distribution of pathogens is in terms of MIC. And then we will expose virtual animals to virtual pathogens.

MIC	Total	Susceptible
0.06	0	0
0.12	0	0
0.25	0	0
0.5	2	2
1	16	16
2	71	71
4	17	17
8	17	17
16	17	17
32	293	293
64	293	293
128	0	0
256	0	0
512	0	0

And so here is a set of data, this is Iowa State University diagnostic lab data from September of 1999 to October 2000. And these are MICs along here; they go from 0.06 to 512. And then the number of isolates of *E. coli* that were susceptible at those MICs. And what I've done here is not assume anything about the distribution, it is called a discrete distribution, meaning that however many



What the VADS user will see

- ◆ An estimate of the proportion of animals that are likely to respond successfully at the dose selected:
 - ▼ Or at least the proportion of animals that have a favorable pharmacokinetic profile

Summary comments by Dr. Apley not transcribed.