For regimen B the combined effect was 2·77 ln units (95% reduction) as compared with 1·58 ln units (79% reduction) for the sum of the individual effects. The interaction was significant ($P < 0.05$), suggesting synergism.

Discussion

The appropriate definition of synergism depends on the nature of the data, and this choice must be made before statistical analysis. In the present case study, the primary interest was in the proportional reduction in worm recovery, leading naturally to a definition of synergism on a multiplicative basis. The analysis was performed on the log transformed data.

If synergism had been incorrectly defined in terms of the additive effect then, for regimen B, the combined effect would be 37·88 units, as compared with 40·53 units for the sum of the individual effects, suggesting antagonism instead of synergism.

This example illustrates how the different definitions may give different results for the same data set.

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Book Review

Pharmacokinetic Modelling Using STELLA on the Apple Macintosh
By Clive Washington, Neena Washington and Clive G. Wilson
Published 1990 Ellis Horwood, London
118 pages
ISBN 0 13 662768 4 £30.00

The title of this book, as well as being rather cumbersome, would seem to suggest it would be of limited appeal to the casual browser. It must first of all attract those interested in pharmacokinetic modelling who have access to an Apple Macintosh and who also happen to have a copy of the program Structured Thinking Experimental Learning Laboratory with Animation (STELLA) installed. The most likely users of this book, then, would be students in an academic department where the staff are enthusiastic about STELLA, and where it would be advantageous for students (and staff) to have their own personal copies. Indeed, the book itself has grown out of manuals developed by the staff at Nottingham University.

The authors have the laudable aim of teaching the concepts of pharmacokinetics without introducing complex mathematical equations. This is done by imagining the disposition of a drug in the body as a series of boxes containing the drug, with simple rules determining how the drug is transferred from one box to another. For example, a drug could be imagined to be in the gastrointestinal tract, systemic blood, body tissue and urine as the four boxes with the rules governing transfer including irreversible transfer from gastrointestinal tract to blood, reversible transfer from blood to tissue, and irreversible transfer from blood to urine. This simple classical pharmacokinetic model has a surprisingly complex mathematical solution; simulation programs would be expected to deal with the complex mathematics once the investigator has defined the concepts.

Interestingly, STELLA itself does not use the pure mathematical approach for the simulation. An initial state is imagined; in the example given above, this would imagine all the drug in the gastrointestinal tract with none in the blood, tissues or urine. STELLA applies the rules to establish where the drug will be next, i.e. a proportion of the drug in the gastrointestinal tract would be transferred to the blood, but as there is no drug in the blood or tissue in the initial state, then none is transferred to tissue or urine. STELLA then recalculates for the next step, again transferring a proportion from the gastrointestinal tract to blood, and proportions from blood to tissue and urine. The third step calculates the same transfers plus one involving transfer from tissue back to blood. Computers can happily perform these calculations thousands of times in a few seconds and if the time scale of each step is chosen to be small enough, then the resulting plot of the results is indistinguishable from the same plot using the pure mathematical approach.

The STELLA method is referred to by the authors as numerical analysis or number crunching. In other disciplines it may be termed force field analysis, where all the forces acting on a system are considered determining any change in the system over a short time period. In this particular context, we might have a Catch-22 situation; if the computer does all the calculations, then why not let it use the pure mathematical approach? If the numerical approach is used then the researcher has to know how it works to avoid such howlers as transferring drug from boxes which are already empty.

However, once the user has mastered the elements of STELLA, and has played with a few simple what-if scenarios, the possibilities appear limitless. The great strength of the method is that quite complex models can be created. The authors rightly warn against drawing conclusions from a complex model (such as rate constants) when the precision of available data does not justify such conclusions. Nevertheless, in this what-if world, such exercises are justifiable in testing the plausibility of postulates.

Nearly half the book is used to present the basics of STELLA and of pharmacokinetics, as is to be expected for a manual. The second half presents detailed examples of more complex situations, including the correlation of pharmacokinetics and the behaviour of sustained-release preparations in the gastrointestinal tract. Individuals who take up this method enthusiastically will surely find most satisfaction in applying it to their own particular field of interest; if STELLA gives the unexpected prediction, then they will have learned something new, or may be forced to reconsider the original concepts. Either way, their knowledge and understanding will have been increased.

JOSEPH CHAMBERLAIN