The minimal model: an evolving methodology

COMMENT

ABSTRACT

After more than 20 years, minimal model analysis of intravenous glucose tolerance test glucose and insulin concentrations continues to be widely employed in studies of insulin sensitivity and insulin resistance. Moreover, problems encountered in solving the minimal model equations continue to find new solutions. Bayesian techniques enable prior knowledge to be incorporated into parameter estimation routines. They offer particular advantages in the measurement of insulin sensitivity with the minimal model, and provide an elegant means of improving model identification success rates and parameter precision. This comment describes the study by Agbaje and colleagues in this issue of Clinical Science that exemplifies a new phase in the evolution of minimal model practice.

Any measurement technique constitutes a domain of investigation in its own right. How accurate is it? we ask – or, how precise? – or, how sensitive? – and, importantly, how can these features be improved? In our attempts to answer these questions, a methodology evolves. The methodology surrounding the use of the minimal model began to develop in 1979 with the publication by Bergman and colleagues [1] of the original description of the model. From a number of alternatives, they selected the most parsimonious description of the decline in glucose concentrations during an intravenous glucose tolerance test (IVGTT) that could be represented in differential equations with a unique solution. The parameters of the equations of this 'minimal model' provided a measure of the sensitivity of glucose disappearance (the net effect of glucose elimination and suppression of hepatic glucose production) to the plasma insulin concentration, in other words, a true measure of insulin sensitivity (SI).

AM edline search on 'minimal model' and 'insulin sensitivity' reveals that over the past 10 years there have been, on average, over 40 publications per year describing studies involving the minimal model, the largest number of reports, 52, being for the year 2002. That the minimal model has been so enduring is, at first sight, surprising, given the variety of problems that have been encountered. The model was initially explored in dogs [2], which have an appreciably higher pancreatic insulin response to glucose than humans. Numerical methods are necessary to solve the equations of the minimal model and these require a sufficient plasma insulin response to intravenous glucose for a solution to the equations to be derived [3]. When the model was applied in studies in humans, a frequent finding was that this response was inadequate, particularly in cases of impaired glucose tolerance or Type II diabetes [3]. Add to this the emergence of physiologically unrealistic parameter values [4], and the recognition that the simplifications necessary to achieve soluble equations could be excessive [5], and it might seem surprising that the minimal model is still being used.

There are two reasons for the minimal model's enduring success. One is that there are a variety of solutions to the problems that have been encountered. The other is the relentless growth in the importance assigned to insulin resistance (abnormally low SI). Insulin resistance is a characteristic feature of obesity and is considered to be a key factor in the development of Type II diabetes. With substantial increases in the incidence of both obesity and Type II diabetes already occurring worldwide, and even greater increases anticipated [6], the need for the evaluation of SI in clinical research has expanded accordingly, and is likely to continue to expand.

The paper by Agbaje and colleagues [7] in this issue of Clinical Science exemplifies a new phase in the evolution of minimal model practice. First suggested for use with the minimal model by Cobelli and colleagues [8,9], Bayesian techniques for the estimation of unknown parameters differ from the more familiar regression techniques in allowing the incorporation of a priori knowledge about the parameters into the model identification process (the process for deriving unique values for the unknown parameters of the differential equations describing the model). There is, in fact, appreciable a priori knowledge about the minimal model measure of SI: we know that SI should not be negative, insulin never acts to increase glucose levels, and we know that there will be a population distribution for SI, characterized by

Key words: Bayesian analysis, insulin sensitivity, minimal model, Type II diabetes.
measures of centrality and the spread of values. Both these features of $S_I$ are exploited in the method proposed by Agbaje and colleagues [7]. $S_I$ is presumed to take on a log-normal distribution and, in Bayesian hierarchical analysis, individual value of $S_I$ are arrived at with reference to the distribution of values in the group as a whole. This approach provides an elegant alternative to some of the other strategies that have been employed to improve parameter estimation. For example, incorporation of an imputed glucose concentration measurement beyond the end of the IVGTT [4], and rejection of $S_I$ values lying beyond four standard deviations from the study group mean [10].

These advantages are, inevitably, bought at some cost. The Bayesian hierarchical approach requires that the entire study group be analysed in a single run, so any post-hoc changes to a particular IVGTT (resulting from, for example, previously unrecognized grounds for exclusion or the discovery of inaccurate glucose or insulin concentrations) require remodelling of the entire set of IVGTTs. Moreover, practical familiarity with Bayesian techniques remains limited. However, seen in the wider context, these considerations are simply aspects of the characteristics of the minimal model approach. Measurement of $S_I$ is necessarily complex, because, rather than a straightforward single measurement, a complex dynamic relationship has to be quantified. In the reference technique for measurement of $S_I$, the euglycaemic hyperinsulinaemic clamp, the necessary complexity is located in the procedure itself. Continuous infusion of insulin and glucose is required with continual glucose measurement and adjustment of the glucose infusion rate to maintain basal glucose levels. Calculation of $S_I$ is then straightforward, being, at its simplest, the glucose infusion rate necessary to maintain basal glucose levels in the presence of the sustained hyperinsulinaemia. In contrast, the procedure employed for the minimal model is relatively straightforward: an intravenous glucose injection, usually with an injection of insulin 20 min later. The complexity then lies in the computational techniques necessary to relate the continually changing glucose concentrations to the accompanying, and continually changing, insulin concentrations. In these techniques, a balance has to be struck between the realities of a complex physiology and the assumptions necessary to enable a computational solution to the minimal model equations. Bayesian approaches may be expected to help tip that balance in favour of physiology and may be especially appropriate given that the minimal model finds its most useful application in studies that require measurement of $S_I$ in large numbers of individuals or in population samples.

ACKNOWLEDGMENT

I.F.G. is supported by the Heart Disease and Diabetes Research Trust.

IAN F. GODSLAND
Endocrinology and Metabolic Medicine, Faculty of Medicine, Imperial College London, London W2 1NY, U.K.

(ON BEHALF OF THE EDITORIAL BOARD)

REFERENCES


Received 17 June 2003; accepted 9 July 2003
Published as Immediate Publication 9 July 2003, DOI 10.1042/CS20030207

© 2003 The Biochemical Society