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Letters to the Editor

Derivation of a quantitative measure of insulin sensitivity from the intravenous tolbutamide test using the minimal model of glucose dynamics

Dear Sir,

We were interested to read of the application of the minimal model of Bergman to the analysis of the intravenous tolbutamide test (IVTT) by Shennan et al. [1]. However, the authors claim that using their method, it was possible to obtain values of insulin sensitivity (S_i)from the ordinary intravenous glucose tolerance test (IVGTT), that were comparable to that of the IVTT, and indeed, go on to speculate that such values would be correlated with the euglycaemic clamp. We feel that such claims are not justified for the following reasons.

The authors have made some major modifications to the original model of Bergman [2]. First, they have defined P_4 wrongly. This is not the extrapolated basal hepatic glucose balance at zero time, but the basal hepatic glucose balance when plasma glucose is extrapolated to zero. They further state that they have arranged their algorithm so that P_4 is zero just after the start of the test. This is totally unnecessary as in the original minimal model the hepatic glucose balance decreases as a function of the rising plasma insulin and glucose. If B(t) is the hepatic glucose balance at any one time during the IVGTT, then this can be expressed thus:

$$B(t) = P_4 - [k_5 + k_6 I'(t)]G(t)$$

where k_5 and k_6 are the constants for non-insulin ans insulin dependent hepatic glucose balance, I′ is the concentration of insulin in a distant compartment from the plasma and G(t) is the plasma glucose at any one time during the IVGTT. Therefore, as glucose and insulin rise during the initial phase of the IVGTT, net hepatic glucose output falls anyway, and the less the greater the insulin resistance.

Secondly, they have assumed that non-insulin mediated glucose disposal (S_g) is zero during the test, i.e. they have defined the rate of change of glucose as a single exponential function which equals X(t).G(t). This effectively produces an insulin concentration dependent measure of K_G, the rate constant of glucose disposal derived from the IVGTT [3]. Non-insulin mediated glucose disposal makes up 75% of the fasting glucose disposal [4]. During the IVGTT, this value may fall, but certainly not to zero, as Shennan et al. have wrongly assumed. We find that there is a very significant correlation between S_g and K_G, with Spearman correlation coefficients of 0.55 in Type 2 (non-insulin-dependent) diabetic patients. In such patients, S_g may account for 30% of the variance in K_G, and is probably not negligible in normal subjects either.

Shennan et al. have stated as a reason why their results differed from those of Beard et al. [5] that they have zero-weighted their values for the IVGTT for the first 3 min of the test whilst Beard et al. have not. This is untrue. Bergman has shown that glucose distributes into the extracellular glucose space in the first 8 min of the IVGTT using extracellular markers [6]. As a result, he and coworkers usually zero-weight the errors for calculating their results for the first 8 min. Zero-weighting the errors for the first 3 min is not sufficient.

Using the above assumptions, it is not surprising that they have fractional standard deviations of S_i from both the IVGTT and IVTT that are lower than those of the unmodified IVGTT done by Beard et al. [5]. Shennan et al. conclude that, because the correlation between the IVGTT and IVTT using their method of analysis was good, their results for their unmodified IVGTT should correlate well with insulin sensitivity derived from the euglycaemic clamp. This may be so, because the value of S_i they derive from the IVGTT is an artefact. During the euglycaemic clamp, hepatic glucose production is suppressed at the levels of plasma insulin achieved, and therefore, most of the glucose disposal is via muscle. During the IVGTT, the fall in glucose is a result not only of clearance of glucose into muscle, but a decline in net hepatic glucose output. In assuming that P_4 is zero during the test, they have artificially made glucose clearance into muscle the predominant mechanism responsible for the decline in plasma glucose during the IVGTT. Further, as they assume that insulin mediated mechanisms alone are responsible, it would be very surprising if S_i calculated using their modification of the IVGTT did not correlate perfectly with the euglycaemic clamp. However, S_i from the IVGTT is a measure of insulin sensitivity not only of the peripheral clearance of glucose by muscle, but also of sensitivity of the inhibition of hepatic glucose production. It is this latter effect which is of major importance in the hypoglycaemic effect of insulin. The other great advantage of the IVGTT over the clamp is the derivation of a measure of non-insulin mediated glucose disposal (S_g) which these authors have dispensed with in their modification of the IVGTT. The S_g in non-insulin dependent diabetes is lower than in normal subjects [7] and may therefore contribute to the glucose intolerance found.

Yours sincerely,
L. L. Ng and T. D. R. Hockaday

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Response from the authors

Dear Sir,

Drs. Ng and Hockaday appear to believe that we have applied our modification of the Bergman/Cobelli [1, 2] minimal model of intravenous glucose tolerance test (IVGTT) glucose dynamics to the derivation of S_i from both the IVGTT and the intravenous tolbutamide test (IVTT). As a consequence of this, they dispute the use of our modification in the derivation of parameter estimates from the IVGTT. Thus we are criticised for (1) assuming unnecessarily that changes in net hepatic glucose balance are negligible when both glucose and insulin are rising, (2) for assuming that non-insulin mediated glucose uptake falls to zero during the IVGTT, and (3) for assuming that the predominant mechanism responsible for the decline in plasma glucose during the IVGTT is insulin-mediated uptake of glucose into muscle. However, these criticisms are based on a misunderstanding of our use of the modified model. The modified model was developed for a specific application, namely the analysis of IVTT glucose and insulin dynamics, and was not used for the analysis of the IVGTT.

During the hypoglycaemic phase of the IVTT, plasma glucose concentrations fall from their basal level due to the marked, rapid elevation in plasma insulin concentrations following tolbutamide administration. As we state in our paper, it is reasonable to assume that, under these conditions, changes in non-insulin dependent glucose uptake are negligible and that hepatic glucose production is suppressed. The simplified model we presented incorporated these assumptions. This model was not intended as a substitute for the original minimal model but rather as an extension of the use of the model to the analysis of changes occurring during insulin-induced hypoglycaemia. Our intention was to validate the estimates of S_i obtained from IVTT data using the modified model by comparing them with estimates derived from IVGTT data using the original, well-validated, minimal model. We regret not having stated explicitly that in our modelling analyses of the IVGTTs we used the original minimal model as described by Bergman and coworkers, and welcome the opportunity to clarify the way in which our study was constructed.

Nevertheless, an important point emerges from Ng and Hockadays' criticism of our use of the term P_4. Bergman and co-workers originally used the term P_4 to specify B_o, i.e. basal hepatic glucose balance when the plasma glucose concentration is extrapolated to zero [1]. In our paper we define P_4 as $(k_1+k_5)G_b$

where

k_1 = rate constant governing non-insulin dependent glucose uptake into peripheral tissues

k_5 = rate constant governing non-insulin dependent hepatic glucose balance

G_b = basal plasma glucose concentration

In fact P_4 and $-(k_1+k_5)G_b$ can be used interchangeably [2]. This is demonstrated below.

The minimal model of glucose dynamics is represented by the following Eq.:

$$dG_t/dt = -(P_1+X_t)G_t + P_4 \quad (A)$$

$$dX_t/dt = -P_2X_t + P_3[I_t-I_b] \quad (B)$$

where

$P_1 = (k_1+k_5)$

P_2 = rate constant of insulin decay from a remote compartment

P_3 = rate constant determining action of plasma insulin via the remote compartment

X_t = net action of insulin from the remote compartment

G_t = plasma glucose concentration at time t

I_t = plasma insulin concentration at time t

I_b = basal plasma insulin concentration

In the basal, steady state:

$dG_t/dt = 0$

$G_t = G_b$

$dX_t = 0$

and, by substitution into Eq. (B):

$X_t = 0$

therefore, by substitution into Eq. (A):

$P_4 = P_1G_b$

i.e.

$P_4 = -(k_5+k_1)G_b$

Our mathematical definition of P_4 was therefore correct, although our description of the term P_4 was misleading. The term P_1G_b would have been more consistent with established terminology. In retrospect, a brief mention of the above equality would have assisted clarity. However, our formulation of the minimal model of glucose dynamics during the IVTT remains unaffected by these considerations. As we describe in our paper, it is assumed that during the early phase of insulin induced hypoglycaemia following tolbutamide injection, hepatic glucose production is suppressed. Furthermore, it is assumed that changes in non-insulin dependent glucose uptake are negligible. Given these assumptions, the equation describing the rate of change of plasma glucose concentration reduces to that given in our paper:

$$dG_t/dt = -X_tG_t$$

We would like to thank Drs. Ng and Hockaday for bringing our attention to the implications of these ambiguities in our paper, and trust that the detailed description of the model given above goes some way towards clarifying and justifying the modifications we have made. We would like to add that the formulation of a model is a continuing process, with modifications made following experience with its application and further consideration of the assumptions it involves; publications regarding model-based research are always, to some extent, progress reports.

Yours sincerely,

I. F. Godsland and V. Wynn

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