Sulphonylurea and insulin: combined treatment in Type 1 (insulin-dependent) diabetes

Dear Sir,

In contrast to the recent observations of Ratzmann et al. [1] that tolbutamide is *not* a useful adjunct to insulin treatment in Type 1 diabetes, I would like to refer to our recent work on a similar theme [2]. We demonstrated that when a combination of insulin and glibenclamide treatment was given to patients with Type 1 diabetes in a randomized and double-blind cross-over trial for periods of 3 months, measurements of diabetic control improved significantly in those patients who retained residual endogenous insulin secretion. During an oral glucose tolerance test 3 months after combined treatment, C-peptide secretion increased by 47%, the mean $\pm$ SD daily blood glucose level fell from 8.4 ± 1.7 to 7.4 ± 1.5 mmol/l ($p < 0.02$) and the mean glycosylated haemoglobin decreased from $8.1 \pm 0.5\%$ to $7.5 \pm 0.9\%$ ($p < 0.05$). These results substantiate a previous study [3] which showed that glibenclamide, when added to the insulin regimen of Type 1 diabetic patients with residual insulin secretion, increased their C-peptide secretion by 60% over a 1-month period.

Less than half of the seven subjects in Ratzmann et al.'s study could be described as having retained residual endogenous insulin secretion according to the criteria of Madsbad [4] of a plasma C-peptide concentration > 0.07 mmol/l. Although limited insulin and glibenclamide treatment may be only of limited value, I believe that further research is needed to follow up our observations and determine how long increased insulin secretion and improved metabolic control persist.

Yours sincerely,

B. J. Burke

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Dr. B. J. Burke
Edgware General Hospital
Edgware
Middlesex HA8 OAD
UK

Reply from the authors

Dear Sir,

Burke et al. [1] demonstrated that combined insulin and glibenclamide treatment for 3 months may produce useful improvement of diabetic control in Type 1 (insulin-dependent) diabetic patients who retained residual endogenous insulin secretion. In contrast to this observation, Ward et al. [2] failed to demonstrate any additive effect of sulphonylurea treatment in addition to insulin on the control of blood glucose in Type 1 diabetes. In addition, Burke and Sherrif [3] showed *no* beneficial effect on metabolic control in Type 1 diabetic patients after 4 weeks' treatment with glibenclamide and insulin, although a significant increase in residual β -cell function was demonstrated.

The mechanism by which sulphonylureas lower blood glucose appears to result from the release of insulin and, possibly, also by extra-pancreatic mechanisms. We examined whether tolbutamide has any *acute* or *short-term* effects on insulin action in Type 1 diabetes [4]. The results suggest that tolbutamide does not exert any acute or short-term effects on insulin action *in vivo*. Our results do not provide support for the idea that this agent is a clinically useful adjunct to insulin in such patients. The failure to demonstrate any extra-pancreatic effects of tolbutamide in Type 1 diabetic patients is in agreement with data on forearm insulin-mediated glucose uptake in non-diabetic and diabetic subjects [5, 6]. Grunberger et al. [7] demonstrated similar results. In our study, treatment with tolbutamide, in addition to insulin, for 6 days failed to increase fasting C-peptide levels in three patients with residual endogenous insulin secretion [4]. A variety of factors, including the type of sulphonylurea, the dose and duration of therapy, could explain the differences between the results of our study [4] and the clinical report on a randomized double-blind with glibenclamide for 3 months [1]. I agree with the view of Dr. Burke that further research is necessary to follow up his observations and to determine how long increased insulin secretion and improved metabolic control persist.

Yours sincerely,

K. P. Ratzmann

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Dr. Klaus P. Ratzmann
Centre for Diabetes and Metabolic Disorders
Klosterstraße 71–72
DDR-1020 Berlin
GDR

Continuing high incidence of diabetes mellitus in Scottish children

Dear Sir,

We reported recently a substantial rise in the incidence of diabetes mellitus in childhood for the years 1968–76 in Scotland [1]. We have continued to monitor admissions to Scottish hospitals of children aged less than 19 years and can now report the estimated incidence rates for the years 1977 to 1979. Table 1 shows first admission incidence rates for the years 1968 to 1979. Rates for the years up to 1976 have been corrected for readmissions as previously described [1].

Table 1. Incidence of diabetes mellitus in Scottish children 1968–79

Year	Estimated annual incidence ^a (per 100 000 children aged 0–18 years)	
	Boys	Girls
1968	10.2	9.8
1969	12.0	10.3
1970	11.3	13.3
1971	13.8	11.4
1972	14.2	13.4
1973	16.0	14.3
1974	15.0	13.9
1975	17.5	14.4
1976	19.6	17.2
1977	17.7	17.6
1978	22.5	22.4
1979	18.1 ^a	17.1 ^b

^a age standardised to 1971 census of Scottish population; ^b excludes 1979 admissions discharged in 1980

Cases were only included for the period 1977 to 1979 if they had no record of a previous admission since 1968. The incidence rate increased to a peak at 22 per 100 000 in 1978 followed by a decline to 18 per 100 000 in 1979.

For the years 1977–1979, seasonal variation was evident only in children aged 5 years or more with increased incidence rates during the autumn and winter months. In addition, significant geographic variation persisted with decreased rates in the central lowland areas.

Although there has been a great deal of work that suggests a genetic influence in susceptibility to Type 1 diabetes as evidenced by the association with certain HLA haplotypes, the increasing incidence and seasonal variation strongly support environmental influences. It is unlikely that admission practices have changed sufficiently during the past 12 years to explain the apparent increase in incidence. Geographical and seasonal variation are consistent with a viral aetiology and may explain the peak incidence in 1978, although they could hardly account for the striking rise overall.

Yours sincerely,

J. A. Grisso, C. C. Patterson, P. G. Smith, M. Thorogood,
M. A. Heasman and J. Webb

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Dr. P. G. Smith
Department of Epidemiology
London School of Hygiene and Tropical Medicine
London WC1E 7HT
UK

Book reviews

E. R. Carson, C. Cobelli, L. Finkelstein. The mathematical modelling of metabolic and endocrine systems. New York, Chichester, Brisbane, Toronto Singapore: John Wiley & Sons 1983. 394 pp, hardback, £ 49.00

This book is one of a series of five on aspects of biomedical engineering and health systems. The authors have all been active in the field of mathematical modelling of metabolic processes over the last ten years, generally in collaboration with colleagues trained in the biological and medical sciences. This has resulted in their having come to terms with current concepts and knowledge in the field of metabolic regulation, but only to a lesser extent has it enabled them to communicate their ideas and approach to those less familiar with mathematics. It has always disappointed at least one of the authors that modelling of endocrine systems has not made more impact in the field of clinical and experimental investigations, and no doubt this has in part been the drive behind the writing of this book.

Two languages are used throughout the text, English and mathematics. The English is commendably clear, marred only by the very liberal use of a vocabulary that will be unfamiliar to those trained only in the biological sciences. The mathematics is represented by equations that appear on perhaps half the pages of the book, and in general will be incomprehensible to anyone who has not had a grounding in integral calculus. Non-mathematicians will therefore find it difficult to read the book in any systematic fashion, though dipping into individual chapters will still give useful insights into what is being attempted. It is this communication gap which probably explains the lack of impact of mathematical modelling on the metabolic world at large, the existence of as many as fifty proposed models of the insulin/glucose system being a surprise to your reviewer, for example.

It is, however, revealing to put oneself in the place of a systems engineer; despite sixteen lines on hormones in Chapter 2, the world of first phase insulin release and glucose-6-phosphate regulation of glycogen synthase might seem extra-galactic. The limitations of modelling and the importance of a knowledge of simple physiology are unintentionally highlighted in Chapter 9, discussing model validation, where model 6 of glucose utilization is only preferred to model 5 on the basis of overall physiological plausibility, the latter model simply ignoring regulation of hepatic glucose output.

If, however, you are mathematically literate, and if you are interested in the possibilities of using modelling of metabolic systems in your work, then this must be the book you always wanted. Aside from useful chapters on the purposes of metabolic modelling and a summary chapter on the modelling process which is an admirably clear exposition of the basic steps in using these techniques correctly, there are long sections on the different model types and on model identification (modification of model structure and parameters to minimize error between model prediction and experimental input/output performance).

Perhaps more important is the emphasis given to model validation (Chapter 9, 75 pages), an area still largely ignored by many scientists dabbling in the field. As with many parts of the book this chapter will be particularly familiar to readers with an interest in carbohydrate metabolism, for many of the examples used in the book are based on the insulin/glucose regulatory system.

My grouses? Well, some of the figures reproduce themselves at intervals throughout the book, while others are unnecessarily spread over two or more pages.

Philip Home (Newcastle upon Tyne)