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Improved effect of tolbutamide when given before food in patients on long-term therapy

The current issue of the British National Formulary (No. 7, 1984) suggests that tolbutamide be given 'with or after breakfast or in divided doses'. Using a simple questionnaire we found that most patients in our diabetic clinic take tolbutamide with, rather than before, their meals. To determine whether the administration of the drug before meals would improve its therapeutic efficacy, we studied the effect on postprandial hyperglycaemia of tolbutamide given before or with food.

Five male and seven female diabetics aged 43–67 years, were studied. All had been on tolbutamide three times a day for at least 6 months, and were well controlled with glycosylated haemoglobin within our normal range (4.5–8.5%), and were within 15% of their ideal body weight. Subjects were studied in hospital and received in random order on 2 consecutive days, their usual dose of tolbutamide, either 30 min before, or with, an identical lunch in keeping with their usual diet. When given with lunch, they swallowed the tablet(s) whole with the first mouthful of food. Plasma glucose was measured using the glucose oxidase method at 30 min intervals from 30 min before till 120 min after the meal.

Results of plasma glucose are shown in Table 1.

Statistical analysis was performed using Student's paired *t*-test. At −30, 0 and 30 min, there was no significant difference. Significantly lower blood glucose values occurred when tolbutamide was given before meals, at 60 min ($P < 0.02$), 90 min ($P < 0.02$) and 120 min ($P < 0.05$) following food intake.

Analysis for change from the baseline value of −30 min, showed significantly lower ($P < 0.05$) blood glucose increments at 60, 90 and 120 min when tolbutamide was given before food.

The predictable effects of drugs may be modified by the concomitant intake of food (Tuttle, 1982). In diabetic patients not previously exposed to a sulphonylurea glibenclamide given 30 min before breakfast showed a

Table 1 Plasma glucose (mmol/l) in response to tolbutamide and food (mean ± s.d.)

	Time (min)					
	−30	*0*	*30*	*60*	*90*	*120*
Tolbutamide 30 min before food	8.4 ± 2.1	8.6 ± 1.9	9.7 ± 2.8	9.9 ± 3.4**	9.2 ± 3.3**	8.7 ± 2.8*
Tolbutamide with food	8.6 ± 2.5	8.6 ± 2.4	9.6 ± 2.9	11.2 ± 3.2	10.5 ± 3.3	9.8 ± 2.8

*$P < 0.05$, **$P < 0.02$

significantly greater reduction in blood glucose when compared to glibenclamide given with breakfast (Sartor *et al.*, 1982). Sartor *et al.* (1980) did not observe any difference due to food in either the absorption or elimination of tolbutamide in healthy volunteers given a single dose of the drug. In contrast, in the diabetic subject, the absorption of another sulphonylurea, glipizide, was significantly delayed by food intake (Wåhlin-Boll *et al.*, 1980). These findings would suggest that although food intake does not appear to significantly alter the pharmacokinetics of sulphonylureas in normal volunteers, the same may not necessarily apply to diabetics. The mechanism of action of tolbutamide is complex. Long term therapy may actually produce a decline in glucose stimulated insulin release, in spite of improved glucose tolerance (Jackson & Bressler, 1981). Lebovitz & Feinglos (1978) have suggested that amongst important extra-pancreatic actions of the drug there is induction of insulin receptors in the peripheral tissues. The net effect of its action will therefore depend on a balance between insulin production and enhanced peripheral action, and so the timing of the insulin peak in relation to food would still be important in the control of postprandial hyperglycaemia.

We have found that administration of the drug 30 min before a meal significantly reduced postprandial blood glucose increments when compared to concurrent administration of tolbutamide and food. It is possible that this effect is achieved because it may be necessary that a critical serum concentration of the drug be attained before the entrance of food into the gastrointestinal tract. We did not observe any unwanted side effects of tolbutamide taken on an empty stomach. Certainly there is improved glucose utilization following food load when tolbutamide is given half an hour before the meal, and this beneficial effect is maintained for up to 2 h after eating.

Our study is interesting in that it has examined the effect of tolbutamide in diabetics on long term therapy, in whom, presumably, both pancreatic and extrapancreatic effects of the drug would be of importance, and is clinically relevant. Our results suggest that in the long term, pre-prandial treatment is more effective than with-food dosing.

Tolbutamide is a very widely used oral hypoglycaemic agent and it would appear appropriate to suggest that it is prescribed 30 min before meals in order to maintain postprandial hyperglycaemia within a narrower and more physiological range.

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Nifedipine and endocrine status in diabetic patients

In a recent article, Semple *et al.* (1984) have observed that oral verapamil in the standard dose has no significant effect on pituitary-testicular or pituitary-thyroid function. It has been shown that purified growth hormone (GH) releasing factor increases ^{45}Ca uptake into pituitary cells in the rat with a concurrent increase in GH release (Milligan *et al.*, 1972). On the other hand, it has been suggested that GH hypersecretion may contribute to development of some of the long term complications of diabetes (Gerich *et al.*, 1984). Nifedipine, a