

Effect of trimethoprim-sulfamethoxazole on blood insulin and glucose concentrations of diabetics

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Summary: Trimethoprim-sulfamethoxazole (TMP-SMX) caused no significant changes in the blood glucose or insulin concentrations of diabetic subjects treated by dietary measures alone or by insulin and diet. In only one of eight subjects receiving oral hypoglycemic agents for the control of diabetes did a significant immediate increase in immunoreactive insulin follow administration of TMP-SMX. In the same patient hypoglycemic symptoms were present after the agent had been taken for 14 days.

Résumé: L'effet du triméthoprime-sulfaméthoxazole sur l'insulinémie et la glycémie de diabétiques

Chez des diabétiques traités par le seul régime alimentaire ou par l'association insuline et régime alimentaire, le triméthoprime-sulfaméthoxazole (TMP-SMX) n'a entraîné aucune modification de l'insulinémie et de la glycémie. Ce n'est que chez un seul des huit diabétiques traités par des médicaments hypoglycémisants oraux qu'on a constaté une augmentation notable immédiate d'insuline immunoréactive après administration de TMP-SMX. C'est chez ce même malade que sont apparus des symptômes hypoglycémiques 14 jours après le début du traitement au TMP-SMX.

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In 1965 Soeldner and Steinke reported the cases of two patients with severe hypoglycemia who were receiving treatment with both tolbutamide and sulfisoxazole.¹ One patient responded well to oral administration of glucose and frequent feeding; the other, in spite of the infusion of 50% glucose and subsequently of a litre of 10% glucose, died 6 hours after its completion and after she had taken food by mouth. The concentration of glucose in blood at autopsy from the left cardiac ventricle 4 hours after death was 8 mg/dl and in the spinal fluid it was 5 mg/dl. Insulin assays done at the same time showed values of 6 and 17 μ U/ml, well within the normal range for a normal subject after an overnight fast.

Christensen, Hansen and Kristensen have called attention to the relation of tolbutamide-induced hypoglycemia to simultaneously administered sulfonamides.² They observed a very considerable increase in the amount of dialyzable (unbound) tolbutamide after the administration of sulfaphenazole and significant delay in the rate of disappearance of tolbutamide from serum—its half-life rose from the normal of 4 to as long as 17 hours.

Both tolbutamide³ and sulfaphenazole⁴ are strongly bound to serum albumin. Very little tolbutamide is found in a free diffusible form. Therefore it has been postulated that an increase in its amount in the unbound form is the result of its displacement from albumin binding-sites by sulfaphenazole. On the other hand, the same effect may be the consequence of delayed breakdown or excretion of tolbutamide. However, the carboxy form has been found to be within the normal range.

Christensen also studied the effects of other sulfonamides on tolbutamide-treated diabetics, viz. sulfadiazine, sulfadimethoxine, sulfamethoxyypyridazine and sulfafurazole. No significant hypoglycemia was observed. There was only a moderate in-

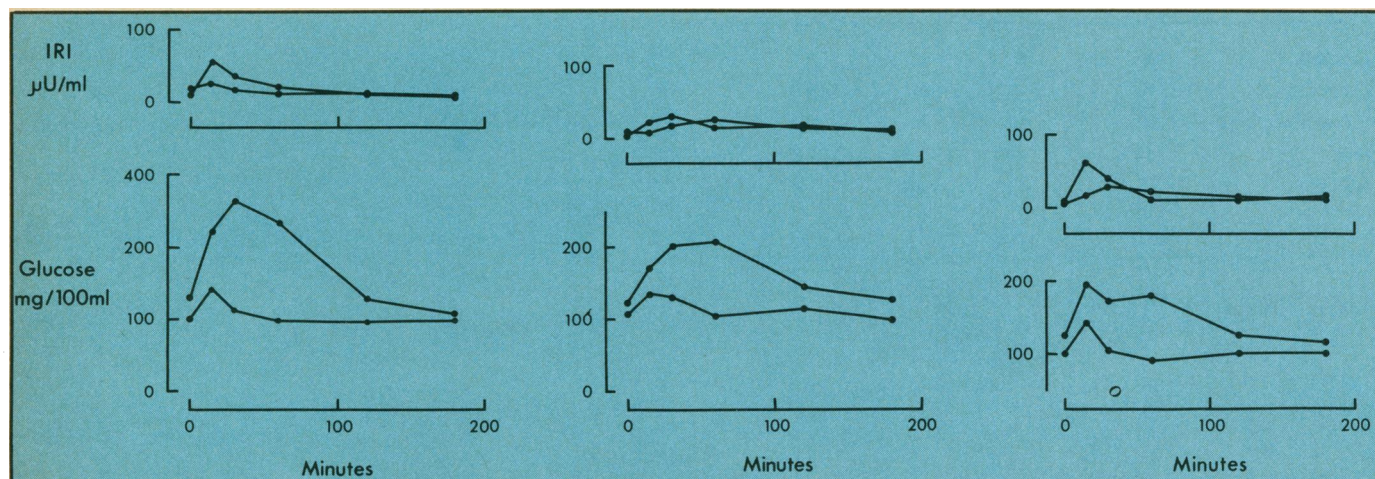


FIG. 1—Blood insulin and glucose concentrations in diabetic patients treated by dietary measures only. Left: control values. Centre: immediate response after TMP-SMX. Right: response after receiving TMP-SMX for 14 days.

crease in the unbound tolbutamide and no significant effect on the serum tolbutamide concentration.

Phenylbutazone⁵ and salicylates³ also cause an increase in the proportion of unbound tolbutamide. Both sulfaphenazole and phenylbutazone contain a pyrazole ring. It has been suggested that these two drugs should not be given concomitantly to diabetics who are being treated with tolbutamide.

The normal insulin values in fatal hypoglycemia reported in their patient by Soeldner and Steinke¹ suggest a disturbance in the relation between the concentration of blood glucose and

insulin release from the pancreas, probably owing to persistent stimulation of the pancreatic islets by tolbutamide.⁶ On the other hand, tolbutamide administration is thought by some to lower significantly the output of hepatic glucose into the hepatic vein.⁷ It is likely that the combination of these factors was responsible for the fatal outcome in the case mentioned.

These reports prompted us to measure serum insulin and blood glucose concentrations in diabetics being treated with oral hypoglycemic agents and diet, after the administration of trimethoprim-sulfamethoxazole (TMP-SMX). The same inves-

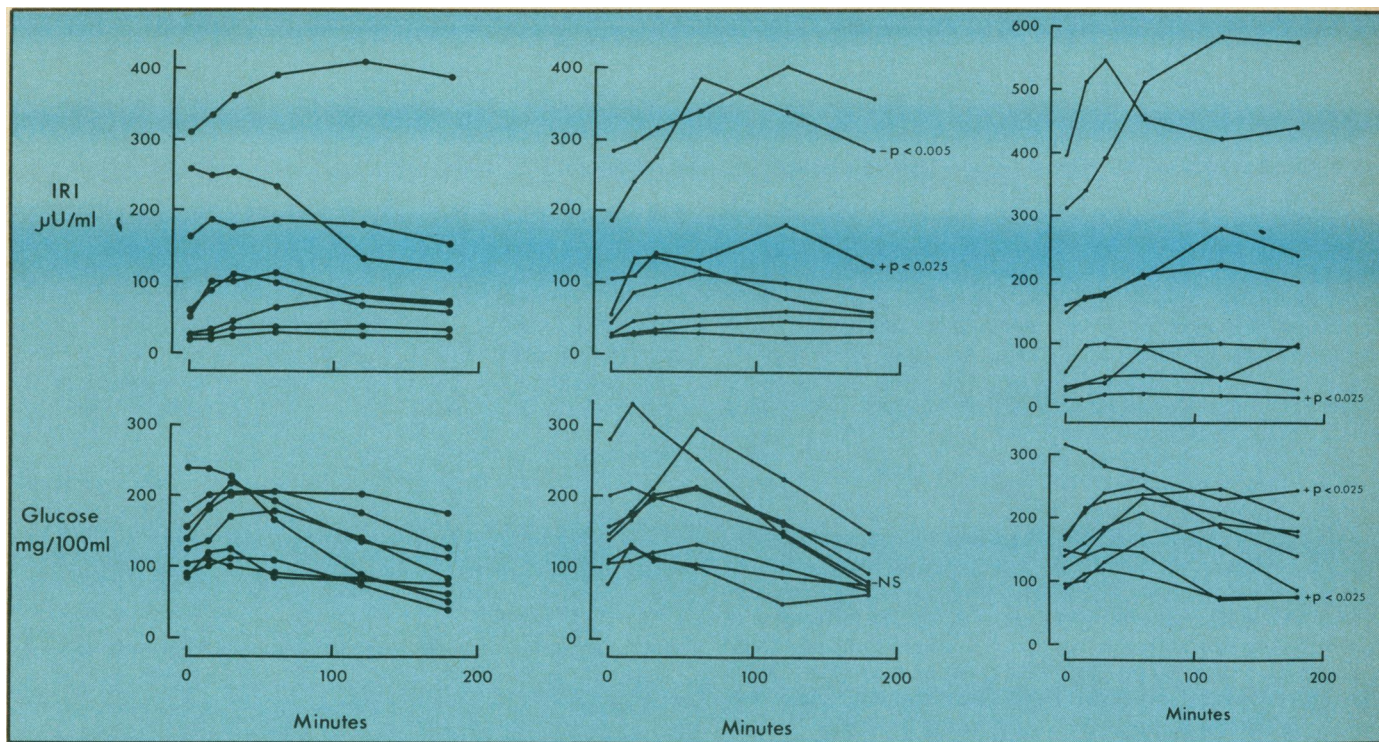


FIG. 2—Blood insulin and glucose concentrations in diabetic patients treated with insulin. Left: control values. Centre: immediate response after TMP-SMX. Right: response after receiving TMP-SMX for 14 days.

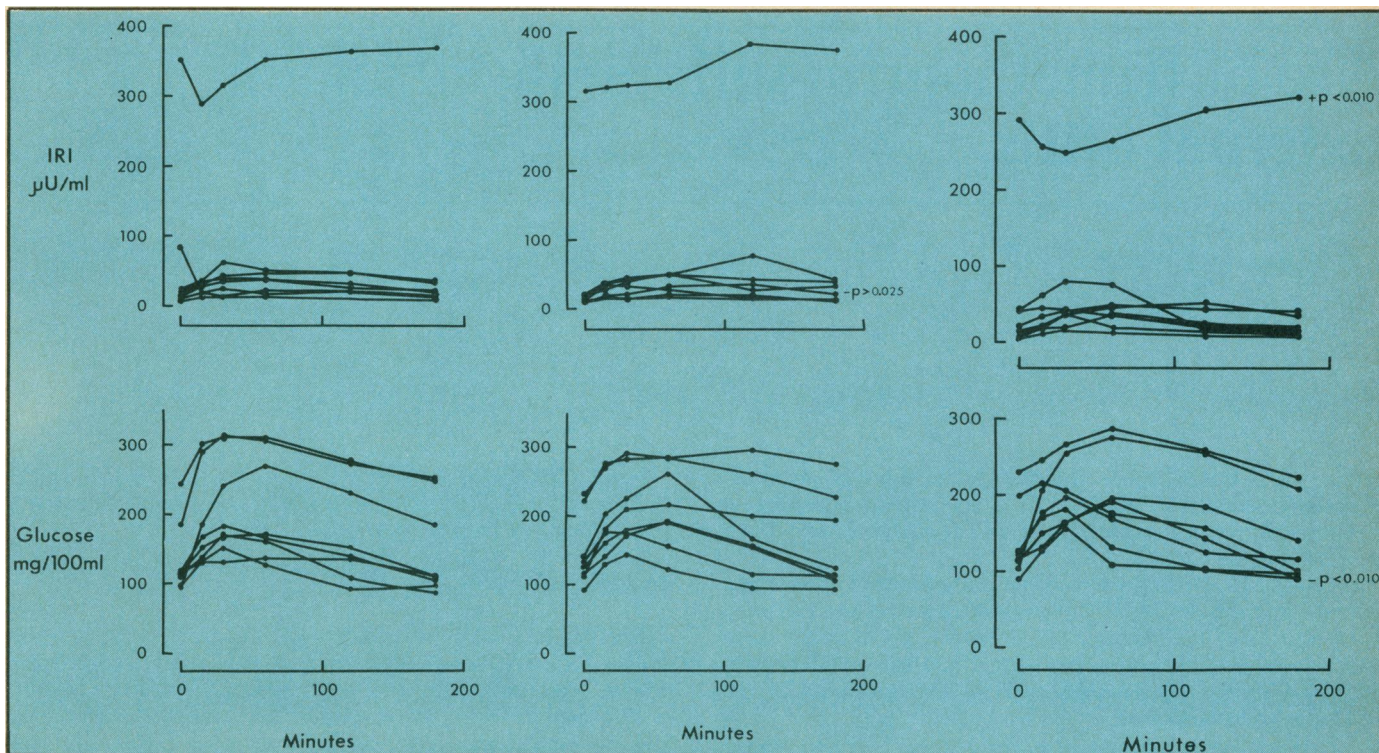


FIG. 3—Blood insulin and glucose concentrations in diabetic patients treated with hypoglycemic agents. Left: control values. Centre: immediate response after TMP-SMX. Right: response after receiving TMP-SMX for 14 days.

tigation was carried out in diabetics who had only recently been started on insulin therapy. However, the rapid development of insulin antibodies and the interference they cause in the immunoassay of insulin render the values obtained meaningless.

Material and methods

A group of randomly chosen patients from our diabetic clinic who were being treated with oral hypoglycemic agents, diet and insulin were the subjects of a clinical trial with TMP-SMX. Patients with hematologic diseases, folic acid deficiency, pregnancy, malignant disease, renal disease, disease of the small or large bowel, or allergy to sulfonamides were not included. The original total of 27 patients was reduced to 18 for various reasons.

Fasting insulin and blood glucose concentrations were determined at the start of the investigation. After the usual oral hypoglycemic agent or dose of insulin had been given, followed by a breakfast of 450 calories, blood samples for measurement of glucose and insulin were taken at 15, 30, 60, 120 and 180 minutes. At the next visit, a week later, the same procedure was followed except that TMP-SMX was given after the meal. Blood samples were again obtained at the same intervals as before. The patients were then given a supply of TMP-SMX to last 14 days and instructed to take two tablets twice daily. When the course was ended a third visit was paid to the clinic and the blood tests were repeated.

Results

For patients whose diabetes was being managed by dietary measures alone, the values for insulin and glucose were not significantly affected by TMP-SMX (Fig. 1). Of eight patients who were receiving insulin, two showed a significant increase in blood glucose concentration and one a decrease in blood insulin concentration after taking TMP-SMX for 14 days (Fig. 2). No tendency to lowering of the blood sugar concentrations was noted. No interpretation of the insulin assays is possible.

In Fig. 3 are shown the data obtained on eight patients who were being treated with oral hypoglycemic agents. In one of

these, a poorly controlled diabetic, a significant increase in immunoreactive insulin concentration occurred as an immediate reaction to TMP-SMX; nevertheless, the value was still within the normal range and not accompanied by a lowering of the blood glucose value. However, after the patient had taken the agent for 14 days the blood glucose at 3 hours was significantly lowered. By this time the patient was complaining bitterly of hypoglycemic symptoms. These disappeared within 2 days when the TMP-SMX was discontinued and insulin substituted for the sulfonylurea he had been taking.

Another patient in this group, also a poorly controlled diabetic, showed a significant decrease in blood insulin concentration after treatment with TMP-SMX for 14 days. However, his concentration had been extremely high initially owing to the development of insulin antibodies.

Conclusions

Based on previous reports of isolated cases of severe hypoglycemia in patients receiving oral hypoglycemic agents, as well as on the observation of one case suggestive of this occurrence within our own experience, we would recommend careful monitoring of the blood glucose concentration in diabetics treated with sulfonylurea to whom the combination trimethoprim-sulfamethoxazole is being simultaneously administered.

References

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Use of trimethoprim-sulfamethoxazole in external otitis

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A study was conducted on the therapeutic value of trimethoprim-sulfamethoxazole (Septra) in otitis externa occurring in swimmers in various vacation areas and at city pools during the summer months.

A total of 28 patients are included in the study. Twenty-three of these were children (under the age of 16 years) and five were adults. In 15 of the children and in only 1 of the adults there was associated otitis media. No patient had used antibiotics in any form during the 14 days prior to the institution of the treatment to be described.

In all cases swabs were taken from both the auditory canal and the external affected areas for culture of organisms present. The findings are presented in Table I.

Treatment of adults

The external auditory canals were cleansed, using alcohol swabs. Trimethoprim-sulfamethoxazole was prescribed as oral tablets, taken twice daily at 12-hour intervals for 7 days. Except in the patient with otitis media, an ointment containing hydrocortisone, polymyxin B, bacitracin and neomycin was applied lightly to the affected area twice during the day and at bedtime.

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