Prevention of Hypoglycemic Attacks by Propranolol in a Patient Suffering from Insulinoma

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SUMMARY

An insulinoma was diagnosed in a fifty-seven-year-old woman suffering from frequent hypoglycemic attacks. Propranolol—a beta-adrenergic blocker—in a dose of 80 mg. per day effectively prevented recurrent hypoglycemic attacks. It also corrected the basal hyperinsulinemia as well as the increased insulin secretion which results from stimulation with glucose or arginine. DIABETES *24*:535-37, June, 1975.

Hypoglycemic attacks in patients suffering from insulinoma can be suppressed by diazoxide or streptozotocin. Both these drugs are potentially toxic and can induce severe hypoglycemic crises within twenty-four hours of initiation of treatment.[1,2]

We herewith report on the effect of short-term treatment with propranolol, a beta-blocking agent that suppresses insulin response to glucose in normal persons, on the frequent hypoglycemic attacks of a patient suffering from an insulinoma.

CASE REPORT

A fifty-seven year old woman was admitted to the Neurosurgical Department of our hospital with the presumptive diagnosis of a cerebral tumor. She suffered from frequent attacks of generalized convulsions with loss of consciousness accompanied by profuse perspiration. An electroencephalographic examination disclosed two irritative bitemporal foci. Contrast examinations of the brain were negative. The serum glucose level during one of the attacks was found to be 20 mg. per 100 ml. and she was transferred to the Department of Internal Medicine.

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Accepted for publication February 1, 1975.

A provisional diagnosis of insulinoma was made on the basis of clinical, biochemical and roentgenological studies. In the course of her stay in the department the patient suffered from daily, often severe, hypoglycemic attacks during which blood glucose values of 20-40 mg. per 100 ml. were registered. Concomitant plasma immunoreactive insulin values ranged between 50-100 μU./ml.

On the assumption that beta-adrenergic blockade might prevent insulin release, propranolol treatment was initiated. Propranolol was administered in four equal doses every six hours. The dosage required to produce beta-adrenergic blockade, as determined by a reduction in pulse rate to 60 per minute, was 80 mg. per day. Treatment was continued for three days during which the patient was symptomless. Propranolol was discontinued but subsequently reinstituted because of recurring attacks of severe hypoglycemia. No side effects were observed during the treatment with propranolol.

The patient was operated on and the tail of the pancreas, which contained a benign insulinoma, was removed. The postoperative course was uneventful except for the transient diabetes that usually follows partial resection of the pancreas.[3] A repeated electroencephalogram was normal.

SPECIAL INVESTIGATIONS

Standard glucose tolerance tests and arginine stimulation tests were performed before and during propranolol treatment and after operation.

Serum glucose was determined as total reducing substances by AutoAnalyzer. Insulin was determined by radioimmunoassay by the method of Hales and Randle[4] as modified according to Quabbe.[5]

Measurements of fasting plasma insulin and serum glucose before treatment with propranolol were in accordance with the typical pattern of insulinoma.[6] These parameters returned to normal during propranolol administration.

The oral glucose tolerance test performed before propranolol treatment showed a rise from 40 mg. per cent at zero time to a peak of 85 mg. per cent at thirty minutes. At the same time insulin values oscillated between 60-84 μU. per milliliter. No definite peak of insulin secretion was observed. When related to the concomitant glucose values the insulin values were high.

On the third day of propranolol treatment the oral glucose tolerance test showed a diabetic curve. The glucose values were 90 mg. per cent at zero time, reached a peak of 220 mg. per cent at ninety minutes and returned to 180 mg. per cent at 180 minutes.

The concomitant insulin values were low, starting from 10 μU./ml. at zero time and reaching a delayed peak of 58 μU./ml. at 120 minutes when the glucose value was 218 mg. per cent. The subsequent insulin values dropped to 50 and then to 38 μU./ml.

Two weeks after operation a tendency for normalization of the oral glucose tolerance test was observed although it remained slightly diabetic (figure 1).

The arginine test performed before starting propranolol treatment showed low glucose values oscillating between 38 and 62 mg. per cent and concomitant high plasma insulin levels with a peak of 106 μU. per milliliter.

Propranolol treatment suppressed insulin secretion stimulated by arginine, the maximal insulin level registered being 34 μU. per milliliter.

After operation the plasma insulin levels during an arginine test were still low with a peak of 32 μU. per milliliter at thirty minutes. The glucose levels oscillated between 104 and 92 mg. per cent (figure 2).

DISCUSSION

Up to the present there has been no completely satisfactory method of treating the acute hypoglycemia resulting from the increased secretion of insulin from an insulinoma.

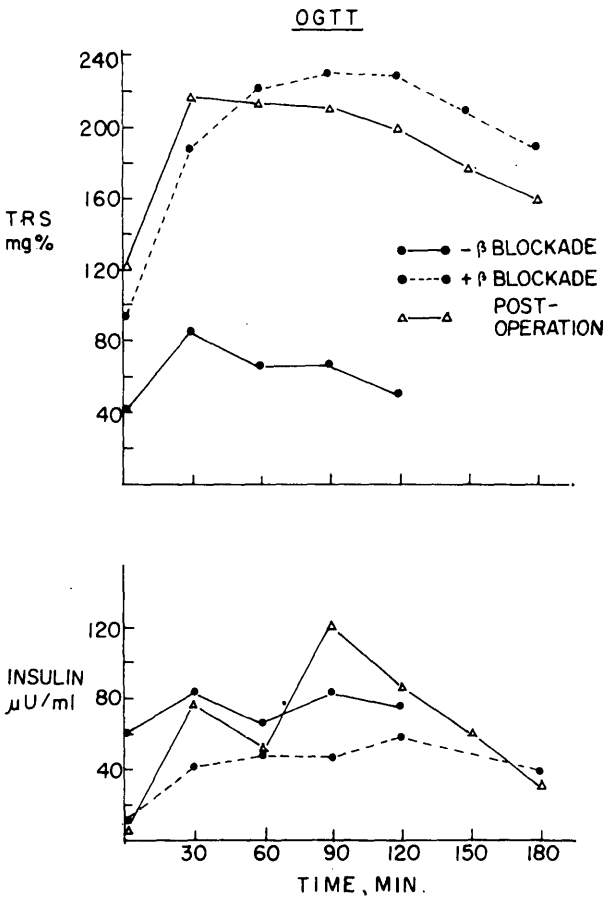

FIG. 1. Oral glucose tolerance test before beta-adrenergic blockade, after beta-adrenergic blockade, and after operation. Each point is the mean of a duplicate examination.

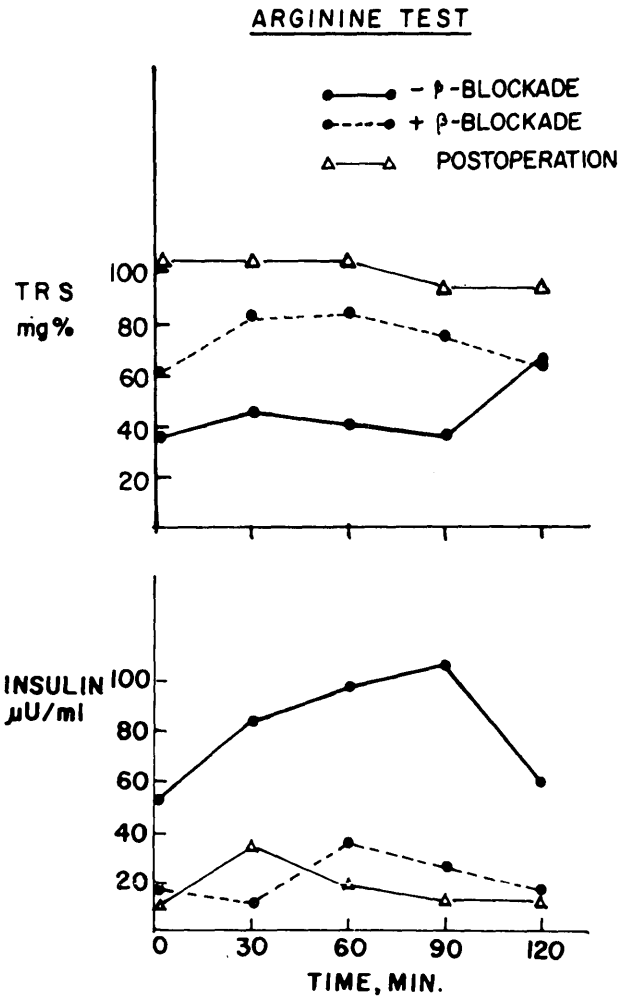

FIG. 2. Intravenous arginine test before beta-adrenergic blockade, after beta-adrenergic blockade, and after operation. Each point is the mean of a duplicate examination.

Recently it was suggested that the glucose receptor of the pancreatic beta cell is closely related to the beta-adrenergic receptor.[7] Propranolol, a beta-adrenergic receptor blocking agent, has been shown to inhibit effectively both initial and late insulin response to glucose infusion in normal subjects.[8] The advantage of propranolol in beta-blocking dosage is its almost complete lack of side effects and its short duration and reversibility of action.

To our knowledge, there have as yet been no reports on the use of propranolol to suppress hypoglycemic attacks in patients with insulinoma. In the patient described above, treatment with propranolol in a dosage which caused blockade of the peripheral beta-adrenergic receptors was completely successful in preventing the recurrent daily hypoglycemic attacks. It was proved that this effect was caused by the lowering

of the insulin secretion. Up to the present there has been no evidence that propranolol reduces basal insulin levels and raises serum glucose in normal subjects.[9] In our case we were able to show that propranolol also inhibited the insulin response to glucose and arginine. Studies carried out in normal subjects showed that propranolol does not suppress the insulin release brought on by arginine stimulation at normal glucose levels. It is not clear whether this difference in the action of propranolol seen in the patients with insulinoma as compared with normal subjects results from a difference in receptor responsiveness or in the method of administration of the drug.[9]

It would be interesting to investigate whether an islet-cell carcinoma would respond in the same way to beta-adrenergic blockade as the benign adenoma described here.

On the basis of the results obtained in the above-described patient, propranolol would seem to show promise of being an effective agent for the control of hypoglycemic attacks in patients with insulinoma until surgery can be undertaken or cytotoxic therapy instituted.

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