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THE INFLUENCE OF β-ADRENOCEPTOR BLOCKING DRUGS WITH AND WITHOUT INTRINSIC SYMPATHOMIMETIC ACTIVITY ON THE HORMONAL RESPONSES TO HYPO- AND HYPERGLYCAEMIA

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1 The effects of oral doses of pindolol (15 mg), metoprolol (200 mg) and propranolol (160 mg) on the response to insulin-induced hypoglycaemia and an oral glucose load were investigated.

2 Serum insulin and serum C-peptide secretion in response to a glucose load were inhibited ($2P<0.01$) by metoprolol and propranolol but not by pindolol.

3 During hypoglycaemia metoprolol and propranolol inhibited the clearance of insulin ($2P<0.01$) and caused a delay of glucose nadirs.

4 Adrenaline secretion during hypoglycaemia was markedly increased by metoprolol and propranolol but not by pindolol.

5 The counterregulatory response of growth hormone, ACTH and cortisol was increased following metoprolol and propranolol but not after pindolol.

6 The hypoglycaemic symptoms and signs showed a prevalence of sweating and prolonged changes in skin conductivity whereas palpitations were not observed during β-adrenoceptor blockade. Asymptomatic hypoglycaemia did not occur.

7 The absence of unphysiological rises in adrenaline, growth hormone, ACTH and cortisol supports the use of a β-adrenoceptor blocker with intrinsic sympathomimetic activity.

Introduction

Simultaneous treatment with antidiabetic drugs and β-adrenoceptor blocking agents is frequent on account of the high incidence of diabetes and cardiovascular disease. Impairment of glucose metabolism (Day, 1975; Waal-Manning, 1976), pronounced hypoglycaemia with masked symptoms (Barnett *et al.*, 1980; Lohmann, 1980, 1981; Lager *et al.*, 1979; Waal-Manning, 1979; Deacon & Barnett, 1976) and decreased insulin secretion (Cerasi *et al.*, 1972; Scandellari *et al.*, 1978; Furman & Tayo, 1973; Holm *et al.*, 1980; Harms *et al.*, 1978) may result from β-adrenoceptor blockade. While there is agreement that cardioselective β-adrenoceptor blocking agents should be preferred to unselective drugs in the treatment of diabetics (Kotler *et al.*, 1966; Deacon *et al.*, 1977; Abramson *et al.*, 1966), there is no information with regard to the significance of intrinsic sympathomimetic activity in this respect. We have therefore compared the effects of pindolol (β_1 and β_2-adrenoceptor blockade; marked intrinsic sympathomimetic activity [ISA]; metoprolol (mainly β_1-adrenoceptor blockade; no ISA); and propranolol (β_1 and β_2-adrenoceptor blockade; no ISA); on hormonal responses to insulin-induced hypoglycaemia in healthy subjects. In addition to metabolic parameters with a significant influence on the short-time regulation of serum glucose (Hökfelt *et al.*, 1978; Staniforth *et al.*, 1980) we also measured growth hormone and cortisol, which are thought to be involved in the development of microvascular disease in diabetic patients (Luft *et al.*, 1952, 1955; Merimee *et al.*, 1973).

Methods

Informed consent was obtained from eight male volunteers (age: 25.1 ± 1.1 years (mean ± s.e.mean), body weight: 72.4 ± 1.6 kg; height: 184.1 ± 3.2 cm) without family or personal history of diabetes. Physical examination, ECG, laboratory chemistry and oral glucose load were normal. Two questionnaires (Freiburger Persönlichkeitsinventar, Freiburger Beschwerdeliste; Fahrenberg, 1975) were used to exclude subjects with abnormal personalities.

Each volunteer received oral doses of placebo,

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pindolol (15 mg), metoprolol (200 mg) and propranolol (160 mg) according to a randomized double-blind *latin* square design with intervals of 10 days between the four drug administrations. Food intake during 3 days before the tests was rich in carbohydrates (> 250 g). After the subjects had fasted overnight (12 ± 1 h), an indwelling catheter (Abbocath 18-G) was inserted into their right antecubital vein. Electrodes for continuous registration of the electrocardiogram and the electrical conductivity of the skin were fixed. The test doses were administered after the subjects had subsequently rested for 30 min. Venous blood samples were drawn at −10, 0, 30, 60, 90, 95, 105, 115, 120, 125, 130, 135, 150, 165, 180, 210, 225, 240, 255, 270 and 285 min. An intravenous bolus (0.1 U/kg body weight) of monocomponent porcine insulin (Actrapid®) was injected 90 min after intake of the test substance. An oral load of glucose (100 g) was given 210 min after the beginning of the test.

Plasma glucose was determined with a Beckmann Glucose Analyzer (GOD-method) in all plasma samples and the following radioimmunoassays were carried out: serum insulin (Phadebas-Insulintest, Pharmacia-Diagnostics, AB, Uppsala, Sweden), serum C-peptide (Riamat, C-peptide assay, Byk-Mallinckrodt, Dietzenbach, FRG), serum cortisol (Cortisol-Ria, Travenol, Cambridge, Mass.), plasma ACTH (CIS, Ceasorin, U.S.A.), and serum growth hormone (Serono, Freiburg, FRG). Interassay variations were reduced by using individual immunoassays for each subject. Interassay variations were below 5.2% with the exception of ACTH (< 9.8%).

Plasma catecholamines were determined by the use of liquid chromatography with electro-chemical detection (LCEC). Prior to liquid chromatography the catecholamines were preconcentrated by a solid extraction onto alumina and then eluted with dilute acid. Details of the method will be published (Wehrli, 1982). Each blood sample for catecholamine determination was collected in test tubes containing two volume percent of antioxidizing and anticoagulating solution (EDTA 90 mg/ml, glutathione 60 mg/ml, pH 6.5). After centrifugation the plasma was kept frozen at −35°C.

Heart rates were recorded automatically from the

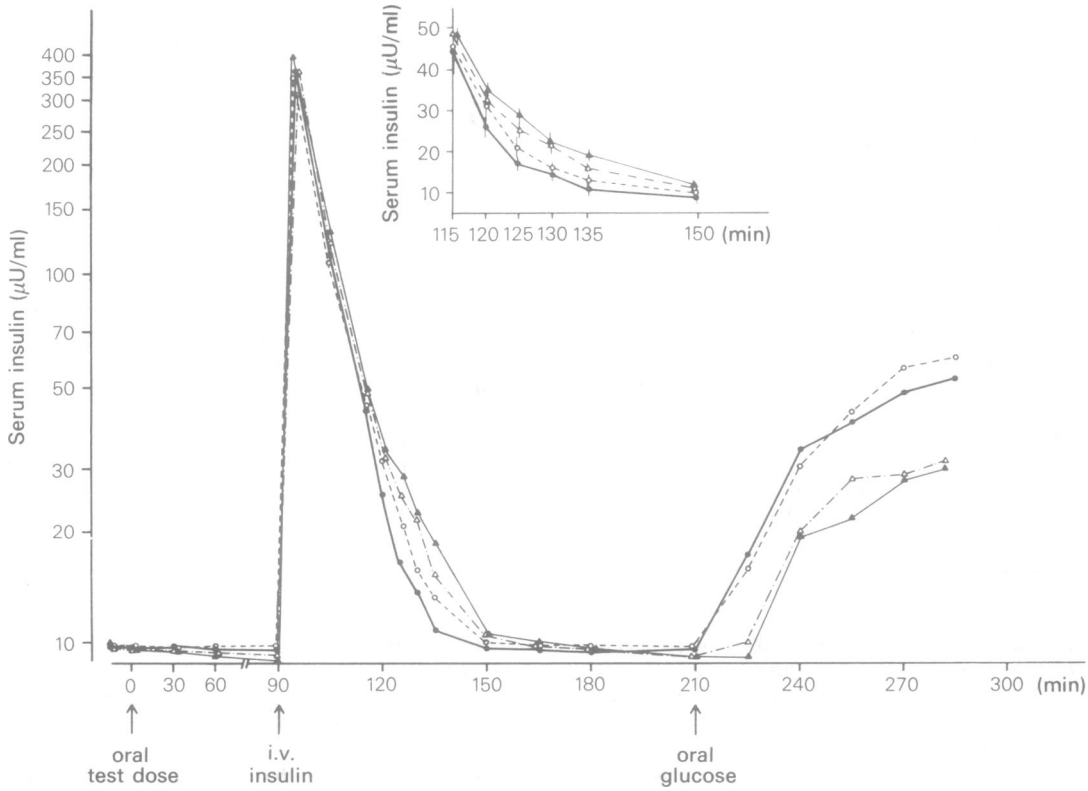

Figure 1 Effects of an oral dose of placebo ●——●, pindolol (15 mg) O– – –O, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on serum insulin concentrations in volunteers ($n = 8$). Mean ± s.e.mean results.

ECG (Rate meter 23601101, Hellige, FGR). Skin resistance reaction (SRR) and skin resistance level (SRL) were determined according to Prokasy & Raskin (1973) (skin conductivity meter 23601701, Hellige FRG). Hypoglycaemic symptoms were quantified by means of a standardized questionnaire using a scale from 0 to 5 to describe the following symptoms: feeling hot, sweating, palpitations, hunger, headache, tremor, jerks, feeling heavy, dizziness and nausea. A final statement about the degree of symptoms was made at the end of the test.

Results are expressed as mean ± s.e.mean. Areas under the concentration-time curves were calculated according to the equation

$$\sum_{n=1}^{n=N-1} \frac{(x_{n+1} - x_n)(y_{n+1} + y_n)}{2}$$

Statistical analysis was by Wilcoxon's test for paired differences.

Results

Serum insulin concentrations are shown in Figure 1. Following the intravenous administration of porcine insulin (0.1 U/kg body weight) 90 min after an oral dose of placebo, pindolol (15 mg), metoprolol (200 mg) or propranolol (160 mg) identical peak values of insulin were obtained. Between 120 and 135 min after test drug administration (30–45 min following the injection of insulin) the serum insulin concentrations were higher after the β-adrenoceptor blocking drugs than after placebo (propranolol > metoprolol > pindolol > placebo) indicating that the β-adrenoceptor blocking drugs caused various degrees of delay in insulin clearance. The differences between propranolol and placebo and between metoprolol and placebo were statistically significant ($2P < 0.01$). After the oral glucose load (100 g) at 210 min serum insulin levels were significantly lower ($2P < 0.01$) following propranolol and metoprolol than after placebo or pindolol.

During hypoglycaemia (90 to 210 min) a significant depression of endogenous insulin secretion meas-

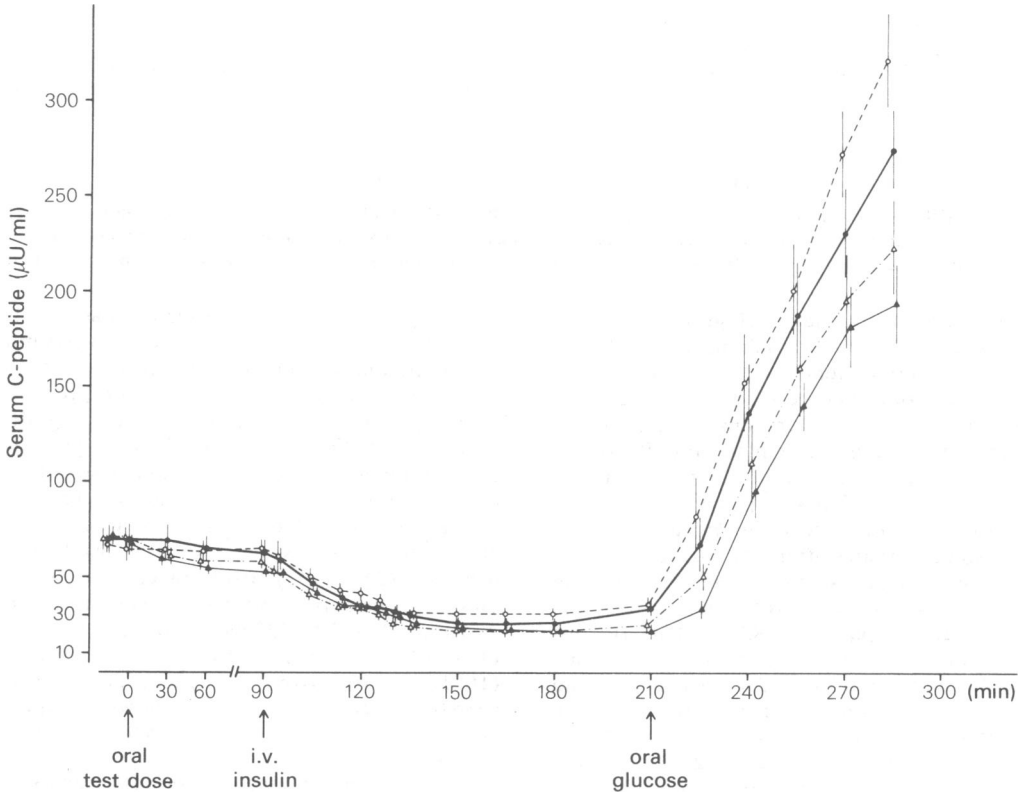

Figure 2 Effects of an oral dose of placebo ●——●, pindolol (15 mg) ○– – –○, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on serum C-peptide concentrations in volunteers ($n = 8$). Mean ± s.e.mean results.

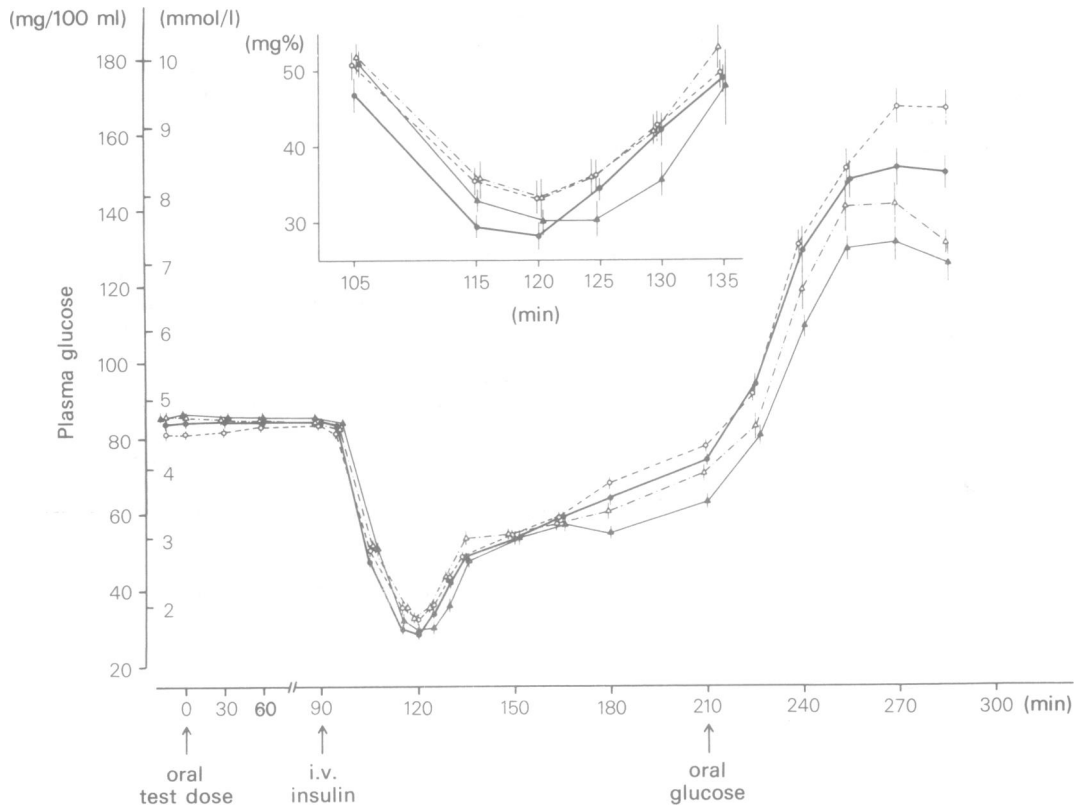

Figure 3 Effects of an oral dose of placebo ●———●, pindolol (15 mg) ○---○, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on plasma glucose concentrations in volunteers ($n = 8$). Mean ± s.e.mean results.

ured by serum C-peptide levels (Figure 2) occurred whether a drug or placebo was administered. During recovery from hypoglycaemia (180–210 min) as well as following the oral glucose load C-peptide levels remained lower following metoprolol and propranolol than after pindolol or placebo ($2P < 0.05$). The time course of endogenous insulin secretion after pindolol was similar to that after placebo.

The plasma glucose concentrations are shown in Figure 3. Ninety minutes after administration of the test drugs identical glucose levels were obtained. The nadirs of hypoglycaemia differed significantly ($2P < 0.05$) between placebo (28.8 ± 1.3 mg/100 ml) and propranolol (30.0 ± 2.0 mg/100 ml) on the one hand and pindolol (33.1 ± 2.1 mg/100 ml) and metoprolol (33.1 ± 2.4 mg/100 mg) on the other. All β-adrenoceptor blocking agents induced a delay of the plasma glucose nadir (placebo 27.5 ± 0.3 min, pindolol 29.4 ± 0.4 min, metoprolol 29.4 ± 0.5 min, propranolol 32.5 ± 0.3 min after i.v. insulin (this delay was significant for propranolol only, $2P < 0.01$)).

During the first 45 min after the nadir of hypoglycaemia (i.e. min 120–165) recovery was similar in all test periods. After that time, however, the reincrease was slower ($2P < 0.05$) after propranolol. Plasma glucose concentrations were thus significantly lower ($2P < 0.05$) at 210 min with propranolol than after placebo and pindolol and these differences were maintained during the oral glucose load.

The counterregulatory output of adrenaline (Figure 4) induced by hypoglycaemia showed a marked increase ($2P < 0.01$) from placebo (area under plasma concentration/time curves from 0 to 270 min: 72372 ± 2732 $pgml^{-1}$ min) to metoprolol (104840 ± 30954 $pgml^{-1}$ min) and propranolol (102539 ± 31075 $pgml^{-1}$ min) but not to pindolol (68816 ± 32223 $pgml^{-1}$ min). Following propranolol peak adrenaline concentrations persisted for about 15 min.

Plasma nor adrenaline secretion showed a significant increase after propranolol; the increase was less pronounced after metoprolol, pindolol and placebo. The plasma dopamine concentrations were not influ-

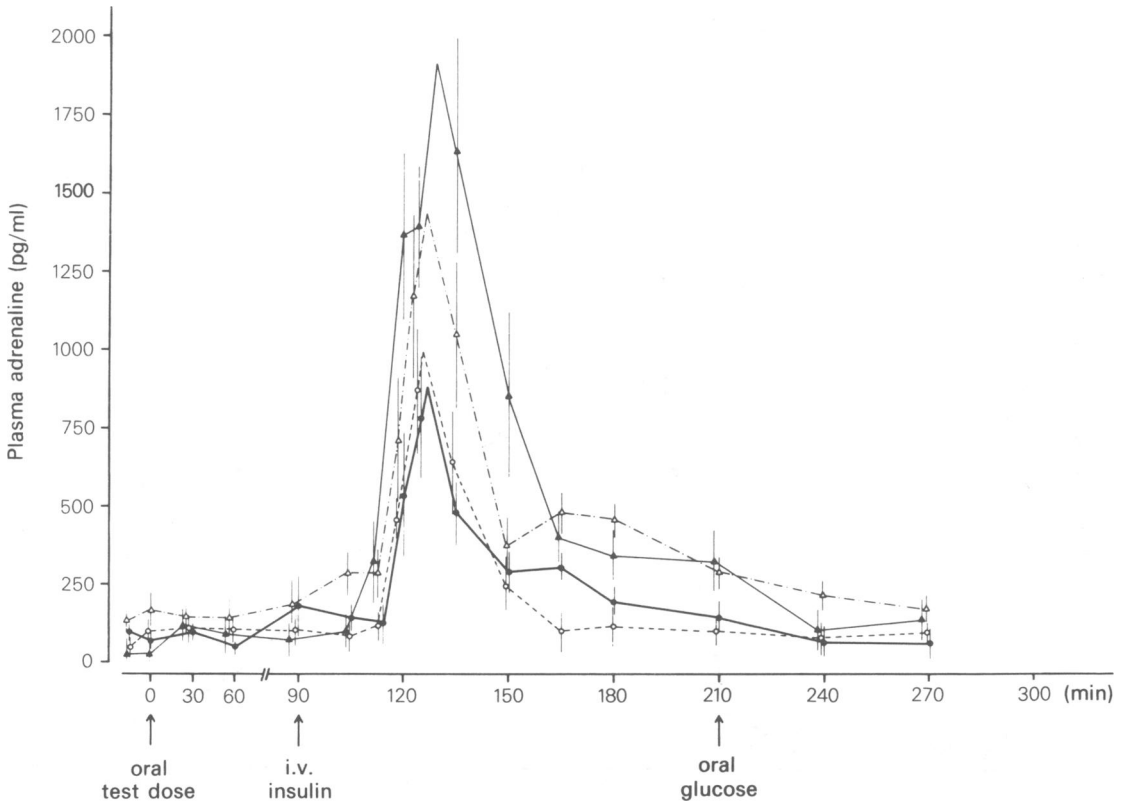

Figure 4 Effects of an oral dose of placebo ●———●, pindolol (15 mg) O---O, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on plasma adrenaline concentrations in volunteers ($n = 8$). Mean ± s.e.mean results.

enced by hypoglycaemia with and without β-adrenoceptor blocking drugs.

Figure 5 shows the serum growth hormone response to insulin-induced hypoglycaemia. While there were almost identical concentrations following placebo and pindolol, the rise of growth hormone was significantly increased after metoprolol ($2P < 0.01$) and propranolol ($2P < 0.01$). The oral glucose load did not promote growth hormone secretion and did not alter the time course of the disappearance of the hormone.

Plasma ACTH concentrations (Figure 6) began to increase 20 min after insulin injection, and the maximal concentrations were measured after 45 min. The highest output was observed after propranolol (179.1 ± 39.7 pg/ml) and metoprolol (160.0 ± 45.6 pg/ml) while placebo (150.9 ± 52.4 pg/ml) and pindolol (150.0 ± 58.7 pg/ml) led to lower and identical peak values. The differences, however, were not statistically significant.

The secretion of cortisol (Figure 7) during hypoglycaemia started after the ACTH secretion 30 min after insulin injection. Maximal concentrations were obtained after 165 min. The clearance of the hormone was not influenced by the oral glucose load. Serum cortisol concentrations following placebo or pindolol were significantly lower than after metoprolol or propranolol ($2P < 0.01$).

During hypoglycaemia plasma adrenaline secretion increased the heart rate significantly in the placebo group. Though adrenaline and noradrenaline levels are increased following β-adrenoceptor blockade, no tachycardia was observed after pindolol or metoprolol (Figure 8). Propranolol induced significant bradycardia which was partly compensated by supraventricular and ventricular ectopic beats.

After placebo administration mean arterial blood pressure (control values 92 ± 2 mm Hg) remained fairly constant throughout the experimental period. After all β-adrenoceptor blocking drugs, however, there was an increase in mean arterial pressure during hypoglycaemia when compared to pre-insulin values: + 12.9 ± 3.5 mm Hg after pindolol, + 8.1 ± 2.2 mm Hg after metoprolol, and

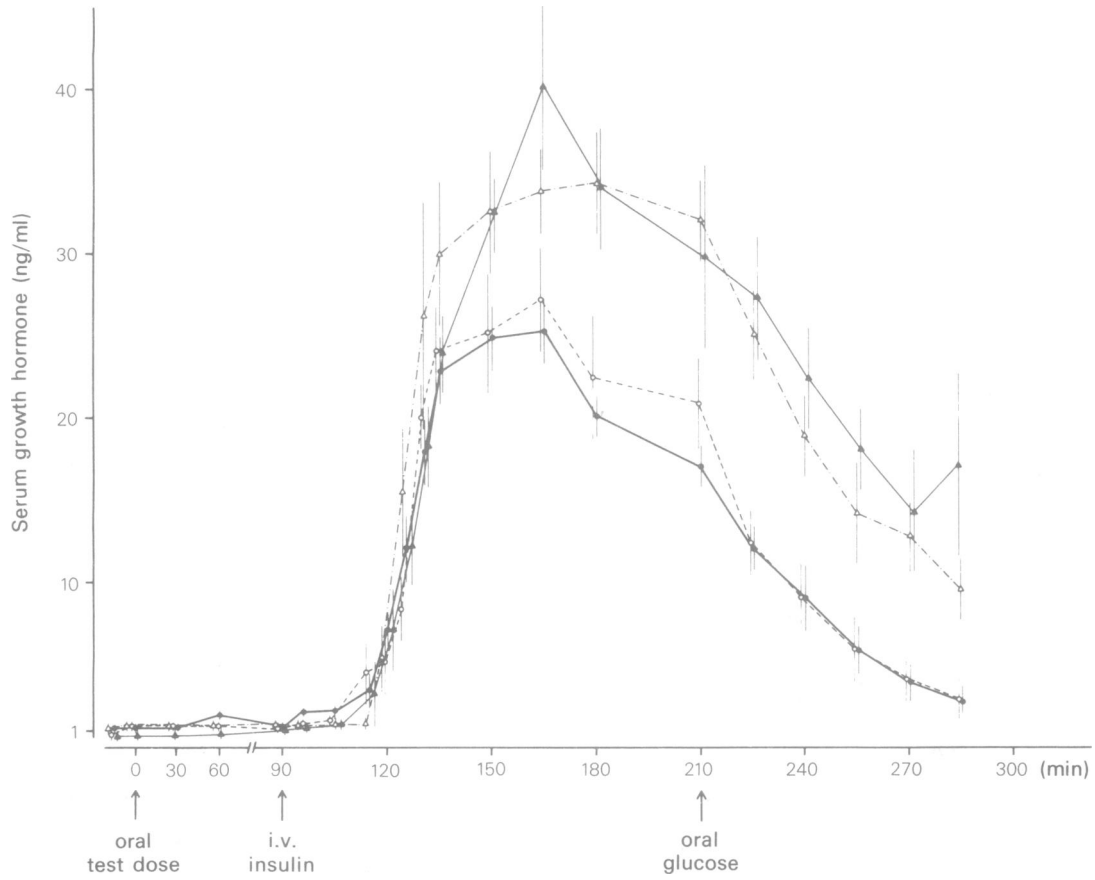

Figure 5 Effects of an oral dose of placebo ●———●, pindolol (15 mg) ○---○, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on serum growth hormone concentrations in volunteers ($n = 8$). Mean ± s.e.mean results.

+ 11.0 ± 4.3 mm Hg after propranolol. There were no statistically significant differences between the three β-adrenoceptor blocking drugs. In the placebo study systolic blood pressure rose after insulin infusions from 115 ± 2 mm Hg to 134 ± 4 mm Hg whereas diastolic blood pressure fell from 83 ± 3 mm Hg to 74 ± 4 mm Hg indicating a marked increase in pulse pressure from 35.6 ± 1.5 mm Hg to 60.6 ± 4.4 mm Hg (Figure 9). This increase in blood pressure amplitude during hypoglycaemia was abolished by all three β-adrenoceptor blocking drugs because the rise in systolic blood pressure was smaller (+ 13 ± 5 mm Hg after pindolol, + 10 ± 6 mm Hg after propranolol and + 11 ± 2 mm Hg after metoprolol) and diastolic blood pressure showed an increase (+ 13 ± 3 mg after pindolol, + 12 ± 4 mm Hg after propranolol and + 7 ± 2 mm Hg after metoprolol).

Of the hypoglycaemic symptoms recorded with a standardized questionnaire headache, tremor nausea and jerks were rarely observed and did therefore not allow statistical evaluation. The symptoms of hunger and feeling heavy exhibited similar frequencies after placebo and β-adrenoceptor blockade. In spite of the observed bradycardia with extrasystoles after propranolol treatment, palpitations during hypoglycaemia were significantly reduced with all three beta-adrenoceptor blocking agents tested (Figure 10a). Sweating, on the other hand, was markedly increased in comparison with placebo (Figure 10b). The high incidence of sweating was reflected by a prolongation of changes in ectodermal activity. The duration of skin resistance reaction (SRR) amounted to 22.8 ± 0.6 min after placebo, 25.2 ± 0.7 min after pindolol, 23.7 ± 0.6 min after metoprolol and 29.7 ± 1.1 min after propranolol.

Estimates of the severity of hypoglycaemic symptoms were given by the volunteers at the end of the test period. In the placebo group no ratings of severe symptoms were obtained, while in the propranolol group the highest incidence of severity ($n = 4$) was observed. Following pindolol ($n = 2$) and metoprolol ($n = 2$) an intermediate estimation of symptoms was given. Asymptomatic hypoglycaemia was not observed on any experimental day.

Discussion

Three different β-adrenoceptor blocking agents were tested with regard to their ability to modify the effects of insulin-induced hypoglycaemia and a subsequent glucose load. Pindolol is characterized by a marked intrinsic sympathomimetic activity (ISA). Metoprolol has no ISA but is cardioselective. Propranolol is the classical compound with neither cardioselectivity nor ISA. The doses of the drugs were approximately equipotent with regard to cardiac β-adrenoceptor blockade. They correspond to doses commonly used in the treatment of hypertension and angina pectoris. During insulin-induced hypoglycaemia 15 mg of pindolol, 200 mg of metoprolol or 160 mg of propranolol inhibited the rise in blood pressure amplitude but elevated mean arterial blood pressure to about the same extent.

The study comprised a hypoglycaemic episode which was followed by an oral glucose load. The metabolic effects of the glucose tolerance test were thus in part influenced by the preceding hypoglycaemia. Preexisting differences in plasma glucose concentrations were not changed during the oral glucose loads. The increase of plasma glucose did not provoke adrenaline, noradrenaline, dopamine, growth hormone, ACTH or cortisol secretion or changes in heart rate, blood pressure, skin conductivity and subjective state. It is thus improbable that in chronically hyperglycaemic diabetics β-adrenoceptor blockade will cause elevated levels of these hormones.

A reduced insulin and C-peptide secretion related

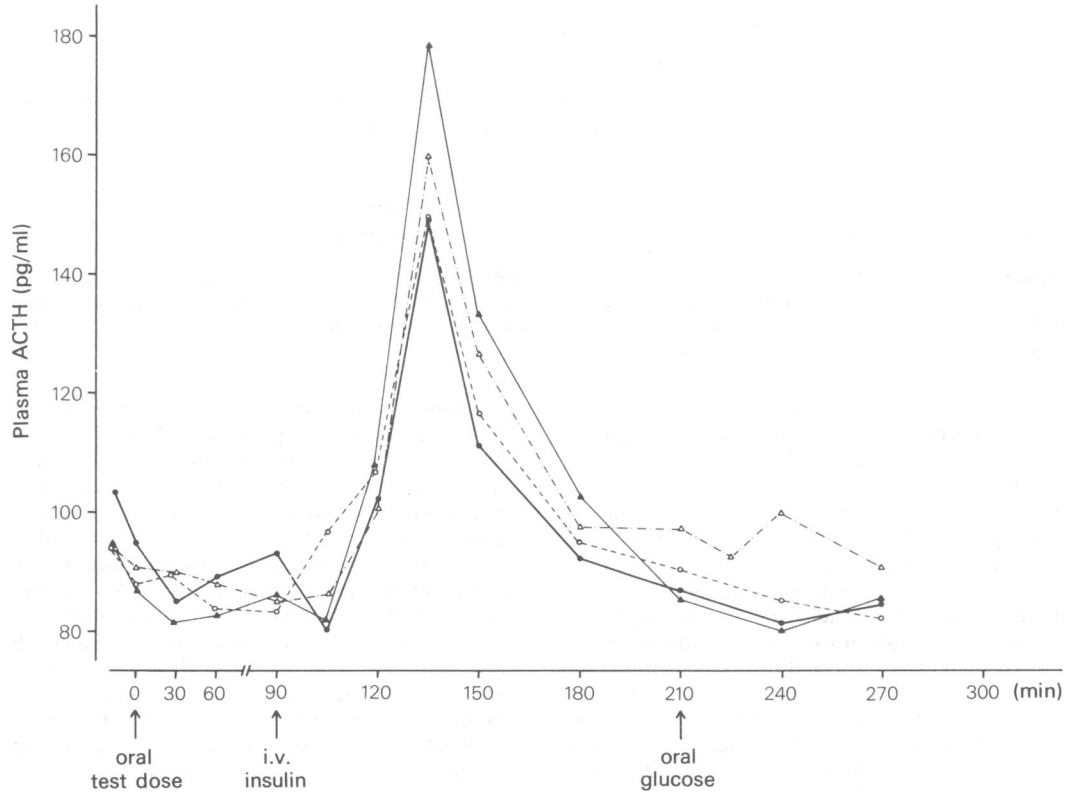

Figure 6 Effects of an oral dose of placebo ●——●, pindolol (15 mg) ○---○, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on plasma ACTH concentrations in volunteers ($n = 8$). Mean results.

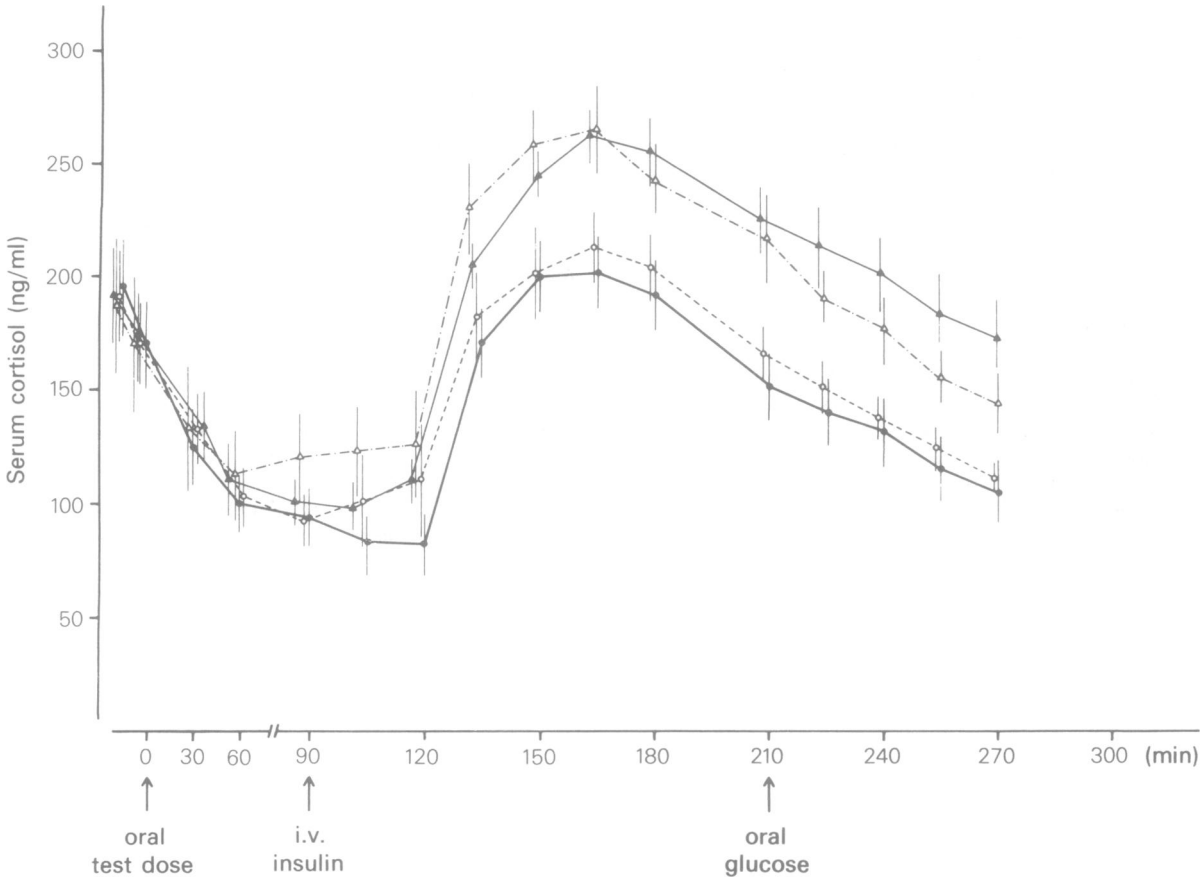

Figure 7 Effects on an oral dose of placebo ●———●, pindolol (15 mg) O---O, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on serum cortisol concentrations in volunteers ($n = 8$). Mean ± s.e.mean results.

to inhibiting effects of metoprolol and propranolol has been described as a possible cause for hypoerglycaemia (Pozza *et al.*, 1972; Gagliardino *et al.*, 1970).

Hypoglycaemia produced several metabolic effects which were modified by β-adrenoceptor blockade. During the acute phase of hypoglycaemia there was a delay in the clearance of exogenous insulin which coincided with a delay of the hypoglycaemic nadirs following β-adrenoceptor blockade. In spite of a marked increase of adrenaline concentrations the recovery from hypoglycaemia was slow following propranolol and bradycardia and ectopic beats were observed (Deacon *et al.*, 1977). These results imply that propranolol treatment carries some risk in insulin-dependent diabetics (Kotler *et al.*, 1966; Wright *et al.*, 1979) who have reduced adrenergic responses due to autonomic neuropathy (Caviezel *et al.*, 1980; Barnett *et al.*, 1980). Pindolol produced the lowest compensatory stimulation of adrenaline secretion. Presumably as a consequence of the antecedent adrenaline peaks a similar pattern of effects was observed with regard to the other counterregulatory hormones. Significant elevations of growth hormone, ACTH and cortisol were observed following propranolol and metoprolol, which are characterized by the absence of ISA. The maintenance of the natural secretion pattern of counterregulatory hormones during insulin-induced hypoglycaemia after pindolol can therefore probably be attributed to the intrinsic sympathomimetic activity of this drug. The difference between the two drugs without ISA, i.e. the cardioselective drug metoprolol and the non-cardioselective drug propranolol are of minor importance though the risk of metoprolol appears to be lower in comparison with propranolol (Hökfelt *et al.*, 1978).

Recently Raptis *et al.* (1981) reported that pin-

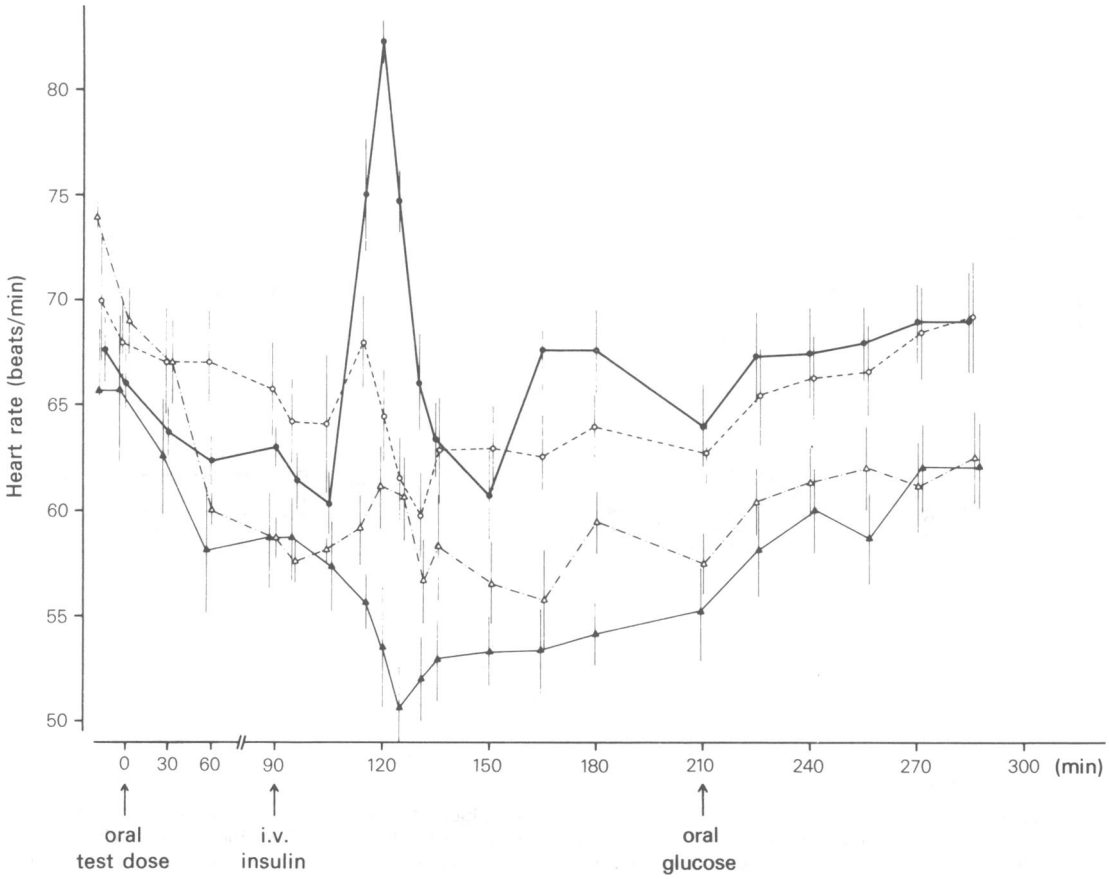

Figure 8 Effects of an oral dose of placebo ●———●, pindolol (15 mg) ○---○, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on heart rates in volunteers ($n = 8$). Mean ± s.e.mean results.

dolol, but not atenolol, reduced the rise of plasma growth hormone due to intravenously infused adrenaline. There is no doubt that high concentrations of ACTH, cortisol and growth hormone deteriorate the metabolic control of diabetic patients (Bolli *et al.*, 1979; Hansen & Johansen, 1970; Hansen, 1972; Alberti *et al.*, 1975). Thus β-adrenoceptor blockade implies a risk in patients prone to hypoglycaemia and in brittle diabetics. Intrinsic sympathomimetic activity prevents an unfavourable hormonal overshoot during hypoglycaemia. The analyses of the psychological parameters did not reveal any masking of hypoglycaemia by beta adrenoceptor blocking agents. In accordance with Strom (1978), and Viberti *et al.* (1978), sweating was observed more frequently whereas palpitations were rare.

We wish to thank Mrs H. Vorwerck for skilful technical assistance.

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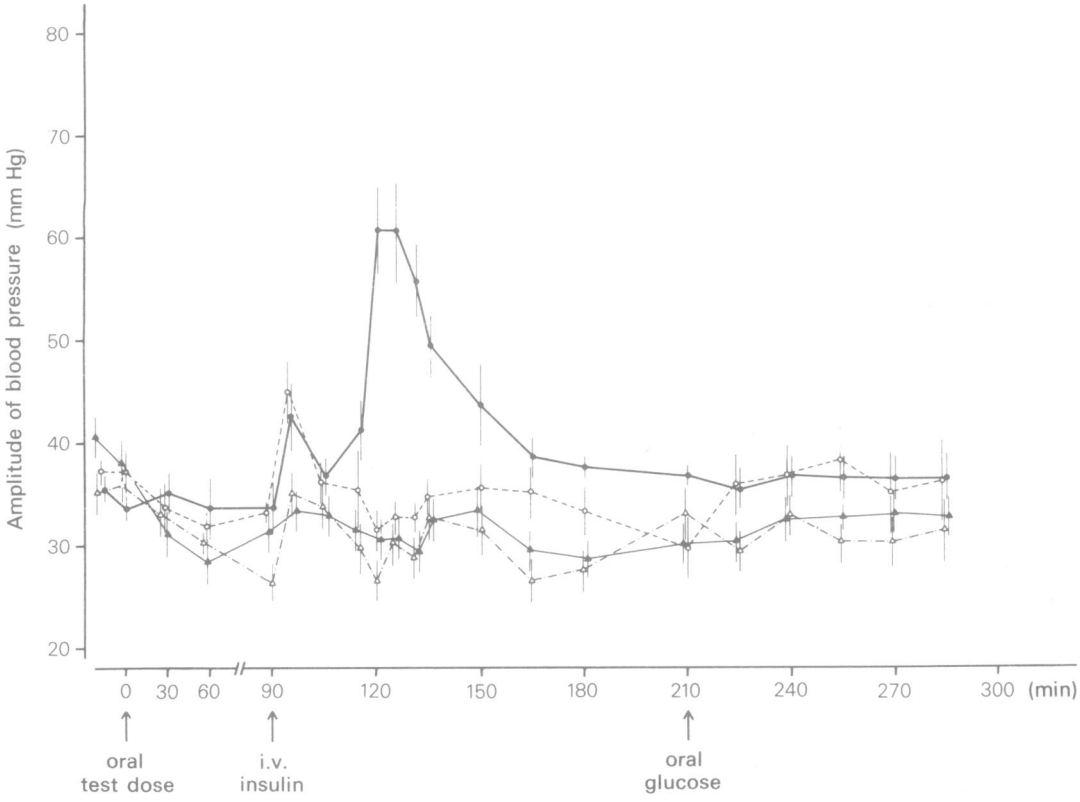

Figure 9 Effects of an oral dose of placebo ●———●, pindolol (15 mg) ○---○, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on the amplitude of blood pressure in volunteers ($n = 8$). Mean ± s.e.mean results.

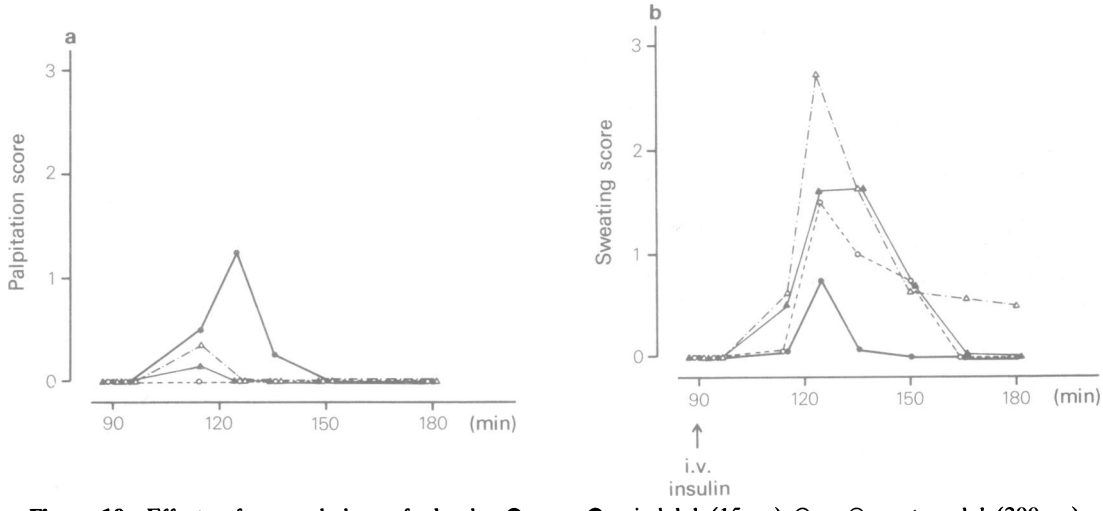

Figure 10 Effects of an oral dose of placebo ●———●, pindolol (15 mg) ○---○, metoprolol (200 mg) △—.—.—△, or propranolol (160 mg) ▲———▲, during insulin- (0.1 U/kg body weight) induced hypoglycaemia and after an oral glucose load (100 g) on the incidence of palpitations and sweating in volunteers ($n = 8$). Mean results.

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