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Insulin hypoglycaemia test guided by a glucose controlled insulin infusion system

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Abstract. Insulin hypoglycaemia test (IHT) for assessment of hypothalamic-pituitary-adrenocortical (HPA) function in patients with pituitary tumours is usually performed by bolus injection of insulin, a procedure which includes the risk of overdosage and/or the need of repeated administration. This study describes that a glucose controlled insulin infusion system (GCIIS) permits to perform the IHT with standardized hypoglycaemia. Ten healthy volunteers and 10 patients with pituitary tumours were studied using the GCIIS (Biostator®) on static control (Mode 1:1, BI 35, QI 10, RI 20, FI 300). Insulin administration was discontinued and the GCIIS used only for monitoring of blood glucose (BG), when BG had fallen below 40 mg/dl and initial clinical symptoms for hypoglycaemia were observed. In controls, the GCIIS guided IHT achieved a sufficient degree of hypoglycaemia (BG 27.6 ± 2.0 mg/dl; mean ± SEM) and physiological responses for GH (peak 49.4 ± 6.7 ng/ml), Prl (peak 1766 ± 614 µU/ml), ACTH (peak 76.0 ± 8.7 pg/ml) and cortisol (peak 252 ± 15 ng/ml). The total amount of insulin given was 0.115 ± 0.012 U/kg. In the patients with pituitary tumours however, the required insulin dose varied markedly from 0.090 (pituitary insufficiency) to 0.340 U/kg (Cushing's syndrome). Minimum BG obtained was 32.5 ± 1.9 mg/dl. Partial impairment of hypothalamic-pituitary function and, in particular, patients requiring exogenous cortisol supplementation during stress, could be identified. In conclusion, special advantages of the GCIIS-guided IHT are:
1) Optimal insulin dosage with standardized hypoglycaemia due to automatic adjustment to the individual insulin sensitivity.
2) Patients' safety by earlier recognition of due insulin discontinuation as a result of continuous blood glucose analysis.

The insulin hypoglycaemia test (IHT) is a sensitive procedure for the assessment of hypothalamic-pituitary-adrenocortical (HPA) function (Faglia et al. 1973; Greenwood et al. 1966; Jenkins & Else 1968; Landon et al. 1966). It may detect subtle abnormalities of pituitary-adrenal function in patients with hypothalamic and pituitary diseases, thus identifying patients who require exogenous cortisol supplementation during severe stress such as trauma or surgery (Borst et al. 1982; Delaloye et al. 1982).

Usually, IHT is performed by bolus injection of insulin, a technique, which includes the risk of severe side effects because of overdosage. On the other hand insulin requirements can be underestimated and the subsequent need of repeated insulin administration may alter pituitary hormone responses. We therefore used a glucose controlled insulin infusion system (GCIIS) for performing the IHT on the basis of a standardized hypoglycaemia with optimal insulin delivery due to automatic adjustment to the individual insulin sensitivity.

The aim of this study was 1) to show that the GCIIS-guided IHT achieved a sufficient degree of hypoglycaemia and physiological hormone responses in healthy subjects and 2) that it permitted the assessment of HPA function in the patients with pituitary tumours studied as examples.

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Table 1.
Clinical data of the patients studied.

Patient	Sex	Age (years)	Diagnosis
1. H. H.-B.	M	54	hormone inactive pituitary adenoma
2. P. H.	F	56	hormone inactive pituitary adenoma
3. W. W.	M	48	hormone inactive pituitary adenoma
4. E. C.	F	29	acromegaly
5. K. H.-P.	M	36	acromegaly
6. H. H.	F	45	Cushing's syndrome
7. B. W.	M	46	prolactinoma
8. F. G.	F	27	prolactinoma (MEA I)
9. P. D.	M	46	pituitary insufficiency postoperative (acromegaly)
10. M. K.	M	47	pituitary insufficiency postoperative (Cushing's syndrome)

Material and Methods

Ten healthy volunteers (4 females, 6 males, 25 ± 0.9 years, 174 ± 4 cm, 66 ± 4 kg; mean ± SEM) and 10 patients with pituitary tumours were studied. Informed consent was obtained from the volunteers. Some clinical data of the patients are given in Table 1.

Glucose controlled insulin infusion system

The details of the GCIIS used for our study (Biostator, Life Science Instruments, Miles Laboratories, Elkhart, USA) have been described elsewhere (Clemens et al. 1978; Fogt et al. 1978; Pfeiffer et al. 1974). The Biostator was used on static control. The following constants were chosen: BI 35, QI 10, RI 20, FI 300.

Experimental protocol

After an overnight fast, the subjects were connected to the GCIIS between 08.00 and 09.00 a.m. Feedback controlled insulin infusion (Insulin Hoechst CS, Frankfurt, FRG) was discontinued and the device was only used for blood glucose monitoring when blood glucose had

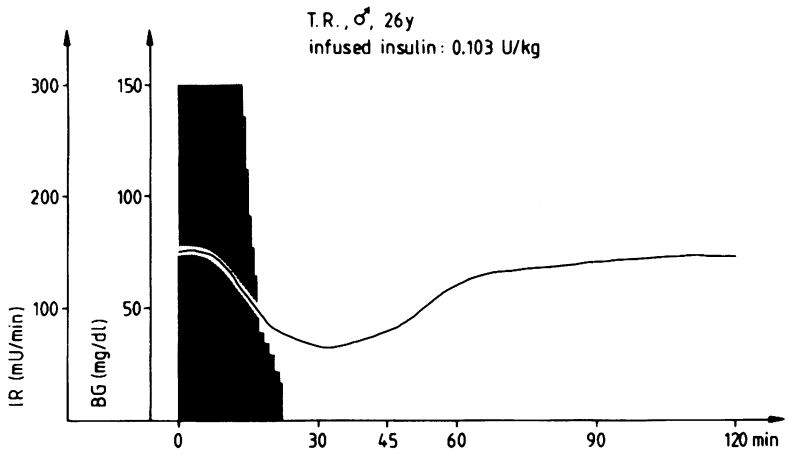

Fig. 1.
Blood glucose (BG) and insulin infusion rate (IR) during GCIIS-guided IHT in a healthy volunteer. Total amount of insulin infused by the GCIIS 0.103 U/kg.

fallen below 40 mg/dl and initial clinical symptoms of hypoglycaemia occurred (palpitations, headache, sweating, tachycardia, drowsiness) (see Fig. 1).

Venous blood samples were drawn at ± 0, 30, 45, 60, 90 and 120 min, respectively, from an indwelling catheter placed in an antecubital vein. For measuring serum insulin concentration, additional samples were collected at 10 and 20 min.

Analytical methods

Serum GH (CIS), prolactin (CIS), cortisol (clinical assays, SP), ACTH (INC, without extraction), insulin (CIS) and C-peptide (Byk Mallinckrodt) were measured by radioimmunoassay.

Statistical methods

The results obtained from the healthy volunteers are expressed as mean ± SEM.

Results

Healthy volunteers

Fig. 2 shows the mean values for blood glucose, serum insulin and serum C-peptide in the healthy volunteers. Peak insulin levels occurred between 10 and 20 min after start of feedback controlled insulin infusion. The secretion of endogenous insulin represented by serum C-peptide levels was clearly inhibited by the exogenous administered insulin, reaching its minimum 60 min after the beginning of the IHT. The intervals until discontinuation of insulin administration was 26.7 ± 1.7 min. The total amount of insulin given by the GCIIS was 0.115 ± 0.012 U/kg and 4146 ± 347 mU/m² body surface, respectively. Clinical symptoms of hypoglycaemia included palpitations, sweating, headache, tachycardia and drowsiness. No severe side effects were observed and there was no need of dextrose administration.

Fig. 3 shows the serum GH, prolactin, cortisol and ACTH responses obtained in the healthy subjects. The mean basal and maximum values ($\bar{x}$ ± SEM) observed were: GH: 2.8 ± 1.1 vs 49.4 ± 6.7 ng/ml; prolactin: 193 ± 25 vs 1766 ± 614 µU/ml; cortisol: 100 ± 12 vs 252 ± 15 ng/ml and ACTH: 21.6 ± 2.6 vs 76.0 ± 8.7 pg/ml.

Pituitary tumour patients

Table 2 gives the results obtained from the patients with pituitary tumours expressed as basal and maximum values. The total amount of insulin given (U/kg body weight) is also shown. Minimum blood glucose was 32.5 ± 1.9 mg/dl. In the 3 patients with hormone inactive pituitary adenoma there was an impairment of GH secretion during IHT. The patients with acromegaly, when studied preoperatively, had an impaired HPA function.

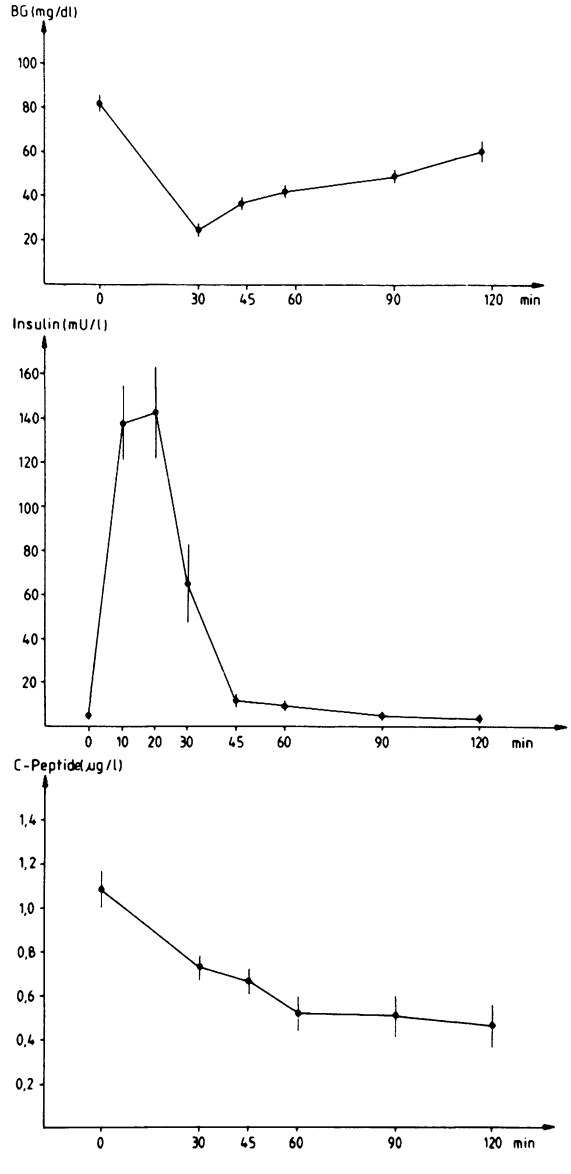

Fig. 2.
Blood glucose (BG), serum insulin and C-peptide (mean ± SEM) during GCIIS-guided IHT in 10 healthy volunteers.

They showed a blunted or deficient cortisol increase. In patient E.C. insulin requirements were markedly high; moreover, abnormal GH secretion was accompanied by elevated prolactin levels. Postoperatively, basal GH levels had returned to normal in both patients. In patient E.C., prolactin levels were now in the normal range, and insulin requirements had decreased from 0.200 to 0.106 U/kg (see Fig. 4). One of the prolactinoma patients studied (B.W.) had complete pituitary insufficiency, whereas the other one (F.G.) showed normal values and sufficient responses for GH, cortisol and ACTH. Complete impairment of the HPA axis was shown postoperatively in patients with acromegaly (P.D.) and Cushing's syndrome (M.K.). In patient H.H. (Cushing's syndrome) insulin requirements for inducing hypoglycaemia were highest (0.335 U/kg) as shown in Fig. 5.

In this patient blood glucose had fallen below 40 mg/dl after 70 min without producing distinct clinical signs of hypoglycaemia so that insulin administration had to be continued for another 10 min.

Discussion

This study indicates that the GCIIS-guided IHT is a safe and sensitive procedure in the assessment of HPA function. Using appropriate constants for the preprogrammed algorithms of the GCIIS, a sufficient degree of hypoglycaemia was achieved in healthy subjects as well as in patients with hypothalamic-pituitary disease. The range of hypogly-

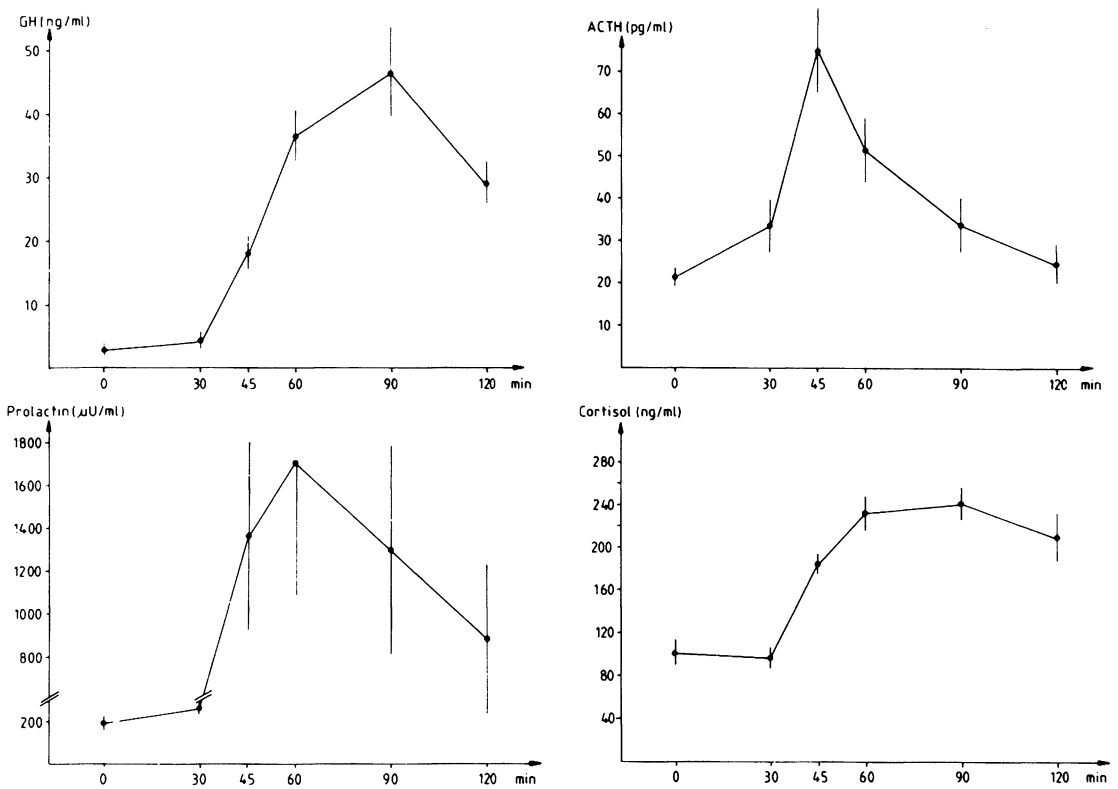

Fig. 3.
Serum GH, prolactin, ACTH and cortisol responses (mean ± SEM) during GCIIS-guided IHT in 10 healthy volunteers.

Table 2.

GCIIS-guided IHT in 10 patients with pituitary tumours (numbers 1–10 refer to Table 1). Insulin requirements (infused insulin) for inducing hypoglycaemia, basal and minimal blood glucose values (BG), basal values and maximal hormone responses for GH, prolactin, ACTH and cortisol are shown. In addition, the corresponding times are mentioned (min after beginning of the test).

	Pituitary adenoma hormone inactive			Acromegaly preoperative		Acromegaly postoperative		Cushing's syndrome	Prolactinoma		Pituitary insuff. postoperative	
	1	2	3	4	5	4	5	6	7	8	9	10
Infused insulin (U/kg)	0.129	0.127	0.151	0.200	0.242	0.106	0.138	0.335	0.114	0.161	0.093	0.124
BG (mg/dl)												
Basal	90	100	83	90	81	77	80	117	78	92	88	81
Minimal	19	21	37	28	37	37	40	37	33	37	34	30
Time (min)	48	40	34	42	60	24	40	70	30	32	40	30
GH (ng/ml)												
Basal	0.6	0.7	0.5	42	78	1.1	1.5	2.3	< 0.5	1.4	0.8	1.1
Maximal	0.9	1.4	0.6	56	230	15.2	2.7	9.5	< 0.5	50	0.8	11.7
Time (min)	30	60	30	120	60	60	60	45		90		45
Prolactin (μU/ml)												
Basal	267	670	547	1470	260	177	114	252	13 640	2290	< 100	< 100
Maximal	330	1049	563	3990	359	872	117	366	15 750	2800	< 100	218
Time (min)	60	90	45	45	60	30	30	60	60	60		60
ACTH (pg/ml)												
Basal	99	38	16	36	59	27	28	26	34	25	< 35	38
Maximal	148	49	18	39	77	37	44	41	39	72	< 35	38
Time (min)	60	45	60	90	45	45	30	120	120	60		
Cortisol (ng/ml)												
Basal	120	114	20	86	39	60	30	281	< 20	103	< 20	< 20
Maximal	195	205	35	109	45	149	46	281	22	313	< 20	< 20
Time (min)	90	60	60	60	90	60	90		90	120		

caemia from 19 to 40 mg/dl (mean: 32.5 ± 1.9 mg/dl) in the pituitary tumour patients compares favourably with the bolus technique where values below 15 mg/dl are achieved more frequently. As a consequence of feedback-controlled insulin administration, an optimal insulin dosage was given according to the individual insulin sensitivity. The total amount of insulin per kg body weight in controls was comparable to the recommended dosage for performing IHT by bolus injection (Borst et al. 1982; Landon et al. 1966), but in the patients with pituitary disease studied, there was a wider range of insulin requirements (see Table 2). So, if IHT is performed by bolus injection in patients with altered insulin sensitivity, the degree of which can not always be predicted exactly, there can be the risk of overdosage or the need of repeated injections, which is avoided by GCIIS-guided insulin administration. In the patients with partial or complete pituitary insufficiency no severe side effects were observed and there was no need of dextrose administration due to suspected insulin overdosage. On the other hand, appropriate insulin supply in the cases with decreased insulin sensitivity was guaranteed by the GCIIS. In healthy volunteers, the GCIIS-guided IHT produced phy-

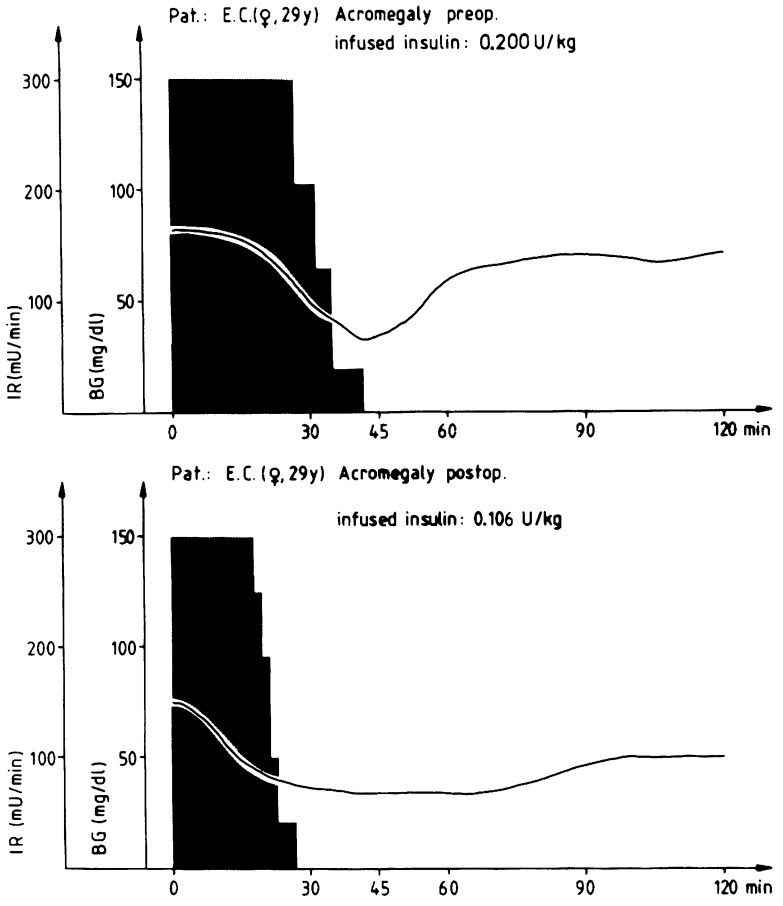

Fig. 4.
Blood glucose (BG) and insulin infusion rate (IR) during GCIIS-guided IHT in a patient with acromegaly preoperatively and postoperatively.

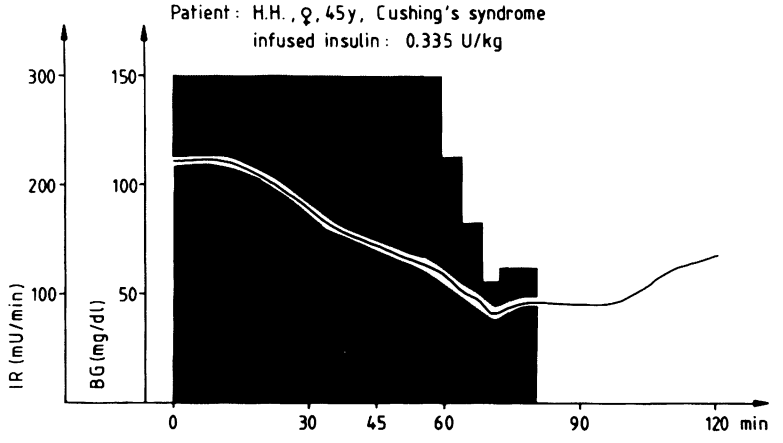

Fig. 5.
Blood glucose (BG) and insulin infusion rate (IR) during GCIIS-guided IHT in a patient with Cushing's syndrome. Total amount of insulin given by the GCIIS: 0.335 U/kg.

siological hormone responses for GH, prolactin, cortisol and ACTH (see Fig. 3), which were comparable to those obtained by bolus injection. In the patients with pituitary tumours, subtle or distinct impairment of HPA function could be detected (see Table 2).

In conclusion, the GCIIS-guided IHT can be recommended as a safe and sensitive procedure in the evaluation of pituitary function in patients with pituitary disease. Compared to the bolus method, it has several advantages:

1) Continuous documentation of blood glucose values.

2) Optimal insulin dosage with standardized hypoglycaemia due to automatic adjustment to the individual insulin sensitivity.

3) Patients' safety by earlier recognition of due insulin discontinuation and the need of dextrose.

Moreover, the use of the GCIIS-guided IHT may not be restricted to the assessment of HPA function in patients with pituitary disease. It seems to be of particular usefulness in studying glucose counterregulation following insulin induced hypoglycaemia in various conditions e.g. counterregulation in diabetes mellitus or hormonal and metabolic effects of different insulin preparations.

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