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EFFECT OF A LONG ACTING SOMATOSTATIN ANALOGUE (SMS 201-995) ON THE GROWTH VELOCITY FO 8 TALL ADOLESCENTS : PRELIMINARY RESULTS.

8 tall adolescents (4 boys and 4 girls) had accepted to be treated by SMS 201-995 for 12 Months in order to reduce their growth velocity and therefore their adult height. This treatment had been submitted to the local ethical committee. At present time 5 patients had undergone 3 months treatment (4 boys and one girl), mean chronological age was 14 years 6 months ± 1 year 2 months, mean SD for height was + 3.1 ± 0.42 SD, mean bone age was 14 years 6 Months ± 1 year 3 months, pubertal development was scored Tanner stage III (n=1) and IV (n=4). Before treatment, physiological 24 hour GH secretion, GH response to TRH and GHRH stimulation tests, SmC levels and others pituitary functions were evaluated. SMS 201-995 was given twice daily using 2 subcutaneous injection of 250 ug at 8.00 AM and 8.00 PM. For the whole group, growth velocity had strongly decreased (2 ± 2.82 cm/y versus 6.9 ± 2.35 cm/y), growth was completely blocked in 3 patients. One boy aged 15 years 9 months had the same growth velocity before and after treatment. The last patient had previously been treated unsuccessfully by bromocryptine during one year and after 3 months of SMS 201-995 therapy growth velocity had decreased (6cm/y versus 10 cm/y before treatment). Tolerance of this therapy was good however transient diarrhea and nausea during the first ten days had occured in all cases. Routine biological parameters remained normal. CONCLUSION : These preliminary results suggest the efficacy of SMS 201-995 in reducing growth velocity in children with constitutional tall stature without major side effects.

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PREDICTION OF EARLY REMISSION IN CYCLOSPORIN-TREATED RECENT TYPE 1 DIABETICS.

Among 40 children with recent type 1 IDDM treated with cyclosporin A (CyA), 27 interrupted insulin injections 48 ± 5 days after the onset of therapy and thereafter maintained their HbA1C level below 7.5% [N: 4.8 ± 0.7 (sd)%]. We compared this group with the 13 patients who could not maintain such glucose control without insulin.
No differences were detected in terms of age (10.2 vs 9.8 yrs), sex, initial blood glucose (3.9 vs 5.1 g/l), presence of islet cell antibodies (ICA: 72 vs 80% ; S-ICA: 84 vs 93% ; CF-ICA: 60 vs 43%), insulin autoantibodies (36 vs 25%), DR3 (61 vs 77%), DR4 (74 vs 69%), DR3,4 (39 vs 46%).
Clearcut differences were observed for the duration of polyuria (27 vs 48 days, $p < 0.01$), weight loss (3.2 vs 10.1% BW, $p < 0.001$), ketoacidosis (11 vs 62%, $p < 0.001$) and C peptide response to iv glucagon (0.5 vs 0.1 nmol/l, $p < 0.02$). Mean CyA dose (8.3 mg kg^{-1} d^{-1}) and 12 hr trough levels (RIA) in blood were similar (273 ng/ml vs 299 ng/ml) in both groups.
These data indicate that the early response to CyA depends primarily on the precocity of immunointervention and the persistence of sufficient beta cell function. Selection of patients based on these parameters should further increase the frequency of early remissions in future trials of immunosuppression in recent IDDM.

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RESIDUAL B CELL FUNCTION IN TRANSIENT NEONATAL DIABETES MELLITUS (TNDM)

In TNDM a delayed maturation of insulin secretion has been suggested. However, concentrations of C-peptide (C-pep) - a reliable measure of pancreatic B cell function - and of proinsulin in plasma (P) have not been reported. In 4 babies (birth weight 1800-1954 g, gestational age 32-37 weeks) with TNDM from day 5-11 of life, P-proinsulin, P-insulin IgG antibody (P-IAb) as well as serial measurements of P-glucose and P-C-pep were carried out. In 3 patients without IAb on admission, P-glucose was 38.7-64 mmol/l, P-proinsulin <1.2-2.2 pmol/l (ref.: 1.2-13 pmol/l). P-C-pep values were <0.06 and 0.06 nmol/l (ref.: 0.18-0.63 nmol/l), respectively, in patients I and II who had an insulin requirement of 4 i.u. per kg and 24h. In patient III, P-C-pep was 0.15 nmol/l initially and the insulin dose 2 i.u. per kg and 24h. Patient IV had an initial P-glucose of 16 mmol/l, a P-C-pep of 0.33 nmol/l, a P-IAb of 3.09 mU/ml, and a moderate insulin requirement (1 i.u. per kg and 24h). In patients I, II, and III, the P-C-pep rose to reference levels concomitantly with a decrease in insulin requirement (withdrawal of insulin after 86, 88, and 15 days, resp.). In patient IV, P-C-pep remained at reference concentrations, the insulin requirement decreasing with a concurrent decrease in P-IAb (withdrawal of therapy after 68 days). Conclusion: P-C-pep and P-IAb - but not the initial P-glucose or birthweight - are of prognostic significance in the treatment of TNDM.

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SEVERE HYPOGLYCEMIC EPISODES ARE NOT PREDICTIVE OF IMPAIRED GLUCOSE COUNTERREGULATION IN TYPE I DIABETES.

Counterregulatory responses to insulin-induced hypoglycemia were measured in 6 diabetics with frequent severe hypoglycemic episodes (group 1) and in 6 without severe hypoglycemia (group 2). Group 1 did not differ from group 2 regarding age (17.8±SD2.5yr vs 18.4±1.6), duration of diabetes (12.7±2.2yr vs 10.0±3.4), HbA1 (9.7±1.0% vs 10.9±1.9), s.c. insulin therapy and glucose levels on the morning of the test (4.9±1.3mM vs 6.2±1.1). The insulin infusion was then adjusted to lower plasma glucose to 2.5±0.4mM and 2.5±0.7 within 2h. Rate of glucose disappearance, calculated from plasma isotopic enrichment of stable dideuteroglucose, increased to 4.4±1.0mg/kg/min and 4.0±1.1, rate of appearance dropped to 2.2±0.5mg/kg/min and 1.7±0.4. Hormonal responses to hypoglycemia (area under curve of glucagon, epinephrine, growth hormone and cortisol) were not different between the groups. Marked decreases occurred in free fatty acids, 3-OH-butyrate and branched-chain amino acids. Alanine did not change. Six patients were found, 1 in each group, who had either no glucagon response to hypoglycemia (below 130pg/mL), or a very low epinephrine response (below 3.0 nmol/L), or both combined. In conclusion, despite severe hypoglycemic episodes, hormonal counterregulation may be unimpaired in some patients. On the other hand, long-term absence of hypoglycemic attacks does not guarantee intact glucose counterregulation.

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LACK OF RELATIONSHIP BETWEEN HYPOGLYCEMIC AWARENESS AND CATECHOLAMINE (CAT) RESPONSE IN INSULIN-DEPENDENT DIABETES (IDD)

We assessed hypoglycemic symptoms in 29 children aged 15.4±2.4 yrs (x±SD) with IDD duration 7.9±3.7 yrs without clinical autonomic neuropathy. An intravenous insulin bolus of 0.15-0.75 u/kg according to basal plasma glucose (PG) was given before and again after 3 days of intensive insulin therapy (IIT). Oral questionnaires regarding hypoglycemic (H) symptoms were completed at each time blood samples were taken for measurements of PG and CATS. An hypoglycemic awareness score (HAS) was assigned to each patient. All but 1 patient reported symptoms during each test. These occurred prior to H(PG> 65 mg%) in 73% before and 52% after IIT. The initial symptoms (usually hunger) appeared at 38±26 min before and 35±18 min after IIT after PG decrements of 121±81 (47±28%) and 88±64 mg% (46±26%) resp. (NS). The CAT increments at this time were very small (174±55, range 0-802 and 70±89, 0-262 pg/ml resp.). The max HAS correlated negatively with PG nadir, before ($r=-.69$, $p < .001$) but not after IIT. The max HAS correlated with peak CAT response before ($r=.42$, $p < .05$) and after ($r=0.42$, $p < .05$) IIT. In patients with PG nadir < 65 mg%, there were no differences in HAS or glucose recovery before and after IIT despite the fact that CAT response was significantly lower after IIT with some patients never achieving an increment >250 pg/ml. Thus, H unawareness is not common in children with IDD & symptoms occur prior to onset of H with minimal if any CAT increments.

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FLUID ADMINISTRATION RATE AFFECTS ONSET OF BRAIN-STEM HERNIATION (BH) IN DIABETIC KETOACIDOSIS (DKA)

Cerebral edema probably occurs universally with insulin and fluid treatment of severe DKA. The cause of life-threatening BH during treatment of DKA is unknown. No recommendations are proffered in recent reviews to suggest ways to prevent BH. History, laboratory data, rate of fluid administration and rapidity of onset from nine new cases of BH plus 33 cases from the literature were analyzed. Of note, calculated sodium conc. (M. Katz, NEJM (1973) 289:843) decreased between initiation of therapy and the hour of onset of BH (138.7 ± 6.2 mM vs 134.1 ± 8.3 mM, $t=2.68$, $p=.02$), and these were correlated: $r=0.61$, $p<0.01$, $n=18$. Serum K^+ conc. decreased during the same time period (5.0 ± 0.9 vs 3.7 ± 1.0 mM; $t=5.54$, $p<0.001$) but were not correlated. These data with the knowledge that vasopressin is inappropriately regulated in DKA, should alert the physician to be aware of the syndrome of inappropriate ADH in exacerbating BH. Unpaired t-test analysis excluded factors of sex, previous diagnosis of diabetes, $NaHCO_3$ in the initial fluid treatment or the presence of stupor on admission as affecting laboratory values, fluid administration rates or onset of BH. Only the rate of fluid administration (7.4 ± 2.8 L/m^2/day; n=40) was significantly related to rapidity of onset of BH ($r=-0.32$, $p=.04$). Only 4 of 40 cases occurred when fluid administration was <4 L/m^2/day. Limitation of the rate of fluid administration to a value <4 L/m^2/day continues to be a prudent recommendation in the treatment of DKA.