

Novo Nordisk

Book of Abstracts

American Diabetes Association
63rd Scientific Sessions
New Orleans, Louisiana, USA
June 13–17, 2003



Foreword

Novo Nordisk Research at the ADA

As the leader in diabetes care for more than 75 years, Novo Nordisk has responded to the alarming growth in diabetes by increasing the funding of its research, development and disease management programmes. The result is seen in the wealth and diversity of our diabetes discovery and development projects. Evidence of this dedicated research is highlighted by a total of 55 abstracts being accepted at this year's American Diabetes Association meeting.


A broad range of therapeutic approaches to diabetes is represented in this Book of Abstracts, including the established oral hypoglycaemic agent repaglinide, the rapid-acting analogue insulin aspart (NovoRapid®/NovoLog®) and the new High Mix biphasic insulin aspart (NovoMix®/NovoLog® Mix). We are particularly excited about the wide range of new data being presented here on insulin detemir (Levemir™). The second generation basal insulin analogue with its unique method of protraction offers a predictable and sustained pharmacodynamic action. Another exciting development is the progress being made with our pulmonary insulin delivery system, AERx® iDMS. The ease of insulin administration, and thus patient acceptance, with this device is one of its many advantages that we look forward to investigating further.

Interest in the GLP-1 hormone as an agent involved in blood glucose regulation and modulation of appetite is increasing. Liraglutide, our long-acting human GLP-1 derivative, has a kinetic profile designed for once-daily dosing and as such has the potential to play a major role in the management of diabetes. Also of value is the potassium-channel opener NN414, which may permit beta-cell rest, thereby potentially postponing the progression to type 2 diabetes, or even intervention in the type 1 diabetes disease process.

You will also find data in the book on several class-leading delivery systems, such as InDuo® – the world's first combined insulin doser and glucose meter. InnoLet® is a product specifically designed to help people who face some difficulties, such as poor eyesight and reduced manual dexterity, to better manage their insulin therapy.

Empowering patients and health professionals to manage diabetes in a timely and effective manner is a need we must all address. At Novo Nordisk, we consider healthcare performance another area of important research. Patient experience, satisfaction, and quality of life with insulin treatment are important measures of outcome we continue to use to mould future therapies.

Together with our drug discovery scientists and the many other products in the development pipeline, we continue to strive towards our mission of defeating diabetes. It is our pleasure to welcome you to New Orleans and to provide this reference to abstracts at this meeting featuring Novo Nordisk's research.



Mads Krosgaard Thomsen
Executive Vice President, CSO



Kirstine Brown Frandsen
Medical Director, Vice President

Please note that many products featured here are in process of research or development and are not yet available for clinical use. Those that are released may not be available in all countries, while product presentations and indications may differ from country to country. Please consult local prescribing information before using any product.

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Abstracts selected as posters will be displayed on Saturday, Sunday and Monday in Hall D of the Convention Center. All posters will remain up for three days. Poster presenters will be at their poster boards to discuss their research for two hours on an assigned day and again during an evening Poster Reception on Saturday or Sunday.

Saturday 14th June

10.00 am–6.00 pm	posters on display
12.15 pm–2.15 pm	poster presenters on-site
5.00 pm–6.00 pm	poster session reception and poster presenters on-site

Sunday 15th June

7.00 am–7.00 pm	posters on display
12.00 pm–2.00 pm	poster presenters on-site
6.00 pm–7.00 pm	poster session reception and poster presenters on-site

Monday 16th June

7.00 am–5.00 pm	posters on display
12.00 pm–2.00 pm	poster presenters on-site

General posters and Publish Only papers are embargoed until 10.00 am (Central), Saturday 14th June. All other papers are embargoed until immediately following their presentation.

The Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of NN414, a β -Cell Targeted (SUR1/Kir6.2) Potassium Channel Opener ($K_{ATP}CO$) Following Seven Days Once Daily Oral Dosing in Healthy Male Subjects

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Experimental data suggests that “resting” or reducing the workload of the β -cell by inhibiting insulin secretion may be beneficial to patients with type 2 diabetes. The present study investigated the effects of NN414 a β -cell targeted potassium channel opener ($K_{ATP}CO$) after 7-days once daily oral dosing (at 10 pm) in healthy males. 40 subj. were enrolled at 5 dose levels (0.625, 1.25, 2.5, 5.0 and 10 mg/kg), with 8 subj./dose-level at a 3:1 active: placebo randomisation. After an overnight fast an OGTT was performed on days 1 and 7. In addition 24-h glucose, insulin and glucagon, and 8-h GH profiles were assessed. Treatment with NN414 was generally well tolerated, with no clinically relevant changes in vital signs, ECG, or safety laboratory assessments. While there was no statistically significant treatment effect (active vs placebo) on insulin and glucagon AUC (area under the curve) 0–8 or 0–11 or 0–24 h postdose (and GH AUC 0–8 h), there was, in accordance with the pharmacological profile, a marked acute inhibition of insulin secretion 1–2 h post dose. This was accompanied by increased glucose levels. On day 1 and 7 there was a significant lowering in the glucose AUC during the OGTT following NN414 treatment vs placebo ($p<0.05$) with a borderline significant effect of dose of NN414 on day 7 ($p=0.06$), but no significant lowering of the 24-h glucose AUC. For the derived parameters from the OGTT no significant treatment effect vs placebo on 1st or 2nd phase insulin secretion was shown at day 1 or 7, but there was a significant effect of dose of NN414 on both parameters on day 7 ($p<0.05$). Furthermore, there was a significant treatment effect vs placebo on the derived insulin sensitivity index and metabolic clearance rate at both day 1 and 7 ($p<0.05$), but no significant effect of dose of NN414 on these parameters. Taken together, these data suggest that resting the β -cell with NN414 may provide a new potential treatment for type 2 diabetes.

Attenuation of Hyperinsulinemia by the New Potassium Channel Opener, NN414, Improves Glucose Tolerance and Plasma Lipids Without Affecting Body Weight or Body Composition in Obese Zucker Rats

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The prediabetic phase of type 2 diabetes is characterized by insulin resistance and hyperinsulinemia despite normal blood glucose levels. By reducing the secretion of insulin from the pancreatic beta-cells with diazoxide (DZ), a non-selective activator of ATP sensitive potassium channels ($K_{ATP}CO$), beneficial effects on glucose metabolism have been seen in animal models. The aim of this study was to investigate the effects of NN414, a SUR1/Kir6.2 selective $K_{ATP}CO$ on glucose/lipid metabolism and body composition in obese Zucker rats. Seven-week-old female Zucker rats (n=14 per group) were treated with vehicle (Veh), NN414 (5 mg/kg), or DZ (50 mg/kg) twice daily for 6 weeks. Plasma lipid levels were determined at baseline, week 3, and week 6. At the end of the study, an oral glucose tolerance test was performed and plasma fructosamine levels determined. Total body fat was determined by DEXA at week 6. Compared with vehicle treated controls, both NN414 and DZ significantly decreased or even neutralized the age related increase in postprandial plasma triglyceride and free fatty acid levels. Likewise, glucose tolerance (AUC) was significantly improved in the two treatment groups (Veh: 393±306; NN414: 223±80; DZ: 188±91 mMxmin). Insulin levels (AUC) tended to decrease in both NN414 and DZ treated animal during the OGTT when compared with vehicle treated controls (Veh: 91±88; NN414: 60±49; DZ: 72±35 μ Mxmin). No significant differences were observed in body weight (Veh: 382±41; NN414: 413±41; 387±51 g), total body fat (Veh: 169±31; NN414: 187±26; DZ: 149±41g), and plasma fructosamine levels (Veh: 134±7; NN414: 137±8; DZ: 136±12 μ M) at the end of the study. Taken together, the results indicate that NN414, like DZ, improves glucose tolerance and plasma lipids without affecting body weight or total body fat in the obese Zucker rat. **In conclusion**, the results suggest that NN414 may be a candidate agent for postponing progression to and treatment of type 2 diabetes.

Improved β -cell Survival in a Type 1 Diabetes Rat Model After Treatment With a β -cell Selective Potassium Channel Opener

KRESTEN SKAK, CARSTEN GOTTFREDSSEN, JOHN BONDO HANSEN, JEPPE STURIS and HELLE MARKHOLST.

Type 1 diabetes results from an immune-mediated destruction of the β -cells. Reduction in β -cell mass during the diabetogenic process will increase the functional stress on the remaining β -cells. This may render them more susceptible to apoptosis, necrosis and autoimmune destruction. It is hypothesized that suppression of insulin secretion by administration of a β -cell selective potassium channel opener, NN414, can induce metabolic "rest" in the β -cells thereby reducing β -cell death resulting from metabolic stress as well as reducing the antigenicity of the β -cells. In this study diabetes was induced in 24–33-day-old BioBreeding Diabetes Resistant (BBDR) rats by combining RT6 depletion with PolyI:C treatment, resulting in 87% diabetes incidence (defined as blood sugar > 20 mM) with mean onset time 14 ± 3 days. The rats were randomized into 3 groups that were treated orally every 8 hrs from day 1–19 with 40 mg/kg NN414, 40 mg/kg diazoxide or vehicle. When blood glucose exceeded 20 mM a supplementary insulin treatment was given 3 times daily. At day 21 the rats were fasted for 5–6 hrs, and an i.v. glucose tolerance test (lvGTT) was conducted to assess β -cell function. The rats were subsequently sacrificed and their pancreas removed for histological assessment of insulinitis and remaining β -cell mass. Insulinitis was scored on a scale from 0 to 4 where 0 indicates normal islets and 4 indicates end-stage destruction with no remaining β -cells. Among NN414-treated rats 45.7% (16/35) had average insulinitis score below 2.0 whereas 13.9% (5/36) rats in both the vehicle group and the diazoxide group had average insulinitis score below 2.0 ($p < 0.002$ by χ^2 test). The presence of functional β -cells in these rats was confirmed by a C-peptide > 300 pM during lvGTT. There was no difference in %HbA_{1c} values among the three groups. Thus, this study demonstrates that β -cell rest induced by treatment with the potassium channel opener, NN414, improves β -cell survival and function, suggesting that therapy with NN414 may be used to rescue remaining β -cells in recent onset type 1 diabetic patients.

Repaglinide *versus* Sulfonylurea in Combination with Bedtime NPH Insulin in Patients with Type 2 Diabetes with Secondary Failure to Oral Treatment

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This multicenter, open label trial was designed to compare repaglinide vs. sulfonylurea in combination with bedtime NPH insulin in patients inadequately controlled on oral treatment. After 3 weeks' run-in, 58 patients were randomized to two groups: group Rep+NPH (n=40; age 63.7 ± 8.87; diabetes duration 11.3±4.77; HbA_{1c} 8.9 ± 1.5%) was switched to repaglinide before meals and bedtime NPH insulin; group SU+NPH (n=18; age 61.7±8.57; duration 9.9±4.93; HbA_{1c} 8.9±1.5%) continued on same SU with addition of bedtime NPH. Treatment was 4 weeks' titration (NPH dose optimized to maintain FPG < 7.8 mmol/l) and 12-weeks' observation; 52 patients completed. Withdrawals were ineffective therapy (FPG > 7.8 mmol/l) in 5 cases (4 Rep+NPH; 1 SU+NPH) and ALT elevation in 1 case.

Changes in HbA_{1c}, FPG and lipid levels from randomization to end of study in completers, and incidence of hypoglycemia, were analyzed (ITT population). In Rep+NPH, HbA_{1c} decreased by 1.0%, from 8.9–7.9% ($p < 0.001$) while FPG decreased by 3.1 mmol/l, from 10.8–7.6 mmol/l ($p < 0.001$). Corresponding values in SU+NPH were 8.9–8.6% for HbA_{1c} (0.3%, non-significant decrease) and 10.5–7.6 mmol/l for FPG (2.8 mmol/l decrease, $p < 0.001$). HbA_{1c} and FPG were significantly lower in Rep+NPH compared to SU+NPH ($p < 0.05$ and $p < 0.001$, respectively). Insulin dose was similar in both groups. Parallel, significant decrease of triglycerides and significant increase of LDL cholesterol was found in both groups (no differences between groups).

Body mass in Rep+NPH increased by 1.6 kg (80.9±14.0 to 82.5±14.1; $p < 0.05$) and in SU+NPH by 1.0 kg (78.9±8.6 to 79.9±14.2, non-significant). Incidence of hypoglycemia was similar in both groups while number of night-time episodes was lower in Rep+NPH (0.3 vs. 0.61 episode/patient).

We conclude that repaglinide is more effective than sulfonylurea in combination with bedtime NPH insulin in treatment of patients with type 2 diabetes uncontrolled on oral hypoglycemic therapy.

Differential Effects of Repaglinide, Nateglinide and Glibenclamide on Apoptosis in Human Beta Cells *In Vitro*

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Loss of β -cell mass and function constitutes a concern to the application of sulfonylureas for the treatment of type 2 diabetes. Previous studies have shown that the sulfonylureas tolbutamide and glibenclamide induce apoptosis in cell lines and rodent islets. Therefore, we investigated the effect of the new insulin secretagogues repaglinide, nateglinide and of the sulfonylurea glibenclamide on β -cell apoptosis in human islets. Human islets from three organ donors were cultured onto extracellular matrix coated plates and exposed to glibenclamide, repaglinide or nateglinide at 5.5 mM glucose. Apoptosis was studied using the TUNEL assay. The doses of the three compounds were chosen according to detected maximal effects – ie efficacy.

Exposure of human islets for 4 h to 0.1 and 10 μ M glibenclamide induced a 2.38- and 2.47-fold increase of β -cell apoptosis, respectively, whereas repaglinide did not change the number of apoptotic β -cells. At low concentration (10 μ M), nateglinide did not induce β -cell apoptosis, however, at high concentration of 1 μ M it induced a 1.49-fold increase in the number of apoptotic β -cells. Prolonged exposure for 4 d of the islets to the secretagogues induced β -cell apoptosis. The increase was of 4.1- and 4.4-fold at 0.1 and 10 μ M glibenclamide, 2.37- and 3.8-fold at 10 and 1000 nM repaglinide, and of 3.2- and 4.6-fold at 10 and 1000 μ M nateglinide, respectively.

Taken together, glibenclamide induced β -cell apoptosis in human islets. Repaglinide and low concentration of nateglinide did not induce β -cell apoptosis after a 4-h exposure. Thus, glibenclamide may precipitate the decrease in β -cell mass observed in patients with type 2 diabetes. In contrast, exposure of β -cells to repaglinide or nateglinide for the duration of their circulating half-life (1.5–1.8 h) may preserve β -cell mass. Investigation of concentration-effect relationships in terms of apoptosis and insulin release may provide insight into relative β -cell sparing effects of non-sulfonylurea containing insulin secretagogues.

The Coupling of Kir6.2 to SUR1 Differentially Affects Potassium Channel Opener Induced Displacement of [³H]Glibenclamide and [³H]Repaglinide Binding

ANN MARIA K. HANSEN, TINNA LARSEN, RICHARD D. CARR, JOHN BONDO HANSEN, FRANCES M. ASHCROFT and PHILIP WAHL.

The pancreatic beta-cell ATP-sensitive potassium (K_{ATP}) channel is composed of four pore-forming subunits (Kir6.2) and four regulatory subunits (SUR1). Glibenclamide and repaglinide bind to SUR1 with high affinity and the N-terminus of Kir6.2 is involved in coupling sulphonylurea binding to closure of the channel pore. In the presence of MgATP, the binding site for potassium channel openers (PCOs) on SUR1 is allosterically coupled to the glibenclamide-binding site. In this study, we compare the interaction of glibenclamide and repaglinide with the Kir6.2/SUR1 channel by displacement of [³H]repaglinide or [³H]glibenclamide binding with the Kir6.2/SUR1 selective PCO, NNC 55-9216. SUR1 was either expressed alone or co-expressed with Kir6.2 or with N-terminally deleted Kir6.2 (Kir6.2deltaN14) in HEK293 cells. Binding studies were performed on isolated membranes. Saturation analysis revealed a single high-affinity [³H]glibenclamide binding site both when SUR1 was expressed alone ($K_D=0.2$ nM) or together with Kir6.2 ($K_D=1.5$ nM) or Kir6.2deltaN14 ($K_D=1.9$ nM). In contrast, repaglinide only showed high-affinity binding to SUR1 co-expressed with Kir6.2 ($K_D=0.6$ nM). The binding affinity of [³H]repaglinide was 500-fold lower for SUR1 expressed alone or with Kir6.2deltaN14. NNC 55-9216 displaced ³H-repaglinide ($IC_{50}= 8.6$ μ M) and [³H]glibenclamide ($IC_{50}= 22$ μ M) binding to Kir6.2/SUR1 in the presence of MgATP. The ability of NNC 55-9216 to displace [³H]glibenclamide binding was largely unaffected when SUR1 was expressed alone. In contrast, NNC 55-9216 produced no significant displacement of [³H]repaglinide binding at concentrations up to 100 μ M when SUR1 was expressed alone. **We conclude** that the high-affinity [³H]repaglinide site is allosterically coupled to the NNC 55-9216 binding site and its formation is critically dependent on functional coupling between Kir6.2 and SUR1.

Combination of Repaglinide and Metformin Results in Greater than Additive (Synergistic) Effects on Glucose Tolerance in Obese Zucker (fa/fa) Rats

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Combination therapy with repaglinide (REP) and metformin (MET) is an effective way to treat patients with type 2 diabetes. In this study, we specifically wanted to investigate whether the combination of REP and MET acutely has additive or possibly synergistic effects on glucose tolerance in male obese Zucker (fa/fa) rats. Twenty overnight fasted Zucker rats were studied in a 2×2 factorial design (n=5 per group). At t=-60 min animals received either MET 200 mg/kg or vehicle (VEH) p.o., at -30 min animals received either REP 0.3 mg/kg or VEH p.o., and at 0 min all animals received 2 g/kg glucose p.o. Tail tip sampling for glucose measurements was performed at -60, -30, 0 (immediately prior to glucose dosing), 30, 60 and 120 min. The area under the glucose curve between 0 and 120 min (AUC₀₋₁₂₀) and the glucose value at 120 min (GLU₁₂₀) were evaluated statistically with two-way analysis of variance. The interaction term was used to test for synergy. Data are presented as mean±SD. As demonstrated in the table, the threshold dose of REP had no effect on either parameter when given alone, but a clear effect when combined with MET dosing. This was evidenced by the interaction terms (significance for GLU₁₂₀) showing that REP and MET have greater than additive or synergistic effects on glucose tolerance in the male Zucker rat.

	VEH/VEH	REP/VEH	VEH/MET	REP/MET	p value, interaction term
AUC ₀₋₁₂₀ (mM×min)	947±128	965±166	811±43	614±106	0.061
GLU ₁₂₀ (mM)	7.16±0.79	7.02±1.39	6.72±0.23	4.28±0.76	0.011

In conclusion, we have demonstrated that the combination of REP and MET has synergistic effects on glucose tolerance in the male Zucker rat. The presence of greater than additive effects may be of relevance for the clinical efficacy of the REP/MET combination.

Balaglitazone, a New Thiazolidinedione, Improves Glucose and Lipid Control in Patients with Type 2 Diabetes

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This was a randomized, double-blind, placebo-controlled, 10 weeks dose-finding trial of 3 doses of balaglitazone (5, 10, and 20 mg) and open-label pioglitazone (45 mg) in patients with type 2 diabetes. The primary endpoint was FPG. 199 patients were randomized. Efficacy results are summarized in Table 1.

Table 1

Efficacy variable	Treatment diff vs placebo (LS estimated mean change) (PP)			
	Bala 5 mg (n=42)	Bala 10 mg (n=38)	Bala 20 mg (n=38)	Pio 45 mg (n=42)
FPG (mmol/L)	-1.03*	-1.72**	-2.54**	-1.91**
HbA _{1c} (%-point)	-0.43	-0.51	-1.03**	-1.14**
Insulin (pmol/L)	-12.5	-29.0	-15.4	-25.3
HDL-C [†]	2	6	14**	14**
LDL-C [†]	4	7	5	4
VLDL-C [†]	4	-8	-10	-17*
Total C [†]	5	5	6	3
FFA [†]	4	-22*	-20	-20*
TG [†]	7	-5	-5	-17*

[†]% change relative to placebo; *P value <0.05; **P value <0.01

Most patients (90%) completed the study. 3 patients experienced a serious adverse event (1 each in the placebo, 5 and 20 mg balaglitazone groups). 2 patients developed edema (in the 5 mg balaglitazone and 45 mg pioglitazone groups). Increases in CK, LDH, and urea were observed following both pioglitazone and balaglitazone treatment. Major safety results are presented in Table 2.

Table 2

Safety variable	Treatment diff vs placebo (LS estimated mean change) (Safety Pop.)			
	Bala 5 mg (n=42)	Bala 10 mg (n=38)	Bala 20 mg (n=36)	Pio 45 mg (n=42)
Abs neutrophil count (×10 ⁹ /L)	-0.39	-0.55	0.0	-0.67*
Hemoglobin (g/L)	-0.33	-4.0 *	-3.63 *	-5.46 **
Body weight (kg)	0.28	0.21	0.91	0.76

P* value <0.05; *P* value <0.01

No major safety concerns were evident from adverse events, laboratory values, physical exam, slit lamp exam and ECGs. Total- and LDL cholesterol were nonsignificantly increased following both pioglitazone and balaglitazone treatment. Balaglitazone resulted in dose-dependent reductions in FPG, HbA_{1c}, VLDL, FFA, and TG; and a dose-dependent increase in HDL. **In conclusion** the data shows that balaglitazone could be a promising treatment for type 2 diabetes.

Balaglitazone a New Partial PPAR γ Agonist has a Better Cardio Vascular Safety Profile and Glycemic Control Compared With the Full PPAR γ Agonist Rosiglitazone

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Thiazolidinediones like rosiglitazone (Rosi) are known to induce good glycemic control and to restore insulin sensitivity in type 2 diabetics. However, cardiovascular (CV) side effects (e.g. oedema) in humans have been observed with these drugs. In the present study, we have identified Rosi as a full PPAR γ agonist in a PPAR-transactivation assay and a new PPAR γ agonist balaglitazone (Bala, NNC 61–0645, DRF2593) as a partial agonist (78% activation of PPAR γ compared to Rosi). The *in vivo* pharmacological activities were characterized by dose response studies in db/db male mice. After 7 days oral treatment with either vehicle or compound, blood samples were analyzed for glucose and insulin. An oral glucose tolerance test (OGTT) was conducted in overnight fasted mice on Day 9 and AUC_{glucose} calculated.

db/db mice	Glucose		Insulin		OGTT (AUC _{glucose})	
	ED ₅₀ /ED ₉₀ (mg/kg)	Max. Reduction (%)	ED ₅₀ /ED ₉₀ (mg/kg)	Max. Reduction (%)	ED ₅₀ /ED ₉₀ (mg/kg)	Max. Reduction (%)
N = 6						
Rosiglitazone	0.9/5.8	35	0.4/2.8	43	0.8/5.9	16
Balaglitazone	0.2/3.0	60	0.9/2.1	82	3.0/6.7	54

Potential CV side effects were evaluated through an assessment of plasma volume (PV) and blood volume (BV) (Evans blue dye dilution method) and heart weight (HW) in normal SD rats after 3 weeks oral treatment: Bala (1.5, 5.0 and 25 mg/kg once daily), Rosi (1.0, 3.0, and 9.0 mg/kg bid.).

N = 10	Vehicle	Rosi 2 mg/kg	Rosi 6 mg/kg	Rosi 18 mg/kg	Bala 1.5 mg/kg	Bala 5 mg/kg	Bala 25 mg/kg
PV (ml/kg)	42.3	43.3	48.1*	52.0***	41.8	43.2	50.0***
BV (ml/kg)	61.9	63.8	70.1**	74.5***	61.8	62.9	71.6***
HW (g/kg)	2.92	2.86	3.08	3.35***	2.78	2.89	3.38***

This study showed that balaglitazone induced better glycemic control than Rosi and had no CV side effects when administrated at pharmacological doses. As seen in the clinic, Rosi was found to induce a dose-related increase of CV side effects at pharmacologically relevant doses. These results raise the possibility that compared to full PPAR γ agonists, treatment with partial PPAR γ agonists may provide better glycemic control without CV side effects.

The Long-acting GLP-1 Derivative, NN2211, Restores Beta Cell Sensitivity to Glucose in Subjects with Type 2 Diabetes

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Glucagon-like peptide 1 (GLP-1) glucose-dependently stimulates insulin secretion, but its very short half-life limits its use as a therapeutic agent. NN2211 is a long-acting GLP-1 derivative suitable for once-daily administration. We tested the effect of NN2211 on beta cell sensitivity in 10 subjects with type 2 diabetes, age 63 ± 8 years (mean \pm SD), BMI 30.1 ± 4.2 kg/m², HbA_{1c} $6.5 \pm 0.8\%$, in a randomized, double-blind, placebo-controlled, crossover study. A single subcutaneous injection of NN2211 (7.5 μ g/kg) or placebo was administered in random order to subjects with type 2 diabetes 9 hours (equal to reported t-max) prior to testing. Beta cell sensitivity was assessed by a graded glucose infusion protocol with plasma glucose levels matched over the range of 5 to 12 mmol/L. Insulin secretion rates (ISR) were estimated by deconvolution of circulating C-peptide concentrations. Findings were also compared to responses of 10 healthy, nondiabetic volunteers to the same glucose infusion protocol. Compared to placebo, a single dose of NN2211 increased insulin and C-peptide levels, increased ISR area under the curve (AUC) (1130 ± 150 vs. 668 ± 106 pmol/min.kg; $p < 0.001$), and increased slope of ISR vs. plasma glucose (1.26 ± 0.36 vs. 0.54 ± 0.18 pmol.L/(min.mmol.kg); $p < 0.014$), to values similar to nondiabetic controls who did not receive the drug (ISR AUC 1206 ± 99 ; slope of ISR vs. plasma glucose 1.44 ± 0.18). Insulin clearance and glucagon AUC were not significantly different between placebo treatment, NN2211 treatment, and healthy individuals. As expected, no hypoglycemic events occurred. Mild treatment adverse events (diarrhea and headache) were reported by 3/10 NN2211-treated and 2/10 placebo-treated diabetic subjects. **In conclusion**, a single dose of the long-acting GLP-1 derivative, NN2211, restores beta cell sensitivity to physiological hyperglycemia in type 2 diabetes patients. These results substantiate the potential of NN2211 as a new therapeutic agent for the treatment of type 2 diabetes.

One Week's Treatment with NN2211, a Long-acting GLP-1 Derivative, Markedly Ameliorates 24-h Glycemia and β -cell Function and Reduces Fasting Endogenous Glucose Release in Type 2 Diabetic Patients

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NN2211 is a long acting GLP-1 derivative designed for once daily administration in humans. The aim of this study was to explore the effect of one week's treatment with NN2211 on 24-hour glucose and hormone profiles, fasting endogenous glucose release (EGR) and β -cell function in type 2 diabetic patients. We examined thirteen patients with type 2 diabetes ((means \pm SD): age 56.4 ± 9.2 years, BMI 31.2 ± 3.6 kg/m², duration of diabetes 3.0 ± 2.6 years) in a placebo-controlled cross-over design. NN2211 6 μ g/kg was administered once daily for one week whereafter 24-h profiles of glucose, insulin, glucagon and C-peptide were obtained. On the following day fasting EGR was determined by tracer dilution technique. Gluconeogenesis (GNG) was assessed using the ²H₂O technique, and glycogenolysis (GLY) was calculated. β -cell function was evaluated by IVGTT, hyperglycemic clamp (16mM) and arginine stimulation test (5g). Statistical analyses were performed by ANOVA.

RESULTS (mean \pmSEM):	NN2211	Placebo	
24-h glucoseAUC (mM.hr)	187.5 \pm 14.0	232.3 \pm 21.9	§
24-h insulinAUC (pmol/l.hr)	3,853 \pm 581	4,154 \pm 881	
24-h glucagonAUC (pg/ml.hr)	2,179 \pm 118	2,371 \pm 135	§
EGR (mg/kg/min)	1.92 \pm 0.06	2.13 \pm 0.09	§
GNG (mg/kg/min)	1.09 \pm 0.04	1.12 \pm 0.04	
GLY (mg/kg/min)	0.83 \pm 0.04	1.02 \pm 0.07	§
IVGTT,insulinAUC (pmol/l.hr)	55.5 \pm 9.9	34.3 \pm 6.4	*
Hyperglycemic clamp, mean insulin conc.(pmol/l)	929 \pm 263	272 \pm 53	§
Hyperglycemic clamp, mean glucagon conc. (pg/ml)	55.5 \pm 3.7	66.7 \pm 3.5	*
Arginine stimulation test, insulinAUC (pmol/l.h)	799.6 \pm 190	307.2 \pm 65.5	*
Arginine stimulation test, glucagonAUC (pg/ml.h)	40.7 \pm 2.5	48.7 \pm 3.0	§

§ $p < 0.05$, * $p < 0.01$

One week's treatment with NN2211 significantly reduces 24-hour plasma glucose levels in type-2 diabetic patients. β -cell function is improved, while glucagon secretion is suppressed. Fasting GLY is significantly reduced by NN2211, which results in a suppressed fasting EGR.

No Impairment of Hypoglycemia Counterregulation via Glucagon with NN2211, a GLP-1 Derivative, in Subjects with Type 2-Diabetes

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The GLP-1 derivative NN2211 is being evaluated as a new treatment for type 2 diabetes. GLP-1 suppresses glucagon secretion, therefore, NN2211 could disturb hypoglycemia counterregulation. This trial examined counterregulation during treatment with NN2211 vs placebo. Eleven subjects with type 2 diabetes (3F, age 56 ± 9 yrs, BMI 30.4 ± 3.4 kg/m², diabetes duration 6 ± 3 yrs, fasting plasma glucose (FG) 151 ± 47 mg/dL, HbA_{1c} 7.5 ± 1.1 %) treated with diet (n=3) or with oral antidiabetic drugs (n=8) were studied in a placebo-controlled cross-over design. A single s.c. dose of NN2211 ($7.5 \mu\text{g/kg}$) was given at midnight. In the morning, regular insulin infusions ($2 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) were administered to obtain fasting euglycemia. Capillary glucose was consecutively clamped for 240 min at levels of 78, 66, 54, and 42 mg/dL for 60 min each. Glucose, insulin, C-peptide, glucagon, cortisol, growth hormone (GH) and catecholamines were determined. Insulin secretion rates (ISR) were derived by deconvolution of C-peptide profiles. NN2211 reduced FG to 135 ± 43 mg/dL (placebo: 145 ± 54 mg/dL). At steady state insulin concentrations of ~ 1000 pmol/L, glucose infusion rates were similar with NN2211 vs placebo ($p=0.2684$). Exposure to hypoglycemia led to clear counterregulatory responses of glucagon (1.6 fold), cortisol (2.2 fold), GH (6.6 fold), adrenaline (14 fold) and noradrenaline (2.3 fold; all $p < 0.0001$, ANOVA). Responses did not differ significantly for NN2211 vs placebo (glucagon, $p=0.76$; cortisol, $p=0.43$; adrenaline, $p=0.27$, noradrenaline, $p=0.57$), except for GH (impaired response with NN2211, $p=0.034$). C-peptide concentrations were significantly higher with NN2211 at all clamp levels ($p < 0.0001$). ISR was significantly different only at baseline and not at any hypoglycemic clamp level. NN2211 reduces fasting glycemia but does not impair glucagon responses during hypoglycemia. NN2211, like GLP-1, does not impair hypoglycemia counterregulation, except for a reduction in GH response. The insulinotropic activity of NN2211 is glucose-dependent like that of GLP-1.

Plasma Protein Binding of NN2211, a Long-Acting Derivative of Glucagon-Like Peptide-1, is Important for its Efficacy

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GLP-1 has a wide spectrum of biological effects and seems ideal for treatment of type 2 diabetes. The native hormone is unsuitable as a drug because it is broken down rapidly by DPP-IV and cleared by the kidneys. NN2211 is a stable derivative suitable for once daily administration. The mechanism of protraction is predicted to be binding to albumin, thereby escaping clearance in the kidneys, as well as stability towards DPP-IV and slow release from the injection site. This study shows the effect of NN2211 plasma binding on GLP-1 receptor activity.

In order to characterize the binding to plasma proteins, we have used assays with the human GLP-1 receptor. NN2211 and GLP-1 were equipotent (EC_{50} 61 ± 7 and 55 ± 19 pM) when analyzed in a buffer without the presence of plasma. The binding to plasma was measured as the difference between the EC_{50} of GLP-1 and NN2211 when analyzed in the presence of plasma. GLP-1 itself does not bind to albumin; however the assay itself changes upon addition of plasma. In the presence of 90% human plasma, the EC_{50} was 99 ± 8.5 nM and 1.7 ± 0.5 nM of NN2211 and GLP-1, respectively. This corresponds to a free fraction of 1.5% in 100% human plasma, assuming linearity. When porcine plasma was used, a free fraction of 1.0% in 100% plasma was measured (EC_{50} was 127 ± 60 nM and 1.4 ± 0.5 nM). Pigs have been used to characterize the pharmacodynamics of NN2211. The half-life in pigs has been reported to be 14 hours, and total plasma levels of 6–8000 pM have been shown to be effective. The 1% free fraction corresponds to 84 pM free NN2211. Plasma concentrations of 50–100 pM have earlier been shown to be adequate for *in vivo* efficacy of natural GLP-1. **In conclusion**, compared to natural GLP-1 relatively high total plasma concentrations of NN2211 are needed for full efficacy. However, the free concentration of NN2211 correlates to those obtained with GLP-1. Thus, the differences in efficacy between NN2211 and native GLP-1 can be explained by differences in free fractions.

The GLP-1 Derivative NN2211 Normalizes Food Intake and Lowers Body Weight in a Hyperphagic Minipig Model

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Glucagon-Like Peptide-1 (GLP-1) is a labile hormone with a wide spectrum of biological activities resulting in lowering of blood glucose and appetite. GLP-1 compounds are promising for treatment of type 2 diabetes and the associated obesity which is intensified by most of the current treatments for type 2 diabetes. NN2211 is a long-acting GLP-1 derivative with a kinetic profile designed for once-daily dosing. We have dosed NN2211 for 7 weeks to extremely hyperphagic minipigs. This model is very relevant for obesity in association with diabetes, because of the hyperphagic element.

Six female, 18 months Göttingen minipigs fed pig chow ad libitum from weaning were used for the study. The bodyweight was 93.7 ± 6.1 kg at onset of the study, approximately 3 times the normal of food restricted minipigs. 24 h food intake and twice weekly body weight were measured over a 21 weeks period. After a 7 weeks basal period the pigs were treated with 0.003–0.007 mg/kg NN2211 once daily for 7 weeks, followed by a new 7 weeks follow-up period post treatment. All data are presented as mean \pm SEM.

NN2211 had a profound effect on food intake over the 7 weeks treatment period, with a >60% reduction in the treatment period, both measured as AUC (pre period: 836 ± 60.0 , NN2211 treatment period: 288 ± 30.3 , post period: 751 ± 47.9 (MJx7 weeks)) and daily food intake (pre period: 18.3 ± 0.5 , NN2211 treatment period: 6.3 ± 0.4 , post period: 18.1 ± 0.6 (MJ)), ($p < 0.001$ for treatment, compared to pre- and post periods). A new steady state in food intake, occurred after 3 weeks of treatment (6.7 ± 0.5 MJ) and after termination of NN2211 administration, the pigs came back to basal food intake within 4 days. Bodyweight gain decreased 4.3 ± 1.2 kg during the 7 weeks treatment and increased 7.0 ± 1.0 kg during the 7 weeks post treatment basal period ($p < 0.01$, ANOVA).

In conclusion NN2211 reduced food intake by more than 60% over a 7 week treatment period in a hyperphagic minipig model and caused a reduction in bodyweight. The results are promising for the treatment of obesity in patients with type 2 diabetes.

A Comparison of the Usability of Two Types of Disposable Pen (FlexPen versus Humalog Kit) containing Rapid-Acting Insulin Analogs

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Selecting the most appropriate insulin delivery device for a given patient is likely to improve patient compliance and promote accurate dosing. It is particularly important to ensure convenient delivery devices for rapid-acting insulin analogs to maximise their potential for reducing prandial glucose levels. This cross-over study investigated 58 diabetic patients (29 male, 29 female, average age 58 ± 16) who had not previously used insulin pen devices to assess the functionality of two pre-filled insulin devices: FlexPen (containing insulin aspart, Novo Nordisk) and Humalog Kit (containing insulin lispro, Eli Lilly). All participants were tested for hand functionality and vision prior to commencing the study, to assess for deficits that could affect ability to use insulin devices. Following instructions, participants made simulated injections into a sponge on the abdomen to determine the usability of each insulin device. FlexPen was rated significantly better than Humalog Kit on measures of number legibility ($p < 0.001$), ease of dose setting ($p < 0.001$), ease of pressing the release button ($p < 0.001$), stability during injection ($p < 0.001$), simplicity ($p < 0.001$), confirmation of injection ($p < 0.001$), and appearance ($p < 0.01$). There was no significant difference between the two devices on measures of grip and portability. Overall, 82.8% of participants said that they would prefer to use FlexPen, with no participant stating a preference for Humalog Kit. FlexPen was also rated as superior to Humalog Kit when subgroups of age, hand functionality and vision were examined ($p < 0.01$ for each subgroup comparison of overall score for each pen). The superior performance of FlexPen is probably due to its scaled analog dial, which clearly shows completion of injection and larger dial numbers. These results demonstrate that FlexPen is an excellent device for use in a wide range of patients including those with mild deficits in vision and dexterity.

Type 1 Diabetes Patients Can Temporarily Switch From Continuous Subcutaneous Insulin Infusion With Insulin Aspart to Basal Bolus Therapy with Insulin Aspart and Insulin Glargine

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The safety and efficacy of multiple daily injection (MDI) therapy of insulin aspart (IAsp) and insulin glargine were compared to continuous subcutaneous insulin infusion (CSII) with IAsp in a multicenter, open-label, randomized, cross-over study of adult type 1 subjects previously treated with CSII (37 men/63 women; BMI (\pm SD), 26.9 \pm 4.0 kg/m²; age, 43 \pm 11 yrs). Before randomization, all subjects were treated for 1 week with IAsp, switching on a unit-by-unit basis from their prestudy CSII insulin. Thereafter, 50 subjects were randomized to MDI therapy (IAsp immediately before each meal and glargine at bedtime) and 50 subjects continued on CSII therapy. For MDI-treated subjects, the glargine dose was equal to the total dose of the 24-hour CSII basal rate. After 5 weeks, subjects were switched to the alternative treatment for 5 weeks. During the last week of each treatment period, subjects wore a continuous subcutaneous glucose monitoring system (CGMS) for 48 to 72 hours. The CGMS showed that glucose exposure was significantly lower with CSII than with MDI therapy, based on AUC glucose \geq 80 mg/dL over a 48-hour glycemic profile (CSII: 2059 \pm 1310 mg·hr/dL; MDI: 2687 \pm 1734 mg·hr/dL; P <0.01). Fructosamine values at the end of each treatment period were significantly less with CSII than with MDI therapy (343 \pm 47 μ mol/L vs 355 \pm 50 μ mol/L, respectively, P <0.001). Incidence of hypoglycemia was similar for both treatment therapies. A similar percentage of subjects reported hypoglycemic episodes (CSII: 92%, MDI: 94%) and nocturnal (midnight to 8 am) hypoglycemic episodes (CSII: 73%, MDI: 72%). Major hypoglycemia (with CNS dysfunction requiring assistance of another individual) had low occurrence in both groups (CSII: 2 episodes, MDI: 3 episodes). **Conclusion:** CSII therapy with IAsp results in lower glycemic exposure without increased risk of hypoglycemia as compared to MDI therapy with IAsp and insulin glargine in type 1 diabetes patients. Type 1 patients can safely switch from CSII therapy to MDI therapy for temporary situations.

Stability of Insulin Aspart in Insulin Infusion Pumps

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Pump users often press the practical limits of trouble-free CSII use by exceeding the approved in-use duration of 48-hrs for the insulin. This *in-vitro* study determined the stability of insulin aspart (NovoLog®; Novo Nordisk) for a period of 6–7 days under conditions of CSII pump use. Testing was conducted in 22 MiniMed (506) pumps and 22 Disetronic (H-Tron plus V100) pumps, at 37°C with constant shaking (30 cycles/min, 1 cm amplitude). Pump specific plastic reservoirs and infusion sets were utilized, infusion sets were replaced every 48-hrs. Pumps were programmed to deliver 40 U/day, distributed as 0.9 U/hr basal rate and three 6 U boluses. Insulin was collected in HPLC tubes, and compared for physico-chemical integrity on day 1, 2, 4, and 6 against the intact formulation (unopen vial, 5°C). Key results (mean±SD) from day 2 and 6 were as follows:

Parameter	Ref. (5°C)	MiniMed System (37°C)			Disetronic System (37°C)	
	Day 0	Day 2	Day 6	Day 2	Day 6	
pH	7.40±0.02	7.46±0.01	7.47±0.03	7.46±0.02	7.46±0.02	
Insulin aspart (nM)	592±5.1	598±6.6	599±7.5	598±4.4	594±3.6	
Di – polymers (%)	0.5±0.11	0.5±0.04	0.6±0.08	0.5±0.05	0.5±0.11	

Biological active products B28isoAsp and desamido insulin aspart increased 2–3 fold over the 6 day period, however the absolute fractions were clinically insignificant (mean < 2%). Antimicrobial Preservatives-Effectiveness (USP) and Particulate Matter (USP) were evaluated from syringes left at 37°C for 7 days with shaking.

Analysis Day 7 (37°C)	MiniMed Syringe	Disetronic Syringe
USP 23 <51> Preservative-Effectiveness	Complies	Complies
USP <788> Particulate Matter	Complies	Complies

Under these test conditions, insulin aspart retained full potency and both preservative efficacy and particle count remained within US requirements. No pump stoppages occurred prior to day 3, after which stoppages occurred in some pumps in connection with bolus injections.

Presently pump insulins in the US are approved for a maximum 48-hrs CSII in-use time. Based on these data it may be clinically viable that insulin aspart be used for a longer duration; however further investigation will be required to confirm this.

No Increase in the Duration of Action with Rising Doses of Insulin Aspart

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Regular human insulin (HI) when injected in high doses shows a considerable prolongation in its duration of action putting patients into a risk of late postprandial hypoglycemia. This double-blind, randomized, 6-way cross-over trial investigated if this undesirable effect is less pronounced with the fast-acting analogue insulin aspart (IA). The pharmacokinetic (PK) and pharmacodynamic (PD) properties of HI and IA were compared in doses of 6, 12, and 24 IU s.c. in 14 healthy subjects (4 female, 28±4 years (mean±SD), BMI 24±2 kg/m) using the euglycemic glucose clamp technique (clamp level 5.0 mmol/l, continuous insulin infusion 0.15 mU/kg/min). In comparison to HI, IA showed higher maximal glucose infusion rates (GIR_{max} , $p=0.006$), an earlier onset of action (lower values for the time to the maximal effect $t-GIR_{max}$, $p<0.001$), and a shorter duration of action (lower $GIR-AUC_{6-12h}$, $p=0.0001$). Whereas HI showed a significant increase in the duration of action with higher doses (indicated by a significant increase in $GIR-AUC_{6-12h}$), there was only a moderate, non-significant rise in $GIR-AUC_{6-12h}$ for IA with higher doses (table). Accordingly, the PK-results (obtained with specific ELISAs for serum insulin (INS) or IA-concentrations) showed a non-significant rise in $INS-AUC_{6-12h}$ for IA with higher doses in contrast to a significant increase for HI. **In conclusion**, insulin aspart does not show a significant prolongation in its duration of action with higher doses. This indicates that insulin aspart, in contrast to regular human insulin, can be safely applied even in high doses without increasing the risk of late postprandial hypoglycemia.

	Human Insulin			Insulin Aspart		
	6 IU	12 IU	24 IU	6 IU	12 IU	24 IU
GIR_{max} (mg/kg/min) [#]	8.7±2.7*	10.3±2.4*	13.6±3.0	9.4±3.0**	14.1±4.5	15.7±4.2
$t-GIR_{max}$ (min) [#]	180±48	190±24	185±37	118±32	130±33	144±18
$GIR-AUC_{6-12h}$ (mg/kg) [#]	1371±394*	1424±346*	1698±215	1166±281	1289±284	1299±251
$INS-AUC_{6-12h}$ (nmol/l)	40.4±12.8**	51.8±17.3	60.9±17.9	1.5±4.5	1.8±3.5	4.9±5.4

Characters denote significant differences: [#]HI vs. IA; *vs. 12 IU; **vs. 24 IU

Subcutaneous Aspart Insulin: A Safe and Cost Effective Treatment of Diabetic Ketoacidosis

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We present the preliminary results of a prospective and randomized study that compared the efficacy and safety of subcutaneous (SQ) aspart (Novolog®) insulin given at different time intervals Q 1h (n= 10) and Q 2h (n= 12) to a standard intravenous (IV) protocol of regular insulin (n= 10) in patients with DKA. Diagnostic criteria included a serum glucose >250 mg/dl, a pH <7.30, bicarbonate <18 mEq/l and positive ketones. Patients treated with SQ insulin were managed in general medicine wards or in the Emergency Department while IV treated patients were managed in the ICU. Patients treated with aspart SQ Q 1h received a dose of 0.3 U/kg followed by 0.1 U/kg/hr until BG<250 mg/dl, then 0.05–0.1 U/kg/hr until resolution of DKA. Patients treated with aspart SQ Q 2h received 0.3 U/kg followed by 0.2 U/kg Q 2h until BG<250 mg/dl, then 0.1–0.2 U/kg Q 2h until resolution of DKA. IV treated patients received a bolus dose of 0.1 U/kg followed by 0.1 U/kg/hr until BG<250 mg/dl, then 0.05–0.1 U/kg/hr until resolution of DKA. Admission biochemical parameters in patients treated with SQ Q 1h (glucose: 771 ± 131 mg/dl, bicarbonate 7 ± 1 mEq/l, pH: 7.12 ± 0.03) were similar to those treated with SQ Q 2h (glucose: 799 ± 108 mg/dl, bicarbonate 9 ± 1 mEq/l, pH: 7.16 ± 0.03) and IV insulin (glucose: 689 ± 81 mg/dl, bicarbonate 7 ± 1 mEq/l, pH: 7.15 ± 0.05). There were no significant differences in the mean duration of treatment until correction of hyperglycemia (7 ± 1 hr, 8 ± 1 hr, and 8 ± 1 hr) and ketoacidosis (11 ± 1 hr, 10 ± 1hr, and 11 ± 1 hr) between patients treated with SQ Q 1h and Q 2h or IV insulin, respectively (*p*= NS). There were no mortality, and there were no significant differences in the length of hospital stay, amount of insulin until resolution, or in the rate of hypoglycemia between treatment groups. The use of SQ insulin resulted in a 34% lower hospitalization cost (SQ 1h: \$10611 ± 1837, SQ 2h: \$9278 ± 1523) than IV insulin treated patients (\$14,945 ± 2242; *p*<0.05).

In conclusion, SQ aspart insulin given Q 1h or Q 2h is a safe and cost effective alternative to IV regular insulin in the management of patients with DKA.

Insulin Aspart in Pregnancy: Protocol for a Randomized Controlled Trial Comparing the Safety and Efficacy of Insulin Aspart and Human Insulin in the Treatment of Pregnant Women with Type 1 Diabetes

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The Novo-Nordisk study group on type 1 diabetes and pregnancy.

The aim of this study is to compare the risk of major maternal hypoglycemia (24-hour, daily and nocturnal) with insulin aspart (IAsp) and human insulin (HI). Fetal outcomes, glycemic control (HbA_{1c} and 8-point blood glucose profiles), minor hypoglycemia, safety profiles and endpoints (RR of major hypoglycemia, diabetic complications, obstetric complications) will also be compared.

In this randomized, controlled, open-label, multinational, parallel-group study, subjects with type 1 diabetes will be recruited before pregnancy and up to a maximum gestational age of 10 weeks until 380 pregnancies are included. Treatment will be IAsp (injected immediately before eating) or HI (injected up to 30 minutes before eating) as mealtime insulin supplemented with NPH insulin administered once, twice or three times daily according to local practice. Subjects will be instructed to maintain/achieve glycemic control targets: preprandial 3.9–5.6 mmol/L; 1-hour postprandial <7.8 mmol/L; 2-hour postprandial <6.7 mmol/L; HbA_{1c} < 6.5%. Trial duration and number of visits for each subject will vary depending on time of conception relative to point of enrolment. Subjects pregnant at inclusion will attend 7 visits: screening, P1 (including randomization), P2 through to T (birth) and a follow-up visit (T+6 weeks). Major hypoglycemia will be analyzed using the gamma-frailty model; HbA_{1c} and blood glucose will be analyzed by ANOVA. Treatment satisfaction will be assessed by the DTSQ.

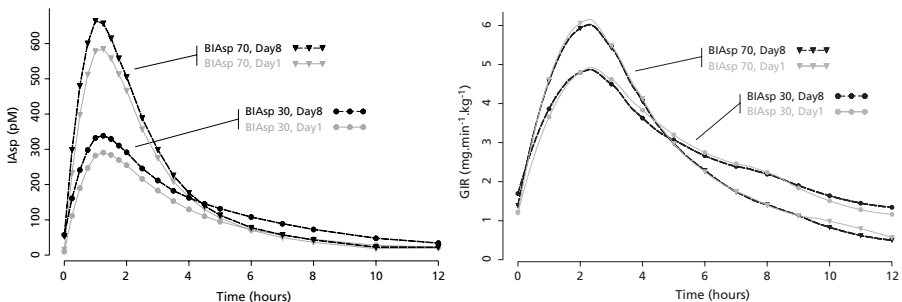
The trial, approved by health authorities and ethics committees, is ongoing and the last patient is expected to complete the trial in August 2004. We hope that the data generated will clarify the efficacy and safety of rapid-acting insulins in the management of pregnancy in type 1 diabetes.

Investigating the Drug Accumulation of Two Premixed Insulins

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Premixed insulin preparations might not exhibit their full metabolic potential after the first injection, as the effect may persist into the next dose. This double-blind, randomised, two-period crossover study investigated both the pharmacokinetics (PK) and pharmacodynamics (PD) of two premixed insulins at the onset (Day 1) and after one week (Day 8) of thrice daily treatment. Twenty-seven patients with type 1 diabetes (18 male and 9 female, age 27 ± 8 years) were included. The patients started treatment for one week with BIAsp 30 or BIAsp 70 (30% and 70% soluble insulin aspart, respectively, the remainder protaminated). Then followed a 2–6 week washout period, before shifting to one of treatment with the alternative insulin. On Day 1 and Day 8 of the two treatment periods, the PK (based on plasma insulin aspart profiles) and PD (based on glucose infusion rate (GIR) profiles) properties of the two insulin preparations were assessed in a 12h euglycaemic clamp (target blood glucose (BG) level: 5mM; BG stabilized during a 3–6h baseline period; basal insulin infusion rate: 0.15mU/(kg min)).

As expected, BIAsp 30 and BIAsp 70 showed clearly different time-action profiles (figure). A slight upward shift in the insulin aspart profiles was seen after one week of treatment, but for PD no difference was seen between Day 1 and Day 8.



In conclusion, this study proves that neither BIAsp 30 nor BIAsp 70 show any clinically relevant accumulation in the metabolic effect.

Future studies investigating accumulation of intermediate-acting or long-acting insulin preparations should investigate both PK and PD properties under multiple dose conditions.

In Inadequately Controlled Patients with Type 2 Diabetes, Biphasic Insulin Aspart 30 Combined with Pioglitazone Provides Better Glycemic Control than Biphasic Insulin Aspart 30 Monotherapy or Pioglitazone/Sulfonylurea Combination

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This open-labelled, parallel group study was designed to confirm the safety and efficacy of combining Biphasic Insulin Aspart 30 and Pioglitazone (BIAsp/Pio) versus BIAsp monotherapy or a combination of Pioglitazone and Glibenclamide (Pio/Glib) in type 2 diabetes subjects inadequately controlled with any kind of sulfonylurea mono- or combination therapy (2-week screening, 18-week treatment). Key efficacy endpoints included HbA_{1c}, fasting and average 8-point blood glucose profiles, lipid profiles, hypoglycemic frequency and adverse events. In total, 246 patients completed the trial. HbA_{1c} at end-of-trial was statistically significantly lower in the BIAsp/Pio than the BIAsp and Pio/Glib groups. The 8-point blood glucose profiles, average blood glucose and breakfast prandial increment decreased over time, and both BIAsp and BIAsp/Pio groups had statistically significantly lower values than Pio/Glib at end-of-trial. No major hypoglycemic events were reported. Minor hypoglycemic episodes were few and mainly in the BIAsp group: 1.5 episodes/year; BIAsp/Pio: 0.5 episodes/year; Pio/Glib 0.1 episodes/year. Risk of hypoglycemic episodes was lower in BIAsp/Pio than BIAsp, and also lower in Pio/Glib than BIAsp/Pio. More patients experienced possibly/probably treatment related adverse events in BIAsp/Pio (28%) than BIAsp (20%) and Pio/Glib (16%). Edema (mild severity) and weight increase were the more frequently reported adverse events (BIAsp: 1–3%; BIAsp/Pio: 5–8%; Pio/Glib: 1–2%). There were no reports of liver toxicity.

BIAsp/Pio provides an improved glycemic control compared with BIAsp 30 monotherapy or Pio/Glib combination therapy. **We conclude** that the best option for type 2 patients who have failed on sulfonylurea mono- or combination therapy is to replace the sulfonylurea mono- or combination therapy with BIAsp + pioglitazone.

Comparison of Biphasic Insulin Aspart and Human Insulin including Biphasic Human Insulin in Children with type 1 Diabetes. A Safety and Efficacy Trial

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Adolescents with diabetes need a treatment which offers optimal blood glucose control and minimal interference with a normal lifestyle. In this randomised, open-labelled, parallel group four-month efficacy and safety trial, two groups of adolescents with type 1 diabetes were compared. One group, BIAsp, had injections three times daily immediately before meals with BIAsp30 (a mixture of 30% soluble and 70% protamin-bound insulin aspart); the other, HI+BHI, had injections 30 minutes before meals with human insulin (HI) twice daily and biphasic human insulin 30 (BHI30) once daily, usually at breakfast. In both groups additional human isophane insulin (NPH) was allowed (usually administered at bedtime). If necessary, insulin aspart (IAsp) or HI was administered with a snack in the BIAsp or HI+BHI group, respectively.

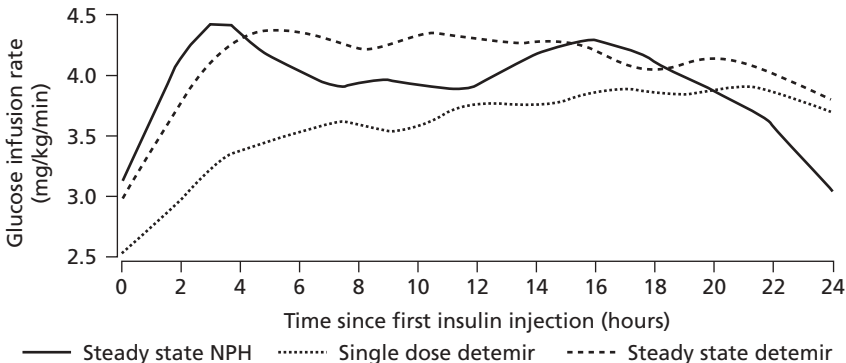
80 boys and 87 girls aged 10–17 years were included in the trial, 86 in the BIAsp and 81 in HI+BHI group. The mean(SD) baseline HbA_{1c} in the groups was 9.7(1.5) and 9.55(1.6) and body mass index (BMI) was 21.1(3.8) and 21.1(2.9), respectively. After 16 weeks of treatment no difference was found between the groups for average prandial increase in blood glucose, the primary endpoint. During treatment the average prandial increase was reduced in both groups by approx. 1 mmol/L and HbA_{1c} decreased by about 0.2% in both groups. BMI increased in both groups (0.1 and 0.5 kg/m², respectively) but the increase was lowest in the BIAsp group ($p=0.004$) in spite of a slightly higher insulin consumption (U/kg). Frequency of hypoglycaemic episodes and adverse events were similar in both groups. Quality of Life questionnaires were answered similarly by the groups.

In conclusion efficacy and safety evaluations were similar for the two treatments. Both led to a slight improvement in blood glucose control and BMI increased significantly less in the BIAsp group compared to the HI+BHI group.

Insulin Detemir reaches Steady-State after the First Day of Treatment and Shows a Peakless Time-Action Profile with Twice Daily-Applications

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This euglycemic glucose clamp-study compared the effect of the basal insulin analog insulin detemir (ID) in single-dose and under steady-state (SS) conditions with that of NPH insulin (NPH) under SS in 25 type 1 diabetic patients (7 female, 39±12 yrs (mean±SD), BMI 24±3 kg/m²). Patients participated in three 24-h glucose clamps (clamp level 5.5 mmol/l) with insulin injections at 0 and 12 h, resp (in fixed, individualized doses). The first clamp determined the metabolic effect of NPH under SS based on glucose infusion rates (GIR). The second clamp investigated the effect of the first two injections of ID (NPH treatment was stopped app. 24 h before the clamp). Patients continued IDet treatment for 7–14 days and after that the third clamp with IDet was performed in SS. IDet showed a comparable overall metabolic effect under SS compared to NPH (total GIR-AUC 5697±1861 vs. 5929±1965 mg/kg) whereas a significantly lower effect (5187±1784 mg/kg, *p*=0.01 vs. SS) was obtained for the first two IDet injections. The metabolic effect after the second IDet injection reached SS. NPH showed a clear peak in the metabolic effect after each injection while IDet provided a flat and peak-less profile over 24 hours (figure). The pharmacokinetic data were in accordance with the GIR-profiles. **In conclusion**, IDet is likely to reach steady-state after 2–3 days depending on dose and dose frequency. In addition, the peak-less time-action profile of IDet may have advantages over NPH insulin in diabetic patients.



Pharmacokinetics of Insulin Detemir is similar in Children, Adolescents and Adults with Type 1 Diabetes

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Until now the pharmacokinetics (PK) of the soluble basal insulin analog insulin detemir (IDet) has only been studied in adults. The aim of this trial was to compare the PK in children (6–12 yrs), adolescents (13–17 yrs), and adults (18–65 yrs) for IDet and NPH insulin, respectively. A total of 34 (16M/18F) subjects with type 1 diabetes on at least twice daily insulin therapy were randomized in this single center, open-label, cross over trial: 13 children, (mean age: 10.4 yrs, BMI: 17.9 kg/m², duration of diabetes: 2.9 yrs), 10 adolescents, (15.1 yrs, 21.1 kg/m², 8.1 yrs) and 11 adults (22.8 yrs, 23.4 kg/m², 9.8 yrs). Subjects received single s.c. injections of 0.5 U/kg of IDet or 0.5 IU/kg of NPH shortly before breakfast on two dosing days separated by a wash-out period of 7 to 14 days. Serum levels of IDet and human insulin were assessed over 24 hours.

		Ratio of AUC _{0–24h} and C _{max}					
		Insulin detemir			NPH insulin		
		Ratio	95%CI	p-value	Ratio	95%CI	p-value
AUC _{0–24h} ^a	Child/adults	1.10	[0.81;1.50]		2.92	[1.14; 7.44]	
	Adolesc/adults	0.95	[0.70;1.30]		1.93	[0.77; 4.83]	
	Child/adolesc/ adults			0.61			0.08
C _{max}	Child/adults	1.24	[0.86;1.79]		3.24	[1.06; 9.95]	
	Adolesc/adults	1.02	[0.71;1.47]		2.07	[0.69; 6.20]	
	Child/adolesc/ adults			0.41			0.12

^a: AUC_{0–24h}: Area under the curve from 0–24 hrs

No significant differences were found in the overall comparison between age groups for AUC_{0–24h} or C_{max} for either IDet or NPH. Pair-wise comparisons between children and adults and between adolescents and adults supported these findings for IDet, while a tendency towards a difference between children and adults were found for NPH. Coefficient of variation (CV) between subjects within each age group for AUC_{0–24h}, ranged between 20–42% for IDet and 70–118% for NPH. CV for C_{max} was also lower with IDet compared to NPH. IDet was well tolerated in all age groups. These data indicate that individual dose-titration of IDet can be based on uniform guidelines in all age groups with the benefit of less between-subject variation compared to NPH.

Treatment with Insulin Detemir is Associated with Predictable Fasting Blood Glucose Levels and Favorable Weight Development in Subjects with Type 2 Diabetes

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Insulin detemir (IDet), a soluble, basal insulin analog, maintains glycemic control effectively with predictable glucose levels in subjects with type 1 diabetes on a basal/bolus regimen. The aim of this 6-month, multinational, open, parallel trial was to compare the effect of a basal/bolus regimen with IDet or NPH insulin (NPH) in combination with insulin aspart (before meals) in subjects with type 2 diabetes. Subjects were randomized 2:1 to IDet or NPH and dosed once or twice daily according to previous treatment. A total of 505 subjects (IDet: 341, NPH: 164) with (mean age: 60 yrs, duration of diabetes 13 yrs, BMI: 30.4 kg/m², HbA_{1c}: 7.85%) were dosed. After 6 months, HbA_{1c} had decreased by 0.26% (IDet) and 0.36% (NPH). Mean difference (IDet-NPH) in HbA_{1c} was 0.16%, 95% CI [0.003; 0.312]. HbA_{1c} values were similar between subjects on a once (40% of subjects in both groups) and twice daily basal regimen ($p=0.73$). Fasting plasma glucose did not differ between the two groups: 9.7 (IDet) and 9.6 mM (NPH), ($p=0.66$). Treatment with IDet resulted in a lower within-subject variation in self-measured fasting blood glucose compared to NPH ($SD=1.3$ vs 1.4 mM, $p=0.02$). Self-measured 9-point blood glucose profiles were similar in the two groups ($p=0.58$). The risk of hypoglycemia was similar with the two treatments ($p=0.48$) as was the incidence of adverse events. Body weight was significantly lower in the IDet group than in the NPH group after 6 months ($p=0.020$), with a weight increase of 0.9 kg in the IDet group vs 1.6 kg in the NPH group. **In conclusion**, similar glycemic control was found with IDet and NPH when used in combination with insulin aspart in subjects with type 2 diabetes. Furthermore, treatment with IDet resulted in less increase in body weight and more predictable levels of fasting blood glucose.

Lower Within-Subject Variability of Insulin Detemir in Comparison to NPH Insulin and Insulin Glargine in Subjects with Type 1 Diabetes

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We compared the within-subject variability of the effect of the novel long-acting insulin analogue insulin detemir (IDet) with that of NPH insulin and insulin glargine (GL) in a randomized, controlled, parallel group, double blind study. Fifty-four patients with type 1 diabetes (32 males; age 38 ± 10 years (mean \pm SD); BMI 24 ± 2 kg/m²; HbA_{1c} 7.5 ± 1.2 %; diabetes duration 18 ± 9 years) received the same dose (0.4 U/kg) of either NPH insulin, GL or IDet s.c. on four identical study days under euglycemic glucose clamp conditions (target blood glucose concentration 5.5 mmol/L). The pharmacodynamic and pharmacokinetic effects of the basal insulin preparations were recorded for 24 and 28 hours post-dose, respectively. IDet showed significantly less within-subject variability compared to NPH and GL (2.5 and 1.8 fold lower CV for GIR-AUC(0–24h), respectively), see table. Similar findings were also observed for pharmacokinetic parameters.

In conclusion, this first systematic investigation of the variability in the pharmacodynamic and pharmacokinetic properties of the most commonly used basal insulin preparations in type 1 diabetes shows significantly less within-subject variability for insulin detemir. This suggests that this novel basal insulin will provide a more predictable therapeutic effect compared to both NPH insulin and insulin glargine.

Within-Subject Variability, expressed as Coefficients of Variations (CV) in %

	Insulin Detemir	NPH Insulin	Insulin Glargine
Pharmacodynamics (assessed by Glucose Infusion Rates (GIR))			
GIR-AUC _(0–12h)	27	59*	46*
GIR-AUC _(0–24h)	27	68*	48*
GIR _{max}	23	46*	36*
Pharmacokinetics (assessed by plasma concentrations of insulin (INS), insulin glargine and insulin detemir)			
INS-AUC _(0–12h)	15	26	34
INS-AUC _(0–∞)	14	28	33

*: $p < 0.001$ compared with insulin detemir (no statistical analyses were performed to compare pharmacokinetic CVs). CVs were determined using an ANOVA model after log-transformation of the parameters.

Insulin Detemir Pharmacokinetics, Safety, and Tolerability Profiles are Similar in Healthy Caucasian and Japanese-American Subjects

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Insulin detemir is the first of a new class of soluble, basal (long-acting) insulin analogues developed to maintain more stable glucose levels with less intra-subject variation. Clinical trials have confirmed that insulin detemir has a sustained blood glucose lowering effect. The pharmacokinetics of insulin detemir in three ascending doses were compared in healthy Japanese and Caucasian subjects in an open label, single center, parallel group design. There were 36 subjects enrolled, with 30 completing the study (15 Japanese and 15 Caucasian). Subjects received 3 subcutaneous injections (one injection per visit) of insulin detemir (0.19, 0.38, or 0.75 U/kg) in ascending order. Following drug administration, subjects received intravenous glucose in 0.5 mg/kg/min increments every 30 minutes, followed by a constant rate of 2.0 mg/kg/min for up to 12 hours in order to prevent hypoglycemia. For pharmacokinetic evaluations, serial blood sampling was performed over a period of 30 hours after dosing. The statistical analysis showed that the average insulin detemir serum concentration increased proportionally with increasing dose for both the Japanese and Caucasian subjects. There was a small difference in the slope between the two ethnic groups; however, the difference was neither statistically nor clinically significant. Two subjects were discontinued due to adverse events. The most frequent treatment emergent adverse events were headache, dizziness, and reactions related to blood draws/infusion sites. **Conclusion:** Taken together, the results show that an increase in insulin detemir dose will result in the same increase in insulin detemir concentration in the two ethnic groups. Therefore, therapeutic dosing of insulin detemir is expected to be similar in both ethnic groups with no special dose adjustment or algorithm based upon race. Insulin detemir at 0.19, 0.38, and 0.75 U/kg was generally well tolerated in both Japanese and Caucasian subjects.

Insulin Detemir and NPH Insulin: Comparison of Pharmacokinetic and Pharmacodynamic Properties in Japanese and Caucasian Volunteers

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Insulin detemir, is a soluble basal insulin analogue, the protraction is primarily caused by molecular self-association and binding to albumin in the interstitial fluid of the subcutaneous tissue. We compared the pharmacokinetic and pharmacodynamic properties of insulin detemir (IDet) with NPH insulin after s.c. injection in two ethnic groups. We investigated 14 healthy Japanese subjects of both genders (age 35±7ys, BMI 21.2±2.2 kg/m², BW 60±10 kg, (mean±SD)) and 14 subjects of Caucasian origin (age 29±7ys, BMI 23.0±2.3 kg/m², BW 72±9 kg). Each subject in this double-blind euglycaemic glucose-clamp study received a single dose of IDet (9 nmol/kg, 0.38 U/kg), and of NPH insulin (0.3 IU/kg) administered s.c. into the thigh. Glucose infusion rates (GIR) were registered for 24 h and IDet serum levels were measured additionally at 32 h. Serum peak IDet levels and overall IDet concentrations were higher in Japanese as compared to Caucasian subjects (Table). Insulin levels following NPH insulin were similar in the two ethnic groups. Insulin time-concentration profiles of IDet, e.g. time to peak insulin level, were similar in Japanese and Caucasian subjects. In line with the higher insulin levels, a trend was noticed towards a higher metabolic overall effect of IDet in Japanese compared to Caucasian subjects ($p=0.15$). Insulin action of either insulin in both groups of subjects was in accordance with the pharmacokinetic results. Higher serum insulin detemir levels together with a trend for a greater overall metabolic activity of IDet were found in Japanese compared to Caucasian subjects. In both ethnic groups the insulin detemir pharmacokinetic profile was in agreement with the pharmacodynamic profile.

	Japanese Detemir	Caucasian Detemir	Japanese NPH	Caucasian NPH
INS _{max} (pmol/L)	3671±714*	2832±488	164±46	174±54
AUC _{INS 0-24/32 h}	2.47±0.52*	1.98±0.26	1.65±0.39	1.63±0.31
GIR _{max} (mg/kg/min)	4.1±1.6	3.4±1.8	4.2±2.1	3.5±1.2
AUC _{GIR 0-24 h} (mg/kg)	3494±1514	2648±1437	3469±1649	3029±989

ANOVA; * between-groups comparison for the respective insulin; mean±SD

Stable isotope studies show differences in effect of insulin detemir and NPH on hepatic glucose output after subcutaneous administration in subjects with Type 2 diabetes mellitus

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The soluble, basal insulin analogue insulin detemir (ID) has a fatty acid side chain allowing binding to albumin protracting its action profile. The effect of ID and human insulin (NPH) on hepatic glucose output (Ra) and peripheral glucose uptake (Rd) were compared in doses with similar effect on blood glucose using stable isotope techniques.

16h euglycaemic clamps were performed in 6 subjects with type 2 diabetes following dosing with ID 18 nmol.kg⁻¹ and NPH 0.6 IU.kg⁻¹ (3.6 nmol.kg⁻¹) with at least 7 days apart. A constant infusion of [6,6-²H₂] glucose was used to determine glucose output and uptake. Plasma glucose was measured using a blood glucose analyser and infusion rate of 20% dextrose (spiked with [6,6-²H₂] glucose) altered accordingly. Blood glucose was controlled before the injection of sc insulin by using iv soluble human insulin. The infusion was stopped just before the sc insulin was injected. This technique led to poor maintenance of euglycaemia in the first 60 minutes of the clamp, Areas under/over the curves were calculated for the entire 16h period and with baseline at 60 minutes post injection. Plasma glucose was clamped at 6.31 mmol.l⁻¹ (SD 0.2) with ID and 6.24 mmol.l⁻¹ (SD 0.31) with NPH (*p*=NS). The total amount of glucose infused was 1869 mg.kg⁻¹ (SD 854) with ID and 1674 mg.kg⁻¹ (SD 517) with NPH (*p*=NS). Areas under/over the Ra and Rd curves were not statistically significant different between ID and NPH when calculated for the 16-h trial period. When calculated from 60 min the area over the curve of suppression of Ra was significantly greater for ID (984 mg.kg⁻¹ (SD 332)) compared to NPH (535 mg.kg⁻¹ (SD 195) (*p*<0.04). The area under the glucose Rd curve was 672 mg.kg⁻¹ (SD 626) for ID and 797 mg.kg⁻¹ (SD 364) for NPH (*p*=NS). The data from these 6 subjects show the glucose lowering effect of 18 nmol.kg⁻¹ of ID is not different to 0.6 IU.kg⁻¹ of NPH. However ID may have a greater effect on hepatic glucose output suppression than NPH.

Compliance With Inhaled Insulin Treatment Using AERx® iDMS insulin Diabetes Management System

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The objective was to demonstrate the ability of patients to use AERx® iDMS to deliver mealtime inhaled insulin doses and explore preliminary data on importance of compliance for glycemic control. AERx® iDMS was evaluated in a 12-week, multicenter open trial with 107 type 2 diabetes patients currently taking insulin. Patients were randomized to treatment with inhaled insulin using AERx® iDMS or fast-acting human insulin injections, both before main meals and in combination with bedtime NPH insulin. AERx® iDMS recorded the date and time of each insulin inhalation, units used, and inhalation technique during aerosol delivery. Preliminary analyses included 32 patients (mean age 57.6±7.0, diabetes duration 10.8±8.0 years) who used AERx® iDMS. Compliance was defined as percentage of prescribed doses taken during treatment period (83±5 days, range 76–92, 237±22 doses, range 186–270). Mean compliance with inhaled insulin was 92.6±14.6% (22%–100%). Mean percentage of missed doses was 7.3±14.4% including 1 patient who omitted 78% of doses, or 4.8±20.4% excluding that outlier. Overall, 25 of 32 patients took ≥90% of prescribed doses, 30 patients took ≥80% of doses (the 2 poor compliers took 22%, 57% of doses). Patients with compliance rates ≥90% achieved mean 0.53±0.98% decreased HbA_{1c} levels. Nine of 12 patients whose HbA_{1c} decreased by ≥1% were excellent compliers (≥93%). HbA_{1c} level increased 0.6 for the patient with the poorest compliance rate (22%). Few patients experienced poor inhalation technique (≤5 doses, <2.5% of doses overall), with only 2 patients experiencing >10 dosing episodes with insufficient inhaled volume. These preliminary data demonstrate that patients converting from insulin injections to inhaled insulin using AERx® iDMS can achieve excellent compliance with a mealtime dosing regimen. High rates of compliance with insulin inhalation suggest that AERx® iDMS is an acceptable and convenient system for self-administration of insulin leading to improved glycemic control. The electronic compliance monitoring feature provides clinicians with valuable information about patient dosing regimens and compliance.

Physicians' Reaction to Inhaled Insulin, a New Insulin Delivery System

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Inhaled insulin is currently in development. This study was conducted in 2001 to determine whether or not this would be an interesting option for physicians and patients. Personal interviews (1h) obtained reactions to inhaled insulin compared to subcutaneous and evaluated 2 potential delivery systems (including AERx[®] iDMS) in a blind test. The sample included general practitioners (313 GPs) and diabetes specialists (289 SPs) in Germany, Spain, UK and USA.

Results indicate that patient fear of self-injecting is perceived as one of the most difficult aspects of initiating insulin: from 20% (UK GPs) to 58% (USA SPs); as well as concern about compliance: from 19% (UK GPs) to 45% (Germany GPs). Many physicians believe that inhaled insulin would address both of these aspects. Substantial proportions of physicians, from 35% (Germany SPs) to 62% (USA GPs), also believe that inhaled insulin would allow them to initiate insulin earlier.

Two AERx[®] iDMS features are perceived as advantages over other inhaled insulin systems: dosing in single unit increments, from 36% (UK) to 62% (US SPs); and compliance monitoring involving electronic storage of 3 months' data, from 18% (Spain SPs) to 46% (UK GPs).

	Germany		Spain		UK		USA	
	GP	SP	GP	SP	GP	SP	GP	SP
N=	71	51	72	68	70	70	100	100
	<i>% of physicians stating</i>							
Most difficult aspects of initiating insulin:								
– patient's fear of self-injecting	39	43	49	56	20	43	55	58
– concern about patient compliance	45	33	21	25	19	37	43	31
Primary benefits of inhaled insulin:								
– patient compliance	37	20	19	29	39	30	42	34
– no injections	46	37	35	54	54	51	38	49
Availability of inhaled insulin will lead to prescribing insulin earlier in course of treatment:								
	51	35	40	37	47	46	62	48
Advantages of AERx[®] iDMS:								
– one unit increment	38	39	39	44	36	36	37	62
– compliance monitoring	34	28	22	18	46	40	36	30

All reported proportions are significantly different from 0 at $p < 0.05$

Inhaled insulin seems to be of benefit for patients fearing injections and could facilitate insulin initiation. Moreover it is likely to lead to higher compliance. The features of an electronic system are highly valued.

Evaluation of Lung Function in Patients with Type 2 diabetes using the AERx[®] insulin Diabetes Management System (iDMS)

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Development of systems for inhalation of insulin requires close monitoring of lung function (LF). We report results of pulmonary function tests (PFT) from a multi-centre, randomized, parallel, open-labelled, 12-week study in 107 non-smoking type 2 diabetic patients where pre-prandial s.c. (n=53), and inhaled human insulin via the AERx[®] iDMS (n=54), both in combination with NPH insulin at bedtime, were compared. The two groups were comparable, with mean age 59 years, BMI 27.7 kg/m², and HbA_{1c} 8.5% (8.6% vs. 8.5%, AERx vs. s.c.). Both groups showed a similar decline in HbA_{1c} after 12 weeks (7.8% vs. 7.8%, *p*=0.60).

The aims of PFT were to 1) assess LF in diabetic patients before treatment with inhaled insulin, 2) assess changes in LF after treatment with inhaled insulin, and 3) assess the reproducibility in PFT in this multi-centre study of diabetic patients. At inclusion, forced vital capacity (FVC), total lung capacity (TLC) and forced expiratory volume (FEV₁) were all significantly lower (*p*<0.01 in all cases) than predicted values, mean values ± SD being 96.4±13.2, 95.3±13.1, and 96.9±12.7% predicted, respectively. The FEV₁/FVC ratio was significantly higher than predicted (102.9±8.6%) and the diffusing capacity for carbon monoxide (D_LCO) was lower than predicted (92.4±16.7% predicted). This indicates restrictive lung function impairment in patients with type 2 diabetes. There were no significant changes in PFT in the groups after 12 weeks. LF does thus not change after 12 weeks of treatment with AERx[®] iDMS. Two patients in the AERx[®] group showed a decrease in PFT that were classified as adverse events by the investigators. One patient in the s.c. group had a similar decrease, not considered an adverse event by the investigator. Since LF is expected to be unchanged in patients undergoing s.c. treatment only, the intra-subject variation in PFT can be calculated in this group. Mean coefficients of variation for FVC, TLC, FEV₁ and D_LCO were 4.2%, 5.0%, 5.0% and 6.7%, respectively. This information about the variability of PFT in diabetic patients should be useful for the design of future trials of inhaled insulin.

A Systematic Review of Medication Compliance With Medications For Diabetes

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The purpose of this study was to define the range of patient compliance with prescribed medications for diabetes, since a poor medication compliance is an important factor in diabetes management.

A Medline and literature search (1995–2002) was performed to identify reports with (a) acceptable data on oral hypoglycemic agents (OHA) and insulin compliance (prescription refill rates using administrative databases, direct electronic monitoring of individual patients), and (b) correlations between compliance rates and HbA_{1c} levels. Compliance estimates based on questionnaires and self-reports were excluded.

Compliance rates were documented in reports of 8 OHA studies and 1 insulin study, some with corresponding HbA_{1c} levels. OHA compliance rates ranged from 36% to 82% using large administrative databases to determine prescription refill rates. Two studies that used MEMS electronic monitoring bottles for OHA to record the date and time of every dose revealed that patients were taking 75% of OHA doses as prescribed over the duration of observation. One group used the electronic monitoring data to identify poor compliers for additional intervention. The insulin study documented that many young diabetes patients filled prescriptions for only one-third of prescribed doses. Low compliance rates were associated with high HbA_{1c} levels and high health care costs for society in every study in which this was assessed.

This review confirms that many patients for whom diabetes medication was prescribed were poor treatment compliers, including both OHA and insulin users. Devices that simplify insulin dosing could promote better compliance. Electronic monitoring systems for insulin administration are needed to record patterns of insulin use by individual patients. This information could help healthcare providers determine which patients need additional support. Further studies with electronic monitoring of diabetes medications may identify and define the characteristics of poorly compliant patients to improve treatment outcomes.

The Effects of Skin Temperature and Testing Site on Blood Glucose Measurements Taken by the InDuo® Integrated System

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Modern blood glucose (BG) monitoring devices (e.g. InDuo®) require very low blood volumes, allowing for testing at sites other than the traditional fingertip, but the reliability of such testing has not been fully elucidated. This randomised study aimed to compare the effects of cold/warm skin temperature combined with alternate site (forearm) testing versus conventional finger tip measurements. Nineteen patients who had previously used InDuo® for 6 weeks participated. Four simultaneous (within 1 minute) BG readings (left and right forearms and fingertips) were obtained from each patient 15, 10 and 5 minutes before eating. Ten minutes before eating, the patient immersed one arm in cold water (T: 15.5°C) and the other in warm water (T: 35.0°C). At time = 0 minutes arms were removed from water baths and the patient was offered a standard meal (of ≤ 15 minutes duration). Arms were again immersed in water baths and BG measured from the same locations 20 minutes after eating and at subsequent 15-minute intervals for 185 minutes. The effects of site testing and temperature were assessed in this period by identifying maximum BG concentration (C_{max}) and time to C_{max} (T_{max}). Significantly lower C_{max} values were observed for: cold forearm versus cold fingertip (-28.58 mg/dL; $p < 0.001$), warm forearm versus warm fingertip (-11.95 mg/dL; $p = 0.028$), cold fingertip versus warm fingertip (-17.16 mg/dL; $p = 0.002$), and cold forearm versus warm forearm (-33.74 mg/dL; $p < 0.001$). Significantly longer T_{max} were reported for cold forearm versus warm forearm (-22.37 minutes; $p < 0.001$) and cold forearm versus cold fingertip (-20.00 minutes; $p < 0.001$). **In conclusion**, these results demonstrate that cold skin and forearm conditions significantly underestimate BG and delay time to maximal value compared with warm skin and fingertip readings.

Efficacy, Safety and Actual Use of Blood Glucose (BG) Monitoring with InDuo® and Separate Meter/Vial and Syringe in Subjects with type 1 Diabetes

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Successful therapy of diabetes requires frequent blood glucose monitoring by the patient and frequent countermeasures by the patient in response to glucose meter findings. InDuo® is the first device to combine an insulin injection and BG meter. The safety (adverse events, adverse device effects, and hypoglycemic episodes), efficacy (fasting plasma glucose and fructosamine levels, 7-point blood glucose profiles, and HbA_{1c}); and actual use of a combined meter and injection device (InDuo®) were compared to separate meter and syringe in a multicenter, randomized, crossover study of adult Type 1 diabetes subjects currently on MDI therapy. The enrolled patients (n=125, mean age 42.1 ± 14.3 years, mean HbA_{1c} 7.9 ± 1.2% and frequency of screening BG monitoring 3.9/day) were randomized to use of either InDuo® or a separate meter (Ultra One Touch) and syringe for 6 weeks. Patients were switched to the alternate treatment for 6 weeks. During the study, the overall enrolled population showed a significant mean reduction of 0.54% in the HbA_{1c} values ($p < 0.0001$). The most common adverse event was upper respiratory tract infection (4% of patients for combination device, 8% of patients for syringe plus monitor). In general, the two device regimens showed no notable differences in incidence of any adverse event. A majority (79%) of the patients preferred treatment with the combination device rather than the syringe and separate monitor. The InDuo® showed small advantages in the frequency of SMBG (1 more reading per week). **In conclusion**, the use of the InDuo® was associated with significant improvements in patient treatment satisfaction. These improvements were reflected in improved compliance (more injections or blood tests per day) in a substantial portion of the patients tested.

Diabetes Management With InDuo® is as Effective and Safe as Use of Separate Insulin Injection and Blood Glucose Monitoring Devices

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InDuo® is a compact and portable system which combines an insulin delivery device and a blood glucose (BG) monitor in one unit. This study compared InDuo® and a non-integrated system, HumaPen® Ergo (an insulin injection device) and Accu-Chek® Sensor Meter (for BG measurement) for efficacy and safety. The trial design was multicentre, randomised, 12-week, open-label, comparative, two-period crossover. A total of 110 patients (with diabetes treated with basal-bolus insulin; mean age 55.6; mean HbA_{1c} 7.5%) were assigned to use either InDuo® or the non-integrated system. After 6 weeks, patients were transferred to the alternative system. To assess efficacy, fasting plasma glucose (FPG), serum fructosamine and HbA_{1c} were measured. Serum fructosamine and FPG were measured at baseline and at 6 and 12 weeks; HbA_{1c} was measured at baseline and week 12. Safety endpoints were number and severity of hypoglycaemic episodes, adverse events and adverse device effects. Analysis with an ANOVA mixed model showed no difference after each treatment between serum fructosamine or between FPG levels: serum fructosamine (µmol/L), difference (InDuo® non-integrated) = -0.22, $p = 0.336$; FPG (mg/dl), difference (InDuo® non-integrated) = 7.74, $p = 0.457$. HbA_{1c} decreased during the trial from 7.5% ±1.2 to 7.1% ±0.8 at 12 weeks. The safety profiles were similar for both treatments for hypoglycaemic episodes: InDuo® 1 major and 137 minor; non-integrated 2 major and 141 minor. The incidence of adverse events was also similar: InDuo® 45; non-integrated 58. There were 10 adverse device effects reported: eight for the Innovo® device in the InDuo®, one for the InDuo® device and one for the Accu-Chek® meter.

Treatment using InDuo® was as effective and safe as treatment using the non-integrated system.

Comparison of Preference and Satisfaction with InDuo® and Separate Meter/Vial and Syringe in Subjects with type 1 Diabetes

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Many factors contribute to infrequent BG monitoring by patients, including not having a meter available when dosing. InDuo® is the first combined insulin injector and BG meter. In a randomized, multicenter, two-period crossover study, patients with type 1 diabetes (N=125, mean age 42.1±14.3 years) were randomized to use of either InDuo® or a separate meter (Ultra One Touch) and syringe for 6 weeks. Subjects were then switched to alternate treatment for 6 additional weeks. Preference and satisfaction questionnaires were completed at the end of the study. Overall, the enrolled patients showed significant glycemic improvement in the HbA_{1c} values during the 12-week study ($p < 0.001$). Patients using InDuo® reported significantly higher overall satisfaction as assessed with the WHO Diabetes Treatment Satisfaction Questionnaire. Use of InDuo® also resulted in significantly higher rating of insulin therapy, lack of interference with lifestyle and ease of injecting when away from home. Overall, 79% of subjects preferred InDuo® to use of separate meter and syringe with convenience, ease of use, and accuracy being major factors ($p < 0.001$). Other factors in patient preference included specific features like the 5-second BG analysis (60%), small blood sample requirement (55%) and memory functions (91% used BG memory several times a week and 66% used the doser memory several times a week). The Patient Device Handling Questionnaire at the end of the study indicated, 49% of patients felt that they tested BG more often with InDuo® than a separate meter. **In conclusion**, use of a combined BG meter and insulin doser was associated with treatment satisfaction that was greater than syringe and separate meter, with substantial preference for the combined device leading to implications in treatment compliance.

Patient Preference for InDuo[®], a Novel Combined Insulin Injection and Blood Glucose Monitoring Device

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Frequent blood glucose (BG) monitoring and insulin administration are necessary in intensive insulin regimens. A new integrated system, InDuo[®] is a compact and portable combined insulin doser and BG monitor designed to overcome some of the limitations of current insulin therapy. The aim of this trial was to evaluate patients preference for either InDuo[®] or a non-integrated system, HumaPen[®] Ergo (insulin administration device) and Accu-Chek[®] Sensor Meter (BG reading). In this multicentre, randomised, 12-week, open-label, comparative, two-period crossover trial, 110 patients (with type 1 or type 2 diabetes on a basal bolus regimen) were randomised to either InDuo[®] or HumaPen[®] Ergo and Accu-Chek[®] Sensor Meter. After 6 weeks, patients switched to the alternative system. Patient preference was assessed by a comparative device questionnaire at 12 weeks.

Assessed	InDuo [®]	HumaPen [®] Ergo/Accu-Chek [®]
Overall preference	74%	19%*
Ease of insulin administration	68	19*
Ease of more frequent BG monitoring	76	15*
More flexibility with eating	58	9*
Less time consuming	75	13*
Less interference in lifestyle	69	14*
Most convenient to use away from home	75	17*
More confidence managing diabetes	67	12
Overall better quality of life	72	15*

* $p < 0.0001$

All questions showed patients strongly preferred InDuo[®] to HumaPen[®] Ergo and Accu-Chek[®] Sensor Meter (all $p < 0.0001$). Of those preferring InDuo[®], more than 60% classified their choice as very or extremely strong. Both memory functions in InDuo[®] (i.e. for insulin dose and for blood glucose readings) were used by more than 70% of the patients. Almost 3 out of 4 patients (74%) preferred using InDuo[®] to the non-integrated HumaPen[®] Ergo and Accu-Chek[®] Sensor Meter.

A Cross-Over Randomized Controlled Trial to Compare Psychological Barriers to Insulin Self-Injection with the Innolet and Vial/Syringe

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InnoLet[®] insulin injection device is specifically designed to overcome practical and psychological obstacles which prevent many patients from effectively managing their insulin treatment. InnoLet is a disposable insulin injection device with a large easy-to-read dial, a large button for injection, and audible clicks representing each unit injected. The objective of this study was to evaluate differences in fear of self-injection of insulin (and perception of barriers to compliance with an insulin regimen) for patients using the InnoLet device as compared to the vial/syringe. Diabetes patients (N=79, mean age 68.2 ± 8.6 years, mean HbA_{1c} $7.5 \pm 1.4\%$) with visual and/or motor disabilities were enrolled in this two-period crossover study. Subjects were randomized to use of either vial/syringe or InnoLet for 6 weeks, and then switched to the alternate treatment for 6 weeks. At baseline and end of each period, subjects completed the Diabetes Fear of Self-Injection Questionnaire (D-FISQ, questions about barriers to insulin self-injection, treatment satisfaction and preference). The D-FISQ showed high internal consistency ($\alpha=0.94$). Overall, InnoLet treatment reduced the number of patients with extreme injection fear (D-FISQ >3) by 53%, while syringe treatment resulted in a 36% increase in extreme injection fear. Changes in fear of self-injection were significantly correlated with changes in treatment satisfaction ($r = -0.29$, $p=0.015$) and perceived barriers ($r=0.30$, $p=0.010$) but not to socio-demographic and impairment variables. The barrier item feeling awkward with other people around correlated most strongly with D-FISQ changes. **In conclusion**, InnoLet device offers important psychological benefits to elderly insulin-dependent diabetes patients with visual and or motor disabilities. The clinical significance of these findings is substantial, given the significant health gains that can be obtained with effective insulin therapy.

A Comparative Study of the Efficacy of the New Insulin Delivery Device 'InnoLet' versus Insulin Pens

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A variety of insulin delivery devices are currently available. InnoLet is one of the most recent developments and incorporates a large analog dosing dial aimed at facilitating use in people with visual impairment, diminished dexterity or learning difficulties. This study investigated the usability of InnoLet in patients who had previously been prescribed insulin pens (including NovoLet, NovoPen 3, NovoPen 150 and Humacart Kit). Seventy-one patients (mean age 64.3 ± 12.7) from four Japanese centers were involved in the study. On the first day of InnoLet use, patients rated their previously used pens on a number of different measures of functionality. Following use of InnoLet for at least three days, the patients assessed InnoLet using the same measures of functionality. Overall, compared to the insulin pen prescribed previously, InnoLet was regarded as providing better legibility of dose scale ($p < 0.001$), greater ease of dose setting ($p < 0.001$), easier pressing of the push button ($p < 0.01$), and increased simplicity ($p < 0.001$). InnoLet also scored significantly higher on overall ease of use ($p < 0.01$). No significant differences were observed for measures of weight or stability during injections, however, InnoLet scored significantly lower on measures of ease of grip ($p < 0.01$) and portability ($p < 0.001$). An analysis of different age groups revealed that the younger groups (under 50 and 50–59 for ease of grip and 50–59 only for portability) were responsible for these significant differences. These results indicate that InnoLet is a useful device in older patients and may also be appropriate for younger patient groups. However, different age groups attribute importance to different features (e.g., portability). Consequently, careful consideration of the individual patient's needs is required to ensure that the most suitable delivery device is prescribed.

The *Ian4/5/411* Gene: The Lymphopenia Gene of the BB Rat

HELLE MARKHOLST

Diabetes in the spontaneously diabetic and T-cell lymphopenic BBDP rat resembles human Type 1 diabetes. Their lifelong T-cell lymphopenia affects both CD4⁺ T cells and even more markedly the CD8⁺ T cells; the absent T cells being characterized by the expression of RT6. Their absence is caused by increased apoptosis, especially among recent thymic emigrant cells, and a reduced thymic output of naïve T cells. In fact, the survival defect can be traced back to the most mature thymocytes. Lymphopenia segregate as a fully penetrant, single recessive trait and more importantly it co-segregates with diabetes. Its diabetogenic effect resides in the absence of RT6⁺ regulatory T cells inasmuch as depletion of RT6⁺ T cells in the diabetes-resistant and non-lymphopenic BBDR rat induces diabetes whereas transfusions of CD4⁺ T cells from BBDR to young BBDP rats reduces their diabetes incidence in a manner dependent on the number of RT6⁺ T cells transferred. Taken together, the lymphopenia gene product is involved in the regulation of apoptosis in the T-cell lineage before the RT6-positive stage incl. during thymic development, and when it is absent the resulting lack of peripheral T-cells involve regulatory T-cells with the ability to suppress autoimmune β -cell destruction.

The gene resides on rat chromosome 4 within a 0.2 cM region corresponding to max. 290 kb. This very narrow region contains *Ian4/11* – a member of the *Ian*-gene family. These so-called Immune Associated Nucleotides have at least 9 members expressed in immune cells. *Ian4/11* is the homolog of the human gene, *IAN4Like1*, named “Like1” due to its homology to the mouse *Ian4* gene. Mouse *Ian4* encodes a mitochondrial membrane protein with GTP-binding properties. Its expression is increased in BCR/ABL-expressing leukemia cells and its mitochondrial localization relies on the C-terminal transmembrane domain. *Ian4/11* contains a frameshift mutation in BBDP and other rat lines congenic for the lymphopenia gene. The mutation results in a truncated protein in which the last 205 amino acids are replaced by 19 other and thus the protein is without the C-terminal transmembrane region and thus most likely non-functional. That this severe mutation is indeed causing the lymphopenic phenotype is inferred by its location and by functional studies.

Friday 13th June 2003

4.15–6.15 pm, New Autoimmune Genes and the Pathogenesis of Type 1 Diabetes

Sensory Nerve Inactivation by Resiniferatoxin Improves Insulin Sensitivity in Male Obese Zucker Rats

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Recent studies have suggested that sensory nerves influence insulin secretion and action in normal rodents. The present study investigated the effects of resiniferatoxin (RTX) inactivation of sensory nerves (desensitization) on oral glucose tolerance, insulin secretion and whole body insulin sensitivity in the glucose intolerant and insulin resistant obese Zucker rat.

Following RTX treatment, fasting plasma insulin was significantly reduced ($p < 0.0005$), and oral glucose tolerance was significantly improved ($AUC_{0-120 \text{ min}}$: 980 ± 29 vs. 860 ± 27 mM.min in RTX treated rats, $p < 0.005$). Pancreas perfusion showed that baseline (at 7mM glucose) insulin secretion was significantly lower in RTX treated rats (1.37 ± 0.17 vs. 0.54 ± 0.17 pmol/min in RTX treated rats, $p = 0.01$). Both 1st and 2nd phase insulin secretory responsiveness (defined as % increase to 20 mM glucose above baseline insulin secretion) was significantly enhanced in RTX treated rats (First phase: 269 ± 39 vs. 701 ± 75 % in RTX treated rats, $p < 0.005$; Second phase: 333 ± 52 vs. 727 ± 65 % in RTX treated rats, $p < 0.005$). However, in stimulated isolated pancreatic islets insulin secretion was unaffected. At the peak of spontaneous insulin resistance in the obese Zucker rat (i.e. 14–15-week old rats) whole body insulin sensitivity was substantially improved following RTX treatment as evidenced by higher glucose infusion rates (GIR) required to maintain euglycemia during a hyperinsulinemic-euglycemic (5 mU/kg.min) clamp (GIR_{60–120min}: 5.97 ± 0.62 vs. 11.65 ± 0.83 mg/kg.min in RTX treated rats, $p = 0.003$).

In conclusion, oral glucose tolerance, insulin secretion and especially insulin sensitivity were all improved in obese Zucker rats following RTX desensitization. These data strongly suggest that sensory nerves play an important role in the regulation of integrated glucose homeostasis.

Tuesday 17th June 2003

8am, Foie Gras on the Brain

Dipeptidyl Peptidase IV Inhibition Improves Glucose Tolerance Without a Concomitant Rise in Plasma Insulin in the GK Rat

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The Goto Kakizaki rat (GK) is a model of type 2 diabetes with impaired glucose induced insulin secretion. Our aim was to investigate if inhibition of Dipeptidyl Peptidase IV (DPPIV) with valine pyrrolidide (VP) treatment increases active GLP-1 levels in GK rats, and if an increment in the incretin hormone GLP-1 improves insulin response and glucose clearance after a mixed meal in GK rats. We also investigated if GK rats respond differently to normal Wistar (W) rats. Fasted GK and W rats were either treated with vehicle (GK_{veh}, W_{veh}) or VP 100 mmol/kg (GK_{VP}, W_{VP}) 30 minutes before a mixed meal was given by oral gavage. Blood was sampled before, and 15, 30 and 60 minutes after the meal. Area under the glucose curve was lower in GK_{VP} (105.6 ±6mM.min, $p<0.01$) than GK_{veh} (125.7 ±5mM.min), but not different between W_{VP} (112.6 ±3mM.min) and W_{veh} (118.5 ±3mM.min). Area under the insulin curve was not different in GKVP (239.4 ±17pM.min) as compared to GK_{veh} (220.6 ±40pM.min), but tended to be lower in W_{VP} (423.5 ±95pM.min, ns) than W_{veh} (684.1 ±208pM.min). DPPIV activity was decreased in both GK_{VP} (5.8 ±1.5%, $p<0.001$) and W_{VP} (11.4 ±2.0%, $p<0.001$) as compared to vehicle treated rats (51.6±6.5%), and (62.7 ±7.6%) respectively. Area under the active GLP-1 curve was increased in GK_{VP} (274.2 ±15pM.min, $p<0.01$) as compared to W_{VP} (178.8 ±28pM.min) and in GK_{VP} ($p<0.001$), and W_{VP} ($p<0.05$) relative to vehicle treated controls (133.5 ±16pM.min) and (104.3 ±12pM.min) respectively. We report that VP treatment inhibited DPPIV activity, and increased active GLP-1 levels in GK and W rats, and that although there was no improvement in insulin response to a mixed meal in VP treated GK rats, glucose tolerance was improved. In VP treated W rats there was a tendency towards lower insulin levels to maintain the same blood glucose levels as in vehicle treated controls. **We thus conclude** that DPPIV inhibition increases active GLP-1 levels in GK and Wistar rats, and this seems to lead to increased insulin sensitivity in GK rats only.

Pulsatile Insulin Secretion as a Predictive Indicator of Pancreatic β -cell Mass in Lean, Obese and β -cell Reduced Göttingen Minipigs *in vivo*

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Extensive stimulation of insulin secretion, using glucose or arginine, has recently been shown to predict β -cell mass *in vivo* in minipigs. In the present study, the relationship between β -cell mass and dynamics of insulin secretion in the basal state or during glucose entrainment were studied. Male minipigs (10 lean and 10 obese) 12–18 months with permanent jugular catheters were used. 11 of the animals were dosed i.v. with nicotinamide (NIA) (67 mg/kg) plus streptozotocin (STZ) (125 mg/kg) (n=6 lean, n=5 obese). At least 3 weeks after reduction of β -cell mass, pulsatile insulin secretion was studied by deconvolution of insulin concentrations obtained every minute during basal and entrained (infusion of 4 mg·kg⁻¹·min⁻¹, glucose over 1 min every 10 min) conditions (40 min each). β -cell mass was measured stereologically *post mortem*. β -cell mass and basal and entrained pulse mass data are summarized in table 1. Reduced β -cell mass resulted in significantly decreased basal and entrained insulin pulse mass in lean animals and reduced entrained pulse mass in obese animals. Basal ($r^2=0.2246$, $p<0.05$) and entrained ($r^2=0.5924$, $p<0.001$) pulse mass correlated significantly with β -cell mass (mg/kg). **In conclusion**, glucose entrained insulin pulse mass in lean, obese and/or β -cell reduced minipigs appears to be the strongest marker and holds promise as a unique method for estimation of β -cell mass *in vivo* under normal physiological conditions.

Table 1: Body weight (kg), β -cell mass (mg/kg) and pulse mass (pmol·l⁻¹·pulse⁻¹) during basal and entrained conditions (mean \pm SD)

Parameter	Lean animals	Obese animals	Lean NIA+STZ	Obese NIA+STZ
n	4	5	6	5
Body weight	36 \pm 3	56 \pm 7**	37 \pm 4	51 \pm 5***
β -cell mass	12.5 \pm 1.6	12 \pm 3.3	2.3 \pm 1.2***	4.9 \pm 1.9***
Basal pulse mass	112 \pm 87	39 \pm 20	23 \pm 13*	32 \pm 15
Entrained pulse mass	171 \pm 93	136 \pm 44	45 \pm 34*	55 \pm 20*

***: $p<0.001$, **: $p<0.01$, *: $p<0.05$ vs. lean animals

Inhibition of Glycogen Phosphorylase Prevents Arrhythmia following a Global Ischemic Period in the Perfused Rabbit Heart

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An acute myocardial infarct is the major cause of death in the diabetic population. In the resulting ischemic myocardium the metabolic status determines the expansion of necrosis. I.e. it has been suggested that lactate and proton accumulation following the breakdown of glycogen precipitate ventricular fibrillation and predicts ischemic myocardial necrosis. Thus, inhibition of glycogen breakdown via inhibition of glycogen phosphorylase (GP) may exert a beneficial effect under conditions of myocardial ischemia. In the present study we investigated the role of the GP inhibitor 1,4-dideoxy-1,4-imino-arabinitol (DAB) in the rabbit Langendorff perfusion model of ischemia-induced arrhythmia. DAB was previously demonstrated as a potent inhibitor of GP originating from various tissue including liver ($K_i = 392$ nM), muscle ($K_i = 374$ nM), and heart ($IC_{50} = >1$ μ M). Briefly, hearts were pre-treated with Krebs-Henselett buffer with or without DAB (0.4 μ g/ml) for 15 min before subjected to a 30-min global normo-thermic ischemic period followed by a 30-min re-perfusion period. Hemodynamic parameters were monitored throughout. Results: (control vs. DAB) DAB dramatically reduced the time with arrhythmia (min.; 18.0 ± 5.6 vs 0.0 ± 0.0 , $p < 0.01$). Also, glycogen content measured following the ischemic period was retained in the DAB treated hearts compared to the untreated heart (mM; 7 ± 1.1 vs. 3 ± 0.8 , $p < 0.05$). In comparison the glycogen content of the control hearts not subjected to ischemia was 17 ± 1.5 mM. In addition DAB improved the morphology of the electro-cardiogram (ECG) (ECG-score (60); 2.4 ± 0.2 vs. 0.7 ± 0.3 , $p < 0.05$) and the monophasic action potential (MAP) (MAP-score (60); 2.3 ± 0.3 vs. 0.9 ± 0.1 , $p < 0.05$). **In conclusion:** DAB significantly decreased the time with arrhythmia which may be ascribed to a prevention of glycogen breakdown via the inhibition of heart GP. The results suggest that inhibition of heart GP may be beneficial under conditions of ischemia as observed following acute myocardial infarction, the major cause of death in the diabetic population.

Insulin Plus Metformin vs. Triple Oral Therapy Following Failure of a Combination of 2 OADs: Efficacy and Costs of Therapy

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Insulin/metformin combination therapy and triple oral antidiabetic drug (OAD) therapy were compared in a multicenter, randomized, open-label, parallel group trial of 24-week treatment. Subjects with type 2 diabetes mellitus (N=183) previously failing treatment with 2 OAD's (HbA_{1c} >8%) were randomly assigned to either addition of a third oral drug, or switching to Novolin 70/30 bid insulin in combination with metformin. Baseline HbA_{1c} were 9.7 ± 1.6 and 9.6 ± 1.6 for insulin and OAD's, respectively. Response to insulin/metformin was more rapid: in the first 6 weeks of treatment, subjects treated with insulin/metformin had significantly greater reductions of HbA_{1c} values compared to treatment with triple OAD therapy (-1.54% vs. -1.05%, *p* < 0.001). However, final reductions of HbA_{1c} values from baseline to end of study were comparable for the two treatment groups (-1.96% for insulin/metformin and -1.77% for triple oral therapy). By the end of the study, 31% of subjects in both treatment groups achieved target HbA_{1c} levels of ≤ 7.0%, and 61% of all subjects had HbA_{1c} levels of < 8%. A subset of 10 subjects who failed to achieve target glycemic control with triple OAD treatment achieved further reductions in HbA_{1c} (-2.53%) when they switched to insulin/metformin therapy (Final insulin dose was 62.9 ± 26 U/day). An additional 4 subjects in the OAD group switched to insulin due to adverse events. Treatment with insulin/metformin was found to be significantly more cost-effective than triple OAD therapy, at \$2.70/day versus \$10.30/day (*p* < 0.001). Both treatments had similar numbers of minor hypoglycemic events (23%). **Conclusions:** In patients failing previous dual oral therapy, an additional oral medication or switching treatment to a regimen of insulin/metformin therapy yielded comparable end-of-study changes in HbA_{1c} and FBG values, but had fewer treatment failures in the insulin group. Insulin/metformin therapy was significantly more cost-effective than triple OAD therapy.

The Development and Validation of the Insulin Treatment Satisfaction Questionnaire (ITSQ) for Assessment of Patient's Perceptions of Their Insulin Regimen

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The increasing options for insulin delivery methods and insulin analogues enable insulin therapies to be tailored to patients' lifestyles and preferences so that insulin acceptance and treatment satisfaction can be improved. The objective of this study was to develop a conceptually sound and psychometrically valid Insulin Treatment Satisfaction Questionnaire (ITSQ) to compare patients' appraisal of different insulin regimens and modes of delivery. A three-stage process was employed: 1) conceptual development of the ITSQ items from patient focus groups; 2) preliminary validation in 170 diabetes outpatients; and 3) confirmatory survey and psychometric validation in 402 diabetes patients.

The confirmatory factor analysis from the confirmatory survey produced a final five-factor, 22-item solution assessing: inconvenience, lifestyle flexibility; glycemic control; hypoglycaemia control; and insulin delivery device satisfaction. The coefficient alpha of the sub-scales ranged from 0.79 to 0.91. The test-retest reliability ranged from 0.75 to 0.94. The reliability and construct validity of the final version were consistently high in the two independent samples of patients. ITSQ scores showed moderate to high correlation with patients rating of blood sugar control, duration of diabetes, duration taking insulin, number of daily insulin doses, and related measures of treatment burden. As predicted, the ITSQ subscales differentiated significantly between insulin delivery methods, degrees of dependency on assistance, and different HbA_{1c} levels.

The ITSQ was found to be a conceptually sound measurement that provides a clinically meaningful and psychometrically valid assessment of patient's satisfaction with their insulin treatment. The ITSQ is therefore recommended for use in clinical and research settings in order to compare patient reported performance of different insulin therapies.

Appraisal of Insulin Therapy Among Type 2 Diabetes Patients With and Without Previous Experience of Insulin Treatment

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Timely initiation and effective self-management of insulin therapy can be impaired by negative perceptions and attitudes among people with type 2 diabetes and their professional care-givers. The objectives of this study were to test the psychometric properties of a newly designed scale, the Insulin Treatment Appraisal Scale (ITAS), and to compare attitudes between insulin-naïve and insulin-treated patients with type 2 diabetes. The ITAS assesses perceptions about insulin treatment and contains 20 items (16 negative, 4 positive statements) scored on a 5 point Likert scale. The ITAS was administered to 282 patients recruited from a national diabetes panel in the US. 146 patients were insulin naïve (mean age 59.7, 46% male, 88% taking OAD, 43% working), while 136 were receiving insulin (mean age 58.4, 46% male, 56% taking OAD, 40% working). The ITAS showed high homogeneity (Cronbach's α , 0.88). Insulin-naïve patients rated insulin therapy significantly more negatively than insulin-treated patients on 15 of the 20 items ($p < 0.001$, controlling for age, gender and duration of diabetes). 57% of insulin-naïve patients, but only 6% of insulin-treated patients feared injecting insulin, and 61% of insulin naïve and 28% of insulin-treated patients agreed that insulin therapy demanded a lot of time and energy ($p < 0.0001$). Only one item, concerning weight gain, showed an opposite trend. Insulin naïve patients scored significantly higher (more negative) than insulin treated patients on the total ITAS score (52.0 (Median 52.5; SD, 16.0) compared to 36.0 (Median, 36.3; SD, 13.9) ($p < 0.001$)). **It is concluded** that the ITAS has satisfactory psychometric qualities for diagnostic and research purposes, and that patients with type 2 diabetes who are insulin naïve have significantly more negative views about insulin therapy (psychological insulin resistance) than those actually taking insulin. These findings highlight an important disparity between the anticipated and actual patient experience of insulin therapy.

Frontier Practice in Diabetes Care: A Method for Estimating Relative Efficiency in Diabetes Care

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We develop a new method for identifying best practice and setting benchmarks for performance in the diabetes care. It exhibits superiority to existing technology by facilitating objective multi-dimensional comparisons across providers without resting on distributional assumptions in identifying benchmarks. The method constitutes a powerful tool for health care professionals to compare performance and set targets for improvement.

The basis for comparison is the concept of relative efficiency. This is understood as the technical efficiency in which one provider transforms processes of care into health outcomes compared to his peers. It is a comparative measure of efficiency and by identifying the highest level of performance – the efficiency frontier – the method quantifies the level of efficiency of each provider under evaluation.

Relative efficiency is determined among 5 diabetes care teams operating at Steno Diabetes Center, Denmark, between 1995 and 2000. The study population constitutes 3,107 type 1 patients between the age of 18 and 65 with a fixed team assignment. The applied outcomes and process measures adhere to the initial set recommended by the Diabetes Quality Improvement Project (DQIP). Relative efficiency is estimated by Data Envelopment Analysis (DEA), a linear programming optimization technique.

The results demonstrate an even split between efficient and less efficient teams over the study period. On average, all teams operated highly efficient. The least efficient team operated at 89% efficiency, while the most efficient team had an efficiency score close to 100%. Despite such high overall performance, the method was sensitive enough to estimate significant differences in required improvements. E.g., in 1999, the least efficient team needed to meet the specific DQIP outcome measures for a total of 86 patients, while the equivalent number for the most efficient team was 10 patients.

We will continue to examine the sensitivity of efficiency estimates to case-mix adjustment as well as the ability to measure efficiency in transforming resources into processes of care.

Impact of Hospitalization in a Diabetes Ward on Long Term Outcomes

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Diabetic patients are hospitalized in Diabetes Wards for various different purposes. Nevertheless, general aims of hospitalizations include improvement of glycaemic control and reduction of cardiovascular risk factors. We have retrospectively analyzed the long term effects of hospitalization of patients at a specialized diabetes hospital – Steno Diabetes Center (SDC) during the period from 1995 until 2000. The following parameters were registered before (–6 to 0 months) and after (+6 to +18 months) hospitalization: HbA_{1c}, blood pressure, Body Mass Index (BMI), total cholesterol as well as urinary albumin excretion.

A total of 1370 Type 1 and Type 2 diabetic patients with valid registrations of both pre- and post hospitalization outcome parameters (SDC out-patient clinic) were included in the analysis. The mean duration of hospitalization was 5.4 days for Type 1 and 5.5 days for Type 2 patients.

We found that HbA_{1c} was significantly reduced when comparing after and before hospitalization for both Type 1 (–1.16%) and Type 2 (–1.61 %) patients, whereas BMI increased significantly in both groups (+0.77 kg/m² for Type 1 and +1.01 kg/m² for Type 2). Somewhat unexpectedly, both systolic and diastolic blood pressures increased slightly, but significantly. Serum total cholesterol decreased for the Type 2 patients (–0.23 mmol/l), but not for the Type 1 s, whereas the urinary albumin excretion rate was unchanged for both groups.

Subgroup analysis performed according to duration of diabetes (0–2 or >2 years), HbA_{1c} before hospitalization (< or > 8.5 %), hospitalization before or after 1998, presence or absence of nephropathy and age revealed virtually identical results.

In conclusion we have documented a long term effect of hospitalization by reduction of HbA_{1c} in Type 1 and Type 2, and serum total cholesterol solely in Type 2 patients. Unintended effects of hospitalization – and perhaps intensified glycaemic control – include slightly elevated blood pressure levels as well as increased BMI. A more intensified approach is needed to reduce non-glycaemic cardiovascular risk factors including blood pressure in hospitalized diabetic patients.

Angiotensin II Receptor Gene Polymorphisms and Occurrence Of Severe Hypoglycemia in Type 1 Diabetes

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We have previously shown a strong relationship between high plasma angiotensinogen concentration, high serum ACE activity and occurrence of severe hypoglycemia (SH) in type 1 diabetes. This study was undertaken to test the hypothesis that genotypes for angiotensin II receptor (ATIIR) subtypes 1 and 2 are also related to rate of severe hypoglycemia.

A cohort of 171 unselected patients with type 1 diabetes, untreated with ACE inhibitors or angiotensin II receptor antagonists, were followed for one year by monthly questionnaires and immediate reporting of episodes of SH (defined as episodes needing assistance from others). ATIIR subtype 1 (A1166C) and 2 (G1675A) genotypes were determined by PCR. Subjects were characterized by C-peptide status, hypoglycemic awareness, HbA_{1c}, and clinical data.

Subjects homozygous for the A-allele of the ATIIR subtype 2 reported a 2.6 (95%CL: 1.3–6.3) times higher rate of SH compared to those not carrying the allele ($p=0.015$). There was no significant relationship between ATIIR subtype 2 genotype and rate of mild ($p=0.79$) or biochemical hypoglycemia ($p=0.68$) or other risk factors as self-reported state of awareness ($p=0.15$), C-peptide status ($p=0.17$) or HbA_{1c} ($p=0.11$). There was no influence of ATIIR subtype 1 on occurrence of SH, awareness, mild or biochemical hypoglycemia.

In conclusion, the A-allele of ATIIR subtype 2 at codon 1675 that confers low expression of the receptor is associated with occurrence of severe hypoglycemia compared to the G-allele. This provides further evidence for a critical role of the renin-angiotensin system in predisposition of patients with type 1 diabetes to severe hypoglycemia.

Saturday 14th June 2003

2.45–4.45 pm, Hypoglycemia

The Impact of ACE Activity on Cognitive Function, Symptoms of Hypoglycemia and Hormonal Counterregulation During Hypoglycemia in Normal Subjects

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We have previously shown a strong relationship between high serum ACE activity and occurrence of severe hypoglycemia (SH) in type 1 diabetes. The aim of this study was explore counterregulatory responses and cognitive function in normal subjects with low or high ACE activity.

In a balanced single-blinded placebo-controlled cross-over protocol, 8 healthy volunteers with low (mean 20 mU/l) and 8 with high (mean 52 mU/l) ACE activity were subjected to a hypoglycemic challenge by subcutaneously injected unmodified human insulin. Catecholamines, glucagon, growth hormone, cortisol and symptomatic responses were measured and cognitive function was assessed by the California Computerized Assessment Package (CalCAP) that includes 4 different reaction time tests of different complexity.

The resulting hypoglycemic stimulus was similar in the two groups (nadir plasma glucose 2.7 mmol/l). There were no significant differences between the groups in counterregulatory responses except for growth hormone that was higher in the group with high ACE activity after normalization of plasma glucose ($p=0.044$). The high ACE group reported higher total and autonomic symptom scores after normalization of glucose level ($p=0.049$ and 0.050 , respectively). In contrast to the group with low ACE activity those with high ACE activity deteriorated in cognitive performance both in terms of speed and precision. The high ACE group made more errors during maximum hypoglycemia ($p=0.014$) and had larger decrements in reaction time in the two most complex CalCAP tasks (121 vs. 2 msec. and 114 vs. 16 msec., $p=0.007$ and $p=0.045$, respectively) in the recovery phase compared to the low ACE group.

In conclusion, normal subjects with high ACE activity more readily develop cognitive dysfunction during moderate hypoglycemia and recover more slowly than subjects with low ACE activity. This seems not to be explained by differences in counterregulatory responses.

Saturday 14th June 2003
2.45–4.45 pm, Hypoglycemia

The Influence of Risk Factors on Hypoglycemia in Type 1 Diabetes Assessed by Continuous Subcutaneous Glucose Monitoring

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Recent studies applying continuous glucose monitoring have indicated that patients with type 1 diabetes are more exposed to hypoglycemia than known from conventional self-monitoring. The aim of this study was to evaluate the influence of known risk factors on occurrence of hypoglycemia assessed by continuous subcutaneous glucose monitoring.

Seventy-six patients with type 1 diabetes underwent a 6-day continuous subcutaneous glucose monitoring with the MiniMed Continuous Glucose Monitoring System (CGMS). Hemocue blood glucose determinations were used to optimize calibration. Participants completed a detailed diary documenting all meals and snacks, insulin doses and episodes with symptoms of hypoglycemia. Endpoints were number and total duration of episodes with subcutaneous glucose <3.5 mmol/l for at least 10 minutes and number and total duration of episodes with subcutaneous glucose <2.2 mmol/l for at least 10 minutes. Hypoglycemic episodes were classified as unrecognized, mild (recognized and managed independently) or severe (needing assistance from others).

During a total valid monitoring period of 372 days, 468 episodes with glucose <3.5 mmol/l were recorded in 74 (97%) subjects and 233 episodes with glucose <2.2 mmol/l were recorded in 60 (79%) subjects. Overall, 15.1% of time was spent at glucose <3.5 mmol/l and 5.9% at glucose <2.2 mmol/l. HbA_{1c} was negatively associated and self-estimated state of awareness of hypoglycemia tended to be negatively associated with total rate of episodes with glucose <3.5 mmol/l ($p < 0.001$ and $p = 0.056$, respectively). HbA_{1c} and state of awareness were negatively associated with rate of unrecognized episodes with glucose <3.5 mmol/l ($p = 0.046$ and $p = 0.031$, respectively) but neither of the two variables were related with rate of episodes with glucose <2.2 mmol/l ($p = 0.10$ and $p = 0.16$, respectively). Women had a higher rate of recognized episodes with glucose <3.5 mmol/l ($p = 0.021$) but there was no relationship between sex and any other endpoint. Age, duration of diabetes and C-peptide status were not related with rate of episodes with glucose <3.5 or <2.2 mmol/l.

We conclude that conventional risk factors are related with occurrence of subnormal glucose but not with profound biochemical hypoglycemia assessed by CGMS.

Diabetes Control in Children and Adolescents with Type 1 Diabetes Mellitus in Asia

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Children Diabcare 2001 was a cross-sectional, non-population based audit. Data were collected from 96 paediatric diabetes centers in Australia, China, Hong Kong, Taiwan, Indonesia, Japan, Malaysia, Philippines, Singapore, South Korea and Thailand from November 2001 to April 2002. Blood samples and information were collected from 2312 children (<18 years old) with type 1 diabetes. Results for the other 10% of patients with type 2 diabetes will not be reported here. The mean (\pm SD) age of the patients was 12.2 ± 3.9 years and duration of diabetes was 5.2 ± 3.4 years. Mean HbA_{1c} was $8.7 \pm 1.9\%$ (n=2237) and 58% had HbA_{1c} >8%. Average HbA_{1c} of patients aged ≥ 10 years was $8.9 \pm 2.1\%$ (n=1586) compared to $8.3 \pm 1.4\%$ (n=651) of patients aged <10 years. The mean insulin dose of the patients was 1.0 ± 0.4 units/day/kg bodyweight (n=2091) and 75% had only one or two daily injections. Hypoglycaemia resulting in unconsciousness and/or convulsion was associated with younger age and better glycaemic control. The incidence of which, based on a 3-month period, was 73 per 100 patient-years for all the type 1 patients. It was 136 compared to 70 per 100 patient-years for children aged < 5 years and those aged ≥ 5 years respectively. The incidences were 98, 77 and 39 per 100 patient-years for patients with HbA_{1c} of <8%, 8–9% and >9% respectively. Diabetic ketoacidosis was associated with worse glycaemic control and shorter duration of diabetes. The incidence of which, based on a 12-month period, was 10 per 100 patient-years for the type 1 patients. It was 13 compared to 9 per 100 patient-years for children with diabetes duration <3 years and ≥ 3 years respectively. The incidences were 4.4, 6.5 and 18.2 per 100 patient-years for patients with HbA_{1c} of <8%, 8–9% and >9% respectively. A few of these young patients already had at least one diabetic complication (4.3%), with microalbuminuria (2.6%), cataract (0.9%) and neuropathy (0.8%) being most common. Most of the children did not achieve adequate glycaemic control of HbA_{1c} $\leq 8\%$. Further studies are needed to identify the strategies to improve glycaemic control so as to delay or prevent chronic complications. Young children are at higher risk of hypoglycaemia and should receive special attention.

