BENEFITS OF INSULIN ASPART VS PHOSPHATE-BUFFERED HUMAN REGULAR INSULIN IN PERSONS WITH TYPE 1 DIABETES TREATED BY MEANS OF AN INSULIN PUMP

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Absorption rates of phosphate buffered insulin analogs aspart and lispro prevail over regular human insulin. However, insulin aspart has not been widely used. The aim of this open controlled clinical study is to compare the metabolic effects of insulin aspart and phosphate buffered insulin when both are used in insulin pumps according to the identical algorithms. Methods: Twenty one persons aged 39.9 ± 2.89 (mean ± SE) years (y) with type 1 diabetes mellitus duration of 17.9 ± 2.21 y treated by an insulin pump for 4.3 ± 0.53 y (at least 3 months), educated in selfmonitoring, entered the study. Mean plasma glucose, rates of hypo- and hyperglycaemias from the glucometer memory and other data from the first 256 ± 19.97 days period with regular human insulin (check-up 1 and 2) and consequent 364 ± 8.78 days long period with insulin aspart (check-up 3 and 4) were compared (paired t-test). Replacement of human regular insulin with insulin aspart after two check-ups was the only change in the treatment of diabetes. No special therapeutic education or training was made during the study. Results: In persons with type 1 diabetes treated by an insulin pump with insulin aspart, despite the lower daily dose of insulin aspart vs human regular insulin, the HbA1c decreased; the frequency of hypo- and hyperglycaemias and the BMI did not change. Conclusions: Insulin analog aspart appears to be more effective for continuous subcutaneous insulin infusion than regular human insulin.

INTRODUCTION

Absorption rates of the phosphate buffered insulin analogs aspart (Novorapid, Novo Nordisk) and lispro (Humalog, Eli Lilly) prevail over regular human insulin[6, 8, 11, 13]. Due to their monomeric structure they are absorbed from the subcutaneous tissue immediately after application, whereas the hexameric form of regular insulin needs to be split into absorbable monomers first. For this reason the absorbtion of regular human insulin takes about 10–20 min longer. Since the beginning of the insulin pump era in the year 1978[10], various kinds of shortacting insulin have been used for continuous subcutaneous insulin infusion. Phosphate buffered human insulin (Velosulin HM, Novo Nordisk) was recommended because of its low aggregability in tubing systems. In recent years good effects of insulin lispro applied in continuous subcutaneous insulin infusion have been described[9, 12]. There was also some positive experience with insulin aspart[2-5]. However, insulin aspart has not been widely used. The distribution of Novorapid in the Czech Republic started as late as in Octobre 2002.

AIMS

The aim of this open controlled clinical study is to compare the effects of insulin aspart and phosphate buffered regular human insulin when both are used in insulin pumps according to identical algorithms:

1. on parameters of carbohydrate metabolism (P-glucose, HbA1c, S-fructosamine);
2. on parameters of lipoprotein metabolism (S-cholesterol, S-HDL-, S-LDL-cholesterol and S-triacylglycerols);
3. on clinical parameters (body mass index, blood pressure and heart rate);
4. on other biochemical parameters of mineral metabolism, liver and kidney function;
5. on patients' satisfaction.

MATERIAL AND METHODS

Persons with type 1 diabetes mellitus

Twenty one persons with type 1 diabetes mellitus treated by means of an insulin pump for least 3 months, educated

in selfmonitoring (SM) on glucometer Optium, Abbott/ Medisense, and attending routine medical check-ups at 1- to 2- month intervals, completed the study (Table 1).

Study design

This trial was performed in the period from January 2002 till March 2004 according to the followinng schedule:

1. At the end of the year 2002 (within several weeks after the registration of insulin Novorapid in the Czech Republic), all persons with diabetes treated with phosphate buffered regular human insulin (Velosulin HM) by means of an insulin pump in our out-patient department (n = 21) received a brief information from his physician about the existence of a new kind of insulin preparation (Novorapid) and they agreed to use this insulin in the next treatment.
2. In each person, clinical and laboratory data from their two routine check-ups in the year 2002 (when only Velosulin HM was used for their insulin treatment), i.e., from the first check-up in 2002 (the study check-up 1) and from the last check-up before the insulin change (the study check-up 2) were registered in the study protocol.
3. Everyone was encouraged to fulfill six steps:
   - to carry out one P-glucose profile consisting of 10 P-glucose estimations (6:00, 9:00, 12:00, 15:00, 17:30, 20.30, 22:00, 0:30, 2:30, 6:00 h) on glucometer Optium;
   - to begin the treatment with Novorapid instead of Velosulin HM;
   - to repeat the ten-point P-glucose profile within one month after the change;
   - to continue his/her usual life style including food, exercise, frequent selfmonitoring;
   - to keep to the same basal rate and to use the same algorithms for the adaptation of preprandial insulin boluses;
   - to contact his/her physician when necessary (as usual).
4. Treatment of concomitant disorders such as hyperlipoproteinaemia, hypertension, renal insuficiency, ischaemic heart disease etc. (see Table 1) continued as before, according to usual principles.
5. Data from two check-ups with insulin Novorapid, i.e. from a check-up about three month after the insulin change (the study check-up 3) and from a check-up about one year after the change (the study check-up 4), were registered in the study protocol.
6. Mean plasma glucose (MPG) and rates of hypo- and hyperglycaemias in the course of the 2-month period before the respective check-up were assessed from glucometer memory.
7. At the check-up 3 and 4 everyone was asked whether he/she would prefer to switch back to Velosulin HM or to go on with Novorapid and the number of local complications resulting from pump therapy was sumarized.

Statistical evaluation

Clinical and laboratory data from the first period with regular human insulin Velosulin HM (check-up 1 and 2) and the consequent period with insulin aspart Novorapid (check-up 3 and 4) were compared. Correlations between HbA1c vs. total daily insulin dose and HbA1c vs. frequency of selfmonitoring were sought.

Table 1. Characteristics of persons with type 1 diabetes in the study (n or mean ± SE).

Parameter	Data
n	21
men/women [n]	9/12
age [years]	39.9 ± 2.89
duration of diabetes [years]	17.9 ± 2.21
neuropathy [n]	11
retinopathy [n]	6
nephropathy [n]	5
dyslipoproteinaemia	8
hypertension	4
coronary artery disease (CABG)	1
renal insuficiency/CAPD	2/1
gastritis	1
focal nodular hyperplasia (liver)	1
duration of insulin pump therapy [years]	4.3 ± 0.53
number of pumps Minimed, Medtronic[n]	18
number of pumps H-tron, Disetronic [n]	3
type of the catheter	Silhouette, Minimed-Medtronic

CABG – coronary artery bypass grafting, CAPD – continuous ambulatory peritoneal dialysis

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Table 2. Control of type 1 diabetes mellitus with human regular insulin (Velosulin HM) and with insulin aspart (Novorapid) administered by means of an insulin pump (mean ± SE).

Insulin	Velosulin HM	Velosulin HM	Novorapid	Novorapid
Check-up	1	2	3	4
No of days from the change	−256 ± 19.97	− 18 ± 4.91	+80 ± 7.05	+364 ± 8.78
Body mass [kg]	68.0 ± 2.55	68.9 ± 2.7	69.4 ± 2.76	69.5 ± 2.84
BMI [kg/m^2]	23.2 ± 0.66	23.4 ± 0.75	23.7 ± 0.79	23.7 ± 0.81
Blood pressure syst. [mm Hg]	125.4 ± 1.91	123.4 ± 2.03	130.2 ± 4.48	123.9 ± 2.56
Blood pressure diast. [mm Hg]	80.2 ± 1.22	77.4 ± 1.89	81.4 ± 3.09	79.0 ± 2.19
Heart rate [min^{-1}]	72.6 ± 1.11	76.6 ± 1.89	74.2 ± 1.39	76.3 ± 2.00
Frequency of SM/d (Optimum)		3.1 ± 0.21	4.0 ± 0.43*	3.0 ± 0.25
MPG (Optium)[mmol/l]		10.0 ± 0.40	9.5 ± 0.39	9.8 ± 0.38
PG < 4 mmol/l (Optium) [%]		8.9 ± 1.24	10.7 ± 1.77	10.8 ± 1.41
PG > 10 mmol/l (Optium) [%]		44.9 ± 3.72	40.7 ± 3.12	42.5 ± 3.54
Fruktosamin [μmol/l]	417 ± 17.44	415.0 ± 17.64	377.1 ± 13.99*	406.8 ± 24.87
Cholesterol [mmol/l]	4.9 ± 0.17	4.8 ± 0.19	4.6 ± 0.17	4.6 ± 0.18
Triacylglycerols [mmol/l]	1.2 ± 0.13	1.1 ± 0.15	1.3 ± 0.19	1.1 ± 0.11
LDL-cholesterol [mmol/l]	2.6 ± 0.16	2.4 ± 0.18	2.4 ± 0.19	2.4 ± 0.16
HDL-cholesterol [mmol/l]	1.7 ± 0.11	1.8 ± 0.10	1.7 ± 0.08	1.7 ± 0.09
K [mmol/l]	4.6 ± 0.09*	4.4 ± 0.1	4.4 ± 0.08	4.4 ± 0.10
Na [mmol/l]	139.2 ± 0.94	137.3 ± 0.80	137.9 ± 0.71	138.6 ± 0.53
Cl [mmol/l]	103.8 ± 0.77	102.5 ± 0.65	103.8 ± 0.71	105.2 ± 0.74*
Ca [mmol/l]	2.4 ± 0.04	2.5 ± 0.04	2.4 ± 0.02	2.5 ± 0.04
P [mmol/l]	1.1 ± 0.06	1.2 ± 0.05	1.3 ± 0.04	1.2 ± 0.05
Mg [mmol/l]	0.9 ± 0.02	0.9 ± 0.02	0.9 ± 0.02	0.9 ± 0.07
Urea [mmol/l]	6.6 ± 1.2	6.5 ± 1.20	6.2 ± 0.85	5.6 ± 0.62
Creatinine [μmol/l]	105.1 ± 12.67	100.6 ± 12.86	99.2 ± 11.27	95.0 ± 10.00
Uric acid [μmol/l]	237.4 ± 17.86	224.0 ± 16.51	244.6 ± 15.49	215.3 ± 14.63
Bilirubin [[μmol/l]	14.4 ± 3.03*	16.2 ± 1.86	13.4 ± 1.8*	13.6 ± 1.55*
ALT [μkat/l]	0.4 ± 0.03	0.4 ± 0.03	0.5 ± 0.09	0.4 ± 0.03
AST [[μkat/l]	0.4 ± 0.02	0.4 ± 0.02	0.4 ± 0.06	0.5 ± 0.05
ALP [[μkat/l]	1.0 ± 0.13	1.1 ± 0.11	1.2 ± 0.09*	1.4 ± 0.09*
GMT [[μkat/l]	0.5 ± 0.18	0.6 ± 0.30	0.7 ± 0.38	0.7 ± 0.44
Total proteins [g/l]	74.5 ± 1.37	72.9 ± 1.1	71.8 ± 1.31	72.5 ± 1.37
Correlation r insulin dose vs. HbA1c	0.50 ^{x}	0.42 ^{x}	0,31	0.36
Correlation r SM frequency vs HbA1c		− 0.42	− 0.40	− 0.26

n = 21; *p < 0.05 vs. check-up 2; ^{x} p < 0.05

PC Link (Abbott/Medisense) enabled transfer of the results of selfmonitoring from glucometer Optium to a PC. MS Excel and SPSS v. 10.1 were used to analyze the data. A paired t-test was applied whenever possible. p < 0.05 was considered to be of statistical significance.

RESULTS

Ten-point P-glucose profiles with Velosulin HM and with Novorapid are shown in Fig 1 (means) and in Fig. 2 (medians). Only the difference at 6:00 h was significant (p < 0.05).

The HbA1c decreased within 12 month after the change to Novorapid; at check-up 4, the differences vs. check-up 1, vs. check-u 2 and vs. check-up 3 were significant (Fig. 3), even though the total daily insulin dose at
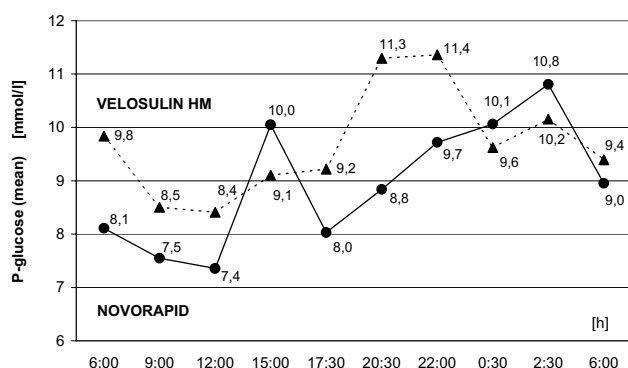
Fig. 1. Ten-point P-glucose profile with phosphate buffered human regular insulin (Velosulin HM) and with insulin aspart (Novorapid); some profiles were not complete, that's why in individual points n varies: n = 20, 21, 21, 20, 20, 17, 17, 14, 17, 21; means
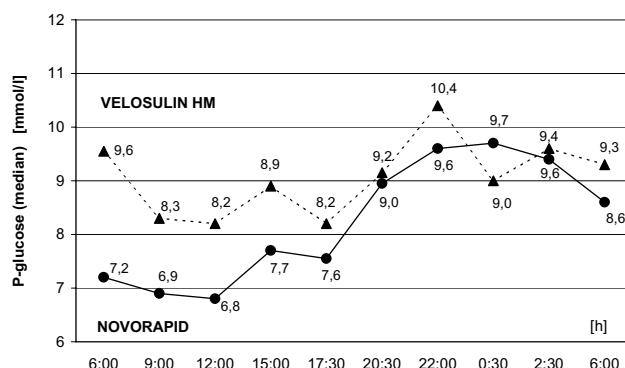

Fig. 2. Ten-point P-glucose profile with phosphate buffered human regular insulin (Velosulin HM) and with insulin aspart (Novorapid); some profiles were not complete, that's why in individual points n varies: n = 20, 21, 21, 20, 20, 17, 17, 14, 17, 21; medians
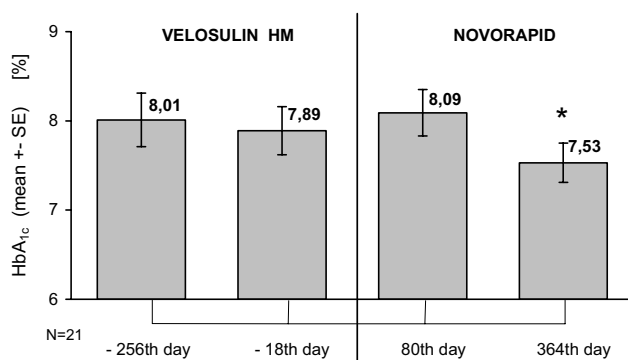

Fig. 3. HbA1c with phosphate buffered human regular insulin (Velosulin HM) and with insulin aspart (Novorapid); means ± SE ; *p < 0.05 vs. check-up 1, 2 and 3; HbA1c values are given according to the DCCT/NGSP scale (reference range 4.20–6.0 %); in order to convert these traditional NGSP values to the recent IFCC values following eqation may be used: IFCC = (NGSP – 2.15) : 0.915 [%]
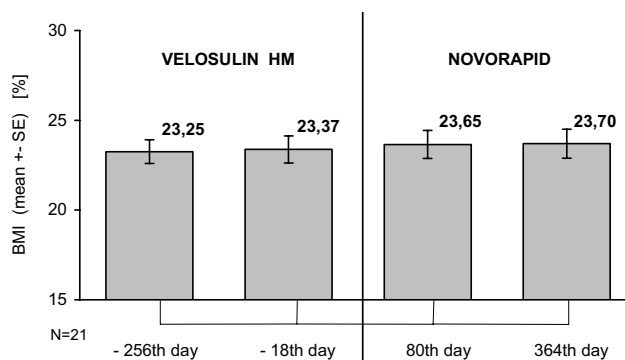

Fig. 4. Body mass index with phosphate buffered human regular insulin (Velosulin HM) and with insulin aspart (Novorapid); means ± SE; no significant difference
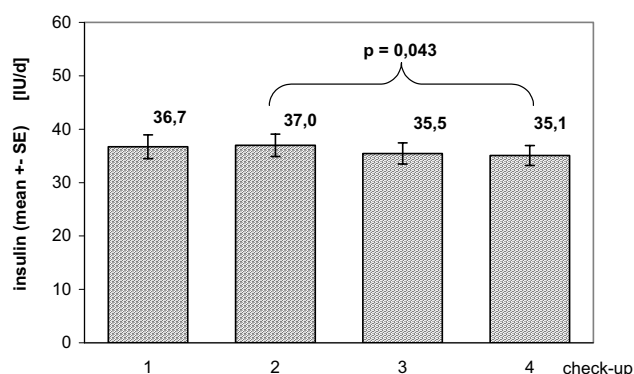

Fig. 5. Total daily insulin dose with phosphate buffered human regular insulin (Velosulin HM, check-up 1 and 2) and with insulin aspart (Novorapid, check-up 3 and 4); means ± SE
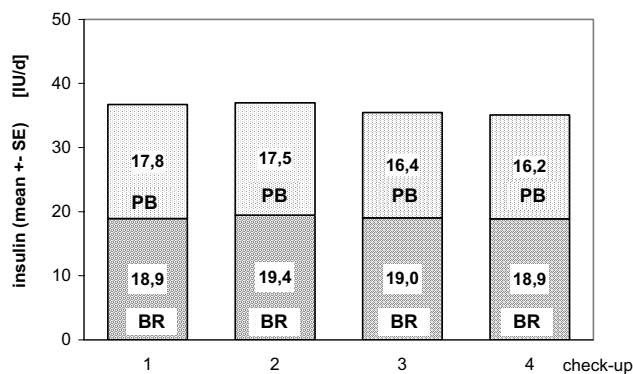

Fig. 6. Mean basal rate (BR) and prandial boluses (PB) with phosphate buffered human regular insulin (Velosulin HM) and with insulin aspart (Novorapid)

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check-up 4 vs. check-u 2 was lower (Fig. 5) as a result of to both smaller prandial boluses and smaler basal rates (Fig. 6).

The BMI did not change (Fig. 4).

There was no significant change in basal heart rate and blood pressure. Changes in laboratory parameters were exceptional (Table 2).

No strong correlation either between HbA1c vs. daily insulin dose or between HbA1c vs. frequency of selfmonitoring could be found. (Table 2).

Concerning the patients'satisfaction, at the check-up 3 only one person (with renal insuficiency) would probably prefer to switch back to Velosulin HM; namely, he felt the sensations of hypoglycaemia appeared more frequently with Novorapid. After the reduction of basal rate and prandial boluses he agreed to go on with Novorapid, as well as at the check-up 4. Fourteen patients were (since the change) undoubtedly enthusiastic with Novorapid because of better flexibility in administration of prandial boluses and generally better felt condition. Six patients would not object to go on with either Novorapid or Velosulin HM as they could not see any particular advantage in the treatment with Novorapid.

In the course of 7 800 patient-days with Novorapid, there was one local infection at the site of catheter Silhouette insertion demanding surgical intervention, and some minor problems (one or two per patient per year) with tubing system Silhouette.

DISCUSSION

The results of two check-ups in the course of the first period (with Velosulin HM) may be considered as "a control group", and, as well, a stable baseline. No significant difference between the check-up 1 and 2 were found.

Replacement of phosphate buffered regular insulin (Velosulin HM) with insulin aspart (Novorapid) after check-up 2 was the only change in the treatment. The patients had no special training or therapeutic education and they were not aware that they are in a study. For this reason, there was (if any) only a little influence of the factor "improvement due to being observed" as it has been seen in some clinical studies. Hence, the significant improvement of HbA1c at check-up 4 by 0.48 % vs. check-up 1 and by 0.36 % vs. check-up 2 may be considered as a benefit of insulin aspart.

The long-term results (check-up 4) are more encouraging than the results from the first 80-day period (check-up 3) where no improvement of HbA1c could be seen. Nevertheless, our results from check-up 3 correspond to the results of the multicenter randomized parallel-group study of Bode et al. (1) comparing the differences between insulin aspart, buffered regular insulin and insulin lispro: 146 adult patients were randomized and no differences in HbA1c concentrations could be found within a 16 weeks period of insulin pump treatment.

There was only a small difference between the P-glucose profiles with Velosulin HM and with Novorapid. In intensive conventional insulin treatment the effects of Novorapid on postprandial P-glucose concentrations are emphasized[7, 14]. In continuous subcutaneous insulin treatment with intensive selfmonitoring, however, the correct basal rate and prandial boluses may better prevent the development of postprandial hyperglycaemia either with Velosulin HM or with Novorapid. It must be also taken into consideration that the timing of P-glucose measurements in ten-point selfmonitoring profiles was not absolutely precise. The patient is often known to get the best results before a check-up. Nevertheless, even though there is little statistical significance between P-glucose profiles (probably due to the methodical factors mentioned), the decisive parameters to assess the effectiveness of insulin treatment are HbA1c, daily insulin dose and BMI.

CONCLUSIONS

In persons with the type 1 diabetes mellitus treated by an insulin pump, the benefits of insulin aspart (Novorapid) on metabolism of carbohydrates was demonstrated: despite the lower daily dose of insulin aspart (Novorapid) vs phosphate buffered human regular insulin (Velosulin HM), the HbA1c decreased. The frequency of hypo- and hyperglycaemia, the BMI, blood pressure and heart rate did not change. No significant influence of insulin aspart on selected parameters of liver or kidney functions and no other side effects were found. Patients' satisfaction with Novorapid was good. Hence, insulin aspart (Novorapid) appears to be more effective for continuous insulin infusion than phosphate buffered regular human insulin (Velosulin HM) and may be recommended.

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