Unchanged Insulin Absorption After 4 Days' Use of Subcutaneous Indwelling Catheters for Insulin Injections

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OBJECTIVE — Since 1985, we have used indwelling catheters (Insuflon, Maersk Medical, Lynge, Denmark; Chronimed, Minnetonka, MN) to lessen pain when injecting insulin. However, some patients experience a rise in blood glucose after using indwelling catheters for a few days. We therefore studied the absorption of ^{125}I-labeled insulin when using indwelling catheters.

RESEARCH DESIGN AND METHODS — Five men and five women participated (age 18–25 years, C-peptide negative, HbA_{1c} 9.0 ± 1.0% [mean ± SD, DCA-2000 method], diabetes duration 5–21 [median 9.5] years). After thyroid blockage with potassium iodide, we injected 5 IU of ^{125}I-labeled short-acting insulin subcutaneously in the abdomen ("ordinary injection") and 5 IU on the contralateral side through an indwelling catheter ("catheter injection"). The injection/insertion area was free of lipohyper- and lipohypotrophies. Disappearance rate was measured for 180 min with a gamma camera. The patients injected all premeal injections of short-acting insulin through the same indwelling catheter in the following 4 days. The investigation procedure was repeated day 3 and 5.

RESULTS — We found no statistically or clinically (95% CI) significant difference in residual activity of ^{125}I-insulin after 60 min or in time for 50% of the injected depot to disappear (T-50%) among catheter injections on days 1, 3, and 5; ordinary injections on days 1, 3, and 5; or catheter and ordinary injections on days 1, 3, and 5, respectively. HbA_{1c} correlated both to T-50% ($r = 0.73$, $P = 0.016$) and residual activity of ^{125}I-insulin after 60 min ($r = 0.69$, $P = 0.028$), indicating that patients with a slower absorption will have a less ideal metabolic control when using premeal bolus injections.

CONCLUSIONS — We conclude that using indwelling subcutaneous catheters for insulin injections for up to 4 days does not affect the absorption of short-acting insulin.

Subcutaneous indwelling insulin catheters can be used to minimize injection pain (1). They have an average indwelling time of 4–5 days, and the frequency of side effects is low (2,3). In general, metabolic control, both short-term, as measured by free serum-insulin levels, and blood glucose levels (4), and long-term, as measured by HbA_{1c} (4,5), does not seem to be altered by using subcutaneous catheters for insulin injections.

However, some patients experience a rise in blood glucose after using an indwelling catheter for a few days. The aim of the present study was to investigate if the absorption of insulin changes when using the same catheter for several days.

RESEARCH DESIGN AND METHODS

Subjects and procedures

The patients avoided excessive physical activity and smoking during the 3 h before coming to the hospital in the afternoon. The thyroid was blocked by potassium iodide. The indwelling catheter (Insuflon, Maersk Medical, Lynge, Denmark; Chronimed, Minnetonka, MN) was inserted by the nurse 5 cm lateral of the umbilicus in an area free of lipohyper- and lipohypotrophy. There was 5 IU of ^{125}I-labeled short-acting insulin (Actrapid, 100 IU/ml, 1 kBq/IU, Novo-Nordisk, Bagsvaerd, Denmark) injected through the indwelling catheter ("catheter injection") and 5 IU of unlabeled short-acting insulin injected subcutaneously on the contralateral side of the abdomen ("ordinary injection"). Table 1 shows patient characteristics.

Fifteen minutes after the insulin injections and a quick dinner, the patient was placed in the supine position under the gamma camera. An uncollimated gamma camera (Picker SX300, Picker, Cleveland, OH) was used to measure the disappearance of ^{125}I-insulin from the injection sites. The sensitivity was found to be ~1,400 cpm/kBq and the spatial resolution good enough to effectively separate the two injection sites (6). The patient examination was performed as a dynamic study using a frame rate of one per minute and stored in the gamma camera computer system (Gamma11, Nuclear Diagnostics, Stockholm, Sweden) in a matrix of 64 × 64 pixels. Regions of interest were defined for each injection site and a background area and the net time-activity curves were calculated. The curves were normalized and plotted in intervals of 15 min.

Table 1—*Characteristics of patients*

Age (years)	18–25 (median 20)
Sex (M/F)	5/5
Diabetes duration (years)	5–21 (median 9.5)
C-peptide (nmol/l)	<0.25 postprandially (radioimmunoassay)
HbA_{1c} (%)	9.0 ± 1.0 (DCA-2000 method, normal range 4.1–5.7%)
Injection mode	Three patients used CSII; seven patients used multiple daily injections with four to five doses per day

Data for HbA_{1c} are means ± SD.

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CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; T-50%, time for 50% of the injected depot to disappear.

The dead space of the indwelling catheter (corresponding to 0.5 IU) was subtracted when calculating the activity measured from catheter injections. T-50% was defined as the time for 50% of the injected depot to disappear. The initial activity at time 0 was not included when calculating the regression line due to the initial lag-phase, presumably due to dissociation, dissolution, and local diffusion in the interstitial tissue (7).

The patients gave injections of short-acting insulin four times daily through the same indwelling catheter in the following days. The bedtime insulin/basal continuous subcutaneous insulin infusion (CSII) was given as usual. The investigation procedure was repeated on day 3 and 5.

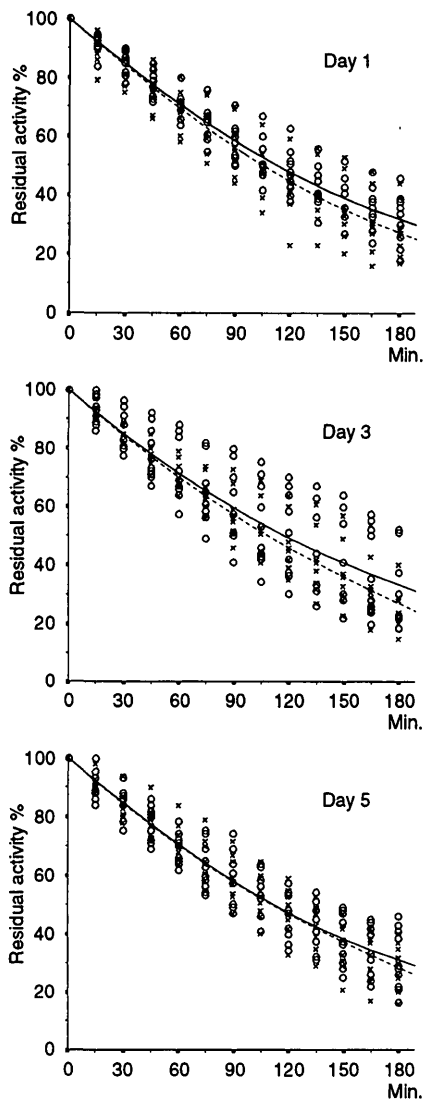

Figure 1—*The residual activity (normalized count rate) of ^{125}I-insulin on days 1, 3, and 5 showing ordinary (x, -------) versus catheter (o,———) injections. The injections were given 15 min before the registration started.*

Statistical analysis

Results are given as means ± SD, except where otherwise stated. Statistical calculations were made using the SPSS statistical package. The method used is stated in the text. Values from two patients were used to calculate that with 10 patients, we would find a difference of no more than 11% in absorption at 60 min significant at the 5% level with 80% power.

RESULTS — The absorption regression lines were quite similar for ordinary versus catheter injections (Fig. 1). The residual ^{125}I-insulin activity at 60 min (Fig. 2) correlated significantly with T-50% (Table 2). We found no significant difference in T-50% or residual ^{125}I-insulin activity at 60 min between ordinary and catheter injections on the different days (Wilcoxon's signed-rank test) nor between catheter or ordinary injections on days 1, 3, and 5, respectively (Friedman's test). The intrapatient coefficient of variation (CV) for T-50% was 14.1% for ordinary injections (median; range 2.5–22.8%) and 17.6% for catheter injections (median; range 2.4–34.5%). The intrapatient CV for the residual ^{125}I-insulin activity at 60 min was 5.9% for ordinary injections (median; range 1.9–9.1%) and 6.8% for catheter injections (median; range 3.7–14.1%).

HbA_{1c} correlated significantly both to T-50% (r = 0,73, P = 0.016) and to residual activity of ^{125}I-insulin at 60 min (r = 0.69, P = 0.028) (Fig. 3), when the mean of the three ordinary injections on days 1, 3, and 5 was used. Blood glucose profiles during the 3 days were without significant differences (Friedman's test).

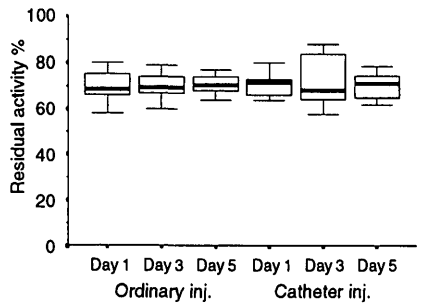

Figure 2—*Boxplot of residual activity of ^{125}I-insulin after 60 min showing median and 25/75 percentile.*

CONCLUSIONS — When using an indwelling catheter, all insulin given through the catheter will be administered at the same site for several days, comparable to the bolus doses of CSII. Pump studies have shown both a constant absorption (8) (9 patients) after 4 days and an increased absorption (9) (15 patients) after 3 days of using the same infusion site. Data from Finland (10,11) (8 patients) show no change in the absorption rate from indwelling catheters (Insuflon) after 4 days of use. These studies all used plasma free insulin to measure insulin absorption. The intra-individual CV in our study was comparable to that of Olsson et al. (8), who found a CV in plasma free insulin of 19% (mean; range 8–30%) after a bolus injection on day 1, 3, and 5. The absorption of insulin is influenced by a variety of factors causing a large interpatient variability with a

Table 2—*Average individual T-50%, residual activity of ^{125}I-insulin at 60 min (residual activity at 60 min), the correlation among these, 95% CIs, and interpatient CV*

Injection type	T-50% (minutes)	T-50% CV (%)	Correlation T-50% and residual activity at 60 min (r/P)	Residual activity at 60 min Percent	Residual activity at 60 min 95% CI	Residual activity at 60 min CV (%)
Ordinary						
Day 1	108 ± 26	24.5	0.95/<0.001	69.6 ± 7.4	64.3–74.9	10.7
Day 3	113 ± 25	22.2	0.87/0.001	70.1 ± 5.5	66.2–74.0	7.8
Day 5	113 ± 18	16.1	0.93/<0.001	71.5 ± 5.7	67.4–75.6	8.0
Catheter						
Day 1	116 ± 22	18.7	0.90/<0.001	70.4 ± 4.9	66.9–73.8	6.9
Day 3	131 ± 50	37.9	0.82/0.004	71.9 ± 10.5	64.4–79.5	14.7
Day 5	115 ± 25	21.4	0.69/0.03	70.4 ± 6.0	66.2–74.7	8.5

Data are means ± SD.

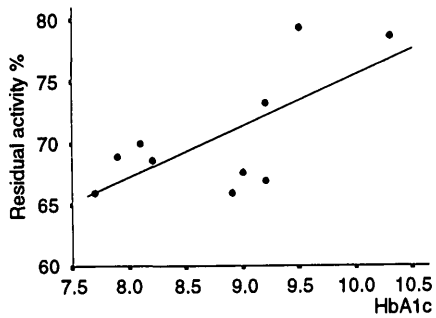

Figure 3—*HbA_{1c} (DCA-2000 method) in relation to residual activity of ^{125}I-insulin at 60 min (mean of the three ordinary injections). r = 0.69, P = 0.028.*

CV of 30–50%, even during stable conditions (12,13). The interpatient CV was in the same size in our study, ranging from 16.1–37.9% for T-50% (Table 2). There is a tendency toward a larger CV on day 3 for catheter injections, compared with both ordinary injections on day 3 and catheter injections on days 1 and 5. Olsson et al. (8) report a wider range of time to reach peak insulin levels on day 3 (41–98 min), compared with both day 1 (45–75) and day 5 (60–75). Liu et al. (9) and Käär and colleagues (10,11) do not report intermediary data.

The null hypothesis that there is no difference in absorption between ordinary and catheter injections on days 1, 3, or 5 could not be rejected because $P > 0.05$. The largest individual difference in residual activity at 60 min was between days 3 and 5 of catheter injections (1.5 ± 9.2%, 95% CI 5.1–8.1; Table 2). To find this difference significant at the 5% level with 80% power, we would have needed 293 patients. However, absence of statistical significance does not prove equality. The 95% CI is the method of choice in this situation to find the clinical significance of our results given the range of expected variation in the population. The 95% CI for the residual activity at 60 min overlaps for both ordinary and catheter injections on all days (Table 2), strongly indicating equality. Because the patient acted with his or her own control on each day of registration by giving an ordinary injection under otherwise identical conditions, the day-by-day comparison is the most representative, with a maximum difference of 6.9% (95% CI day 3, ordinary vs. catheter injections, Table 3) between ordinary and catheter injections, which we find clinically insignificant in comparison with the abovementioned much larger variation of insulin absorption found in clinical practice.

The patient has to lie completely motionless during the registration, which could be a problem when registering for 3 h. However, the residual activity 60 min after the injection also correlates to the T-50% of ^{125}I-insulin absorption (Table 1). Sixty minutes was the time to the peak of plasma free insulin found by Olsson et al. (8) on days 1, 3, and 5 using CSII, while Knip et al. (11) found the peak at 81 ± 5 min on day 1 and 79 ± 8 min on day 5 (data on day 3 were not reported) when using indwelling catheters. Sixty to eighty minutes represents the time when the injected insulin will affect the postprandial blood glucose with the multiple injection treatment that our patients used. Thus, the residual activity of ^{125}I-insulin at 60 min would inversely represent the amount of insulin available in the circulation at that time. The interpatient CV was considerably smaller for the residual ^{125}I-insulin activity at 60 min than for T-50% (Table 2).

The correlation found between absorption rate and HbA_{1c} may be explained by all of our patients having used premeal injections or bolus doses of short-acting insulins. These regimens depend on a fairly rapid absorption of the insulin, even if it is given 30 min before the meal. If the insulin is absorbed more slowly, the individual will have a high postprandial blood glucose resulting in a higher HbA_{1c}.

In conclusion, we did not find a statistically or clinically significant difference in the absorption among insulin injections through subcutaneous indwelling catheters and ordinary subcutaneous injections. However, as shown earlier, there was a large individual difference in the absorption rate of ^{125}I-insulin, both with ordinary and catheter injections.

There is normally a large day-to-day variation in absorption of injected insulin. This variation (and not a decreased absorption) probably explains why some patients experience a deterioration of metabolic control after use of indwelling catheters for a few days. However, a change in absorption resulting in an unexpected change in blood glucose is of course also possible in sporadic cases. This might be the first sign of an infection of the insertion site, and the patient should therefore replace the indwelling catheter as a precaution when home testing is impaired. Also, if the insertion sites are not rotated, there might be a lipohypertrophy, causing decreased absorption of insulin.

Absorption studies with ^{125}I-insulin and a gamma camera with a reading of residual activity at 60 min could be helpful for the individual patient in obtaining information on the rate of absorption, indicating which insulin regimen might be preferable. The relationship between speed of absorption of short-acting insulin and HbA_{1c} is interesting, but needs to be studied further. From this study, we conclude that using indwelling catheters for up to 4 days does not affect the absorption of short-acting insulin when the catheter is inserted in an area free from lipohypertrophies.

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Table 3—*Correlations among modes of injection and injection days and differences and 95% CIs of the residual activity of ^{125}I-insulin at 60 min*

Injection type	Correlation (r/P)	Residual activity at 60 min	
		Difference (%)	95% CI
Ordinary/catheter			
Day 1	0.45/0.19	−0.8 ± 6.8	−5.7–4.1
Day 3	0.79/0.006	−1.8 ± 7.1	−6.9–3.2
Day 5	0.64/0.045	1.1 ± 4.9	−2.5–4.6
Ordinary			
Day 1/day 3	0.43/0.22	−0.5 ± 7.1	−5.6–4.6
Day 1/day 5	0.59/0.08	−1.9 ± 6.4	−6.4–2.6
Day 3/day 5	0.56/0.09	−1.4 ± 5.1	−5.1–2.3
Catheter			
Day 1/day 3	0.68/0.03	−1.5 ± 8.0	−7.3–4.2
Day 1/day 5	0.50/0.15	−0.0 ± 7.6	−5.5–5.4
Day 3/day 5	0.04/0.92	1.5 ± 9.2	−5.1–8.1

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