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# Insulin Aspart

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## Content



## Abstract

▲ Insulin aspart is a recombinant analogue of human insulin. Following subcutaneous insulin injection (0.15 to 0.2 U/kg), significantly higher serum insulin concentrations are achieved in a shorter time with insulin aspart than with human insulin. The subsequent decline in serum insulin concentrations is also more rapid with insulin aspart.

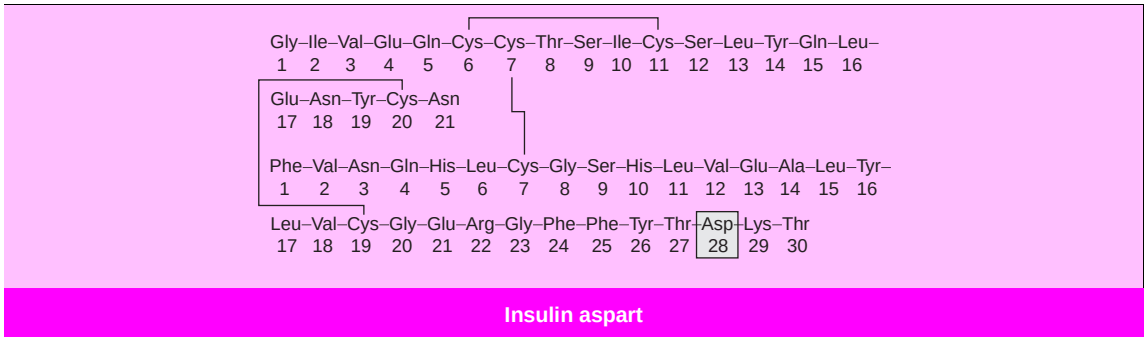
▲ In healthy individuals undergoing euglycaemic glucose clamp testing, glucose infusion rates were higher and reached maximum concentrations significantly earlier after insulin aspart than after human insulin.

▲ Interindividual variability in pharmacodynamic and pharmacokinetic parameters with insulin aspart was generally less than that with human insulin, whereas the intraindividual variability in these parameters was similar after each insulin.

▲ In patients with type 1 diabetes postprandial glucose excursions were less pronounced with insulin aspart than human insulin. Daytime glucose control was better and minimum glucose levels during the night were not as low with insulin aspart as with human insulin.

▲ In diabetic patients treated with insulin aspart there was generally a lower frequency of hypoglycaemic events than in patients treated with human insulin.

| Features and properties of insulin aspart (B28-Asp) | |
|---|---|
| **Indications** | |
| Type 1 & type 2 diabetes mellitus | Late phase III clinical trials |
| **Mechanism of action** | |
| Recombinant insulin analogue | Ornithine carboxylase, phosphokinase and tyrosine kinase stimulant |
| **Dosage and administration** | |
| Usual dosage in clinical trials | 0.15 to 0.20 U/kg bodyweight |
| Route of administration | Subcutaneous |
| Frequency of administration | Before each main meal |
| **Pharmacokinetic profile (after 0.15 to 0.20 U/kg)** | |
| Peak plasma concentration | 334 to 514 pmol/L |
| Time to peak plasma concentration | 32 to 71 min |
| Area under the plasma concentration-time curve for 0 to 2 hours | 3.23 nmol/L • 120 min |
| Area under the plasma concentration-time curve for 0 to 10 hours | 4.33 nmol/L • 600 min |
| **Adverse events** | |
| Most frequent | Hypoglycaemia |




The current treatment of choice for patients with type 1 diabetes mellitus is the injection of human insulin approximately 30 minutes before a meal. This time delay is inconvenient and reduces patient compliance and treatment consistency. Advances in recombinant DNA technology have led to the production of several insulin analogues with single or multiple substitutions in the A or B chains of human insulin. Some of these analogues are more rapidly absorbed from the injection site than human insulin because of a lower tendency for self-association into hexameric complexes. This results in an earlier glucose-lowering effect, avoiding the need for a time delay between the injection and the meal and more accurately mimics the physiological action of insulin in response to food.

Insulin aspart (human insulin B28 Asp), in which the proline at position B28 of the insulin molecule is replaced with a negatively charged aspartic acid residue, is a novel short-acting insulin analogue which consists of a mixture of monomers and dimers in solution.

## 1. Pharmacodynamic Profile

• In a human hepatoma cell line (Hep-G2 cells) insulin aspart had an association rate constant of $3.3 \times 10^5$ and a dissociation rate constant of $2.8 \times 10^{-4}$; which were similar to the values for human insulin ($3.3 \times 10^5$ and $2.5 \times 10^{-4}$, respectively).[1]

• The *in vitro* and *in vivo* potencies of insulin aspart were similar to those of human insulin as assessed by displacement of $^{125}$I-insulin into Hep-G2 cells (79% *vs* human insulin),[2] incorporation of [$^3$H]glucose into lipids (99%)[2] or rat aortic smooth muscle cells [concentration producing 50% maximal effect ($IC_{50}$) of 5.4 *vs* 8.9 pmol/L][3] or a blood glucose assay in mice (104%).[2] However, potency was 104% greater than that of human insulin according to activation of the receptor tyrosine kinase from Hep-G2 cells.[4]

• Glucose infusion rates (GIR) were higher and reached maximum levels significantly earlier after insulin aspart than after human insulin. This was shown in 4 studies in healthy male volunteers (n = 8 to 24) undergoing euglycaemic glucose clamp testing. Two were double-blind,[5,6] but information regarding blinding was not stated in the remainder.[7,8] Monitoring for 4 to 10 hours after doses of 0.15 to 0.20 U/kg revealed values for maximum glucose infusion rate ($GIR_{max}$) ranging from 10.2 to 12.2 mg/kg/min after insulin aspart and 8.4 to 10.6 mg/kg/min after human insulin. The times to reach maximum glucose infusion rate [$t_{max(gluc)}$] were between 104 and 108 minutes, and 146 and 165 minutes and the times to reach 50% of the maximum glucose infusion rate [early $t_{50\%(gluc)}$] were between 41 and 44 minutes, and 58 and 65 minutes for insulin aspart and human insulin, respectively.[5-8]

• Results of 2 trials, not using a glucose clamp technique, and involving 19 and 7 male volunteers who had fasted overnight, also indicated that greater and earlier decreases in plasma glucose concentrations are achieved after insulin aspart than after human insulin.[9,10] Monitoring for 8 hours after a single injection of either insulin aspart or human

insulin (0.1 U/kg) revealed maximum changes in plasma glucose concentration of –2.1 versus –1.4 mmol/L ($p < 0.0001$) after 94 or 226 minutes ($p < 0.0001$), respectively, in one study,[9] and –2.9 versus –1.9 mmol/L ($p < 0.001$) after 65 or 201 minutes ($p < 0.005$), respectively, in the other.[10]

- In several studies the area under the glucose infusion rate curve ($AUC_{gluc}$) after insulin aspart was significantly greater than after human insulin in the first 2 hours but equivalent to human insulin over longer periods.[5-8] In a representative double-blind study in 24 male volunteers (undergoing euglycaemic glucose clamp testing) given 0.2 U/kg insulin aspart or human insulin, the $AUC_{gluc}$ was initially greater with insulin aspart (0 to 2 hours: 0.76 *vs* 0.45 g/kg/120 min in human insulin recipients, $p < 0.001$). However, because of a more rapid return of glucose activity toward baseline levels, as measured by the time to decline to 50% of maximum glucose concentrations [late $t_{50\%(gluc)}$] [256 *vs* 337 min, $p < 0.001$], the $AUC_{gluc}$ values over the entire 10 hour study period for the 2 insulins were not significantly different (2.48 *vs* 2.46 g/kg/600 min).[6]

- Similarly, after 8 hours there was no significant difference between the area between the baseline plasma glucose level and the plasma glucose concentration-time curve after insulin aspart and human insulin (445 *vs* 436 mmol/L · min) in a double-blind, crossover study in which 19 evaluable fasting male volunteers not under glucose clamp conditions were given 0.1 U/kg of each insulin preparation.[9]

- The mean intraindividual variability of pharmacodynamic parameters after treatment with insulin aspart (n = 10) and human insulin (n = 9) [0.2 U/kg each] was similar (≈25%) between 60 and 360 minutes after injection in volunteers. The interindividual coefficient of variation values (CVs) were ≈30 to 50% for both insulins and the interindividual CVs for several main pharmacodynamic parameters were significantly less for insulin aspart than human insulin.[8]

- Insulin aspart reduced postprandial glucose excursions to a greater extent than human insulin in patients with type 1 diabetes (n = 6 to 24) in 3 crossover trials (2 double-blind[11,12] and 1 in which blinding was not stated[13]). For example, peak incremental increases in glucose levels after 72 nmol (≈12 U) of either human insulin (30 minutes before a meal) or insulin aspart (immediately before a meal) were significantly lower in the 4-hour period following the meal in insulin aspart recipients than human insulin recipients (3.6 mmol/L *vs* 6.3 mmol/L, $p < 0.02$). The $AUC_{gluc}$ from 0 to 240 minutes after insulin aspart was 315 mmol/L · min, compared to 737 mmol/L · min after human insulin ($p < 0.02$).[13] In another study that used the same administration schedule (dose not stated) glucose excursion with insulin aspart was 32% less than that after human insulin administered 30 minutes before the meal ($p < 0.0001$) and 16% less than that after human insulin given immediately before the meal ($p < 0.02$).[11] When individualised doses of the 2 insulins were both delivered immediately before the meal, maximum blood glucose levels of 9.3 versus 12.8 mmol/L were reached in 60 and 90 minutes after insulin aspart and human insulin, respectively.[12]

- In patients with type 2 diabetes administration of insulin aspart immediately prior to a meal resulted in improved postprandial glucose control compared with human insulin at the same time ($hIns_0$), but similar control to human insulin administered 30 minutes before the meal ($hIns_{30}$). Glucose excursion from 0 to 6 hours was significantly smaller after insulin aspart (899 mmol/L · min) than after $hIns_0$ (1101 mmol/L · min; $p = 0.01$), but not different from that after $hIns_{30}$ (868 mmol/L · min). Maximum serum glucose concentration was also significantly lower after insulin aspart than after $hIns_0$ (10.8 *vs* 12 mmol/L; $p < 0.02$), but similar to $hIns_{30}$ (11 mmol/L).[14]

- There was less variability in postprandial glucose levels after insulin aspart than after human insulin for 2 of 3 meals over 24 hours in a randomised, double-blind, sequential study in 11 male patients with type 1 diabetes. Insulin doses were

adjusted to keep blood glucose levels between 4.0 and 7.0 mmol/L. Mean increases in plasma glucose levels after the morning and afternoon injection of insulin aspart were significantly less than those after human insulin. Conversely, there was no significant difference between treatments after the noon injection (fig. 1). The mean time to reach maximum glucose levels after breakfast was 55 minutes with insulin aspart treatment, which was not significantly different from that with human insulin (74 minutes). Similar findings were reported after other mealtimes (values not reported).[15]

## 2. Pharmacokinetic Profile

• In scintigraphic studies in rats, insulin aspart was taken up into the liver and kidneys in a pattern similar to that of human insulin.[16]

• Insulin aspart was absorbed approximately twice as fast as human insulin in 7 male volunteers randomly given a subcutaneous dose of each insulin (0.6 nmol/kg ≈ 0.1 U/kg) in a randomised, crossover trial (blinding not stated). The time to 50% residual radioactivity at the injection site was 83 minutes after insulin aspart compared with 182 minutes after human insulin.[10]

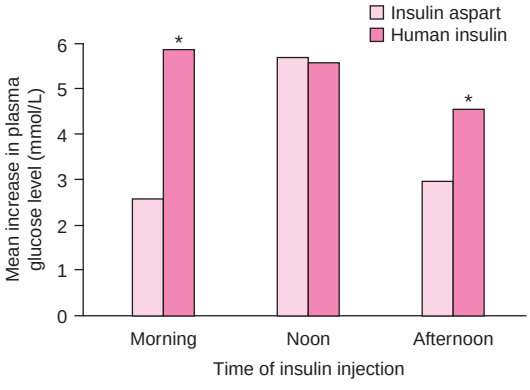



**Fig. 1.** Blood glucose variations over 24 hours in 90 patients with type 1 diabetes after 4 weeks treatment with insulin aspart or human insulin (mean doses 40.9 and 39.7 U/day, respectively) in a multicentre, randomised, double-blind, crossover trial.[15] *p < 0.02 versus insulin aspart.

• Serum insulin levels were significantly higher and maximum levels were attained significantly earlier following treatment with insulin aspart than with human insulin in healthy volunteers. In studies that did not use glucose clamping, in which individuals fasted overnight, maximum serum concentrations [$C_{max(ins)}$] after insulin aspart versus human insulin (0.1 U/kg) were 246 versus 108 pmol/L ($p < 0.0001$) in one study[9] and 227 versus 133 pmol/L ($p < 0.005$) in another;[10] the time to $C_{max(ins)}$ [$t_{max(ins)}$] values were 52 and 145 minutes ($p < 0.0001$)[9] and 39 and 80 minutes (not significant), respectively.[10] In individuals under euglycaemic glucose clamp conditions, $C_{max(ins)}$ values ranged from 334 to 514 pmol/L and were achieved 48 to 71 minutes after insulin aspart (0.15 to 0.20 U/kg), whereas serum insulin concentrations after human insulin (same dose) plateaued at 45 to 60 minutes before $C_{max(ins)}$ values of 195 to 288 pmol/L were attained after 97 to 133 minutes in 4 crossover trials (2 double-blind[5,6] and 2 in which blinding was not stated[7,8]).

• After $C_{max(ins)}$ was attained, serum insulin concentrations declined more rapidly after injection of insulin aspart than after human insulin. Results from 10-hour observations of male volunteers (n = 8 and 24) enrolled in crossover studies (1 double-blind,[6] 1 in which blinding was not stated[7]) showed that serum insulin concentrations had returned to baseline values 311 or 343 minutes after insulin aspart (0.2 U/kg), significantly earlier ($p < 0.001$) than after the same dose of human insulin (474 or 496 minutes). Mean residence time in a double-blind crossover trial in 19 male volunteers was 149 minutes after insulin aspart (0.1 U/kg), compared with 217 minutes after the same dose of human insulin ($p < 0.0001$).[9]

• The area under the concentration time curve for serum insulin ($AUC_{ins}$) soon after injection was greater after insulin aspart than after human insulin. However, over longer time periods the values for the 2 insulins were similar.[6-8] Results from a representative double-blind, crossover trial in which 24 healthy male volunteers were observed under euglycaemic glucose clamp conditions over 10

hours showed that $AUC_{ins}$ values between 0 and 2 hours after insulin aspart (0.2 U/kg) were significantly greater than those after the same dose of human insulin (3.23 *vs* 1.75 nmol/L · 120 min, $p < 0.001$). However, when the entire 10-hour period was considered $AUC_{ins}$ values for each insulin preparation were similar (4.33 *vs* 4.75 nmol/L · 600 min).[6] Results from non-glucose-clamped male volunteers, who had fasted overnight (n = 19), indicated that $AUC_{ins}$ values from 0 hours to ∞ were similar following treatment with 0.1 U/kg of either insulin aspart or human insulin (6740 ± 1294 *vs* 6961 ± 4192 mU/L · min).[9]

• After insulin aspart (0.2 U/kg) there was lower intraindividual variability in $t_{max(ins)}$ and lower interindividual CVs in $C_{max(ins)}$, $t_{max(ins)}$ and $AUC_{ins}$ over 0 to 2 hours than after the same dose of human insulin in 10 and 9 healthy volunteers, respectively.[8]

• $C_{max(ins)}$ values were significantly higher and were reached significantly earlier after insulin aspart than after human insulin in patients with type 1 diabetes in 3 crossover trials (2 double-blind,[11,12] 1 in which blinding was not stated[13]). For example, plasma free insulin concentrations peaked at 32 minutes after injection of 72 nmol (≈ 12 U) insulin aspart (administered immediately before a meal) compared with 111 minutes after the same dose of human insulin (given 30 minutes before a meal) [$p < 0.05$]. The 30-minute postmeal free insulin concentrations were also significantly higher after insulin aspart than after human insulin (414 *vs* 157 pmol/L, $p < 0.001$).[13] In another study which used the same administration schedule (dose not stated) a $C_{max(ins)}$ value of 493 pmol/L after 39 minutes was achieved after insulin aspart compared with 239 pmol/L ($p < 0.0001$) after 85 minutes ($p < 0.01$) after human insulin.[11] When individualised doses of both insulins were given immediately before the meal, serum free insulin concentrations peaked at 356.0 pmol/L 45 minutes after injection of insulin aspart, whereas after human insulin, concentrations peaked at 252.6 pmol/L 90 minutes after injection.[12] $AUC_{ins}$ values were 264 mol/L · min and 196 mol/L · min, respectively, for insulin aspart and human insulin ($p < 0.05$).[12]

## 3. Therapeutic Potential

• The efficacy of insulin aspart has been evaluated in a multicentre, randomised, double-blind, crossover trial in 90 patients with type 1 diabetes. Insulin aspart or human insulin were administered for 4 weeks each, before each meal to optimise blood glucose control (mean dose 40.9 U/day insulin aspart; 39.7 U/day human insulin). Over a 24-hour period, the glucose excursion outside the range of 4.0 to 7.0 mmol/L was significantly less pronounced (22% less) with insulin aspart than with human insulin. Mean 24-hour $AUC_{gluc}$ values outside the range of 4.0 to 7.0 mmol/L were calculated as 4713 mmol/L · min after insulin aspart and 5260 mmol/L · min after human insulin ($p < 0.01$).[17] However, serum fructosamine levels were not significantly different between insulin treatments (insulin aspart 3.76 mmol/L *vs* human insulin 3.82 mmol/L) indicating no difference in blood glucose control. Daytime glucose control, as assessed by maximum and minimum glucose levels, was better with insulin aspart than with human insulin, whereas during the night minimum glucose levels were not as low with insulin aspart as with human insulin (fig. 2).[17]

## 4. Tolerability

• The incidence of hypoglycaemic events after administration of insulin aspart was similar or less frequent than after human insulin in double-blind, randomised, crossover trials of single, individualised doses of insulin aspart or human insulin before a meal.[12,15] A total of 16 hypoglycaemic events (8 after each insulin) with blood glucose levels ≤3.3 mmol/L occurred in 9 patients out of 14 in 1 study.[12] In contrast, there were significantly more hypoglycaemic events after human insulin (17 in 10 patients) than after insulin aspart (11 in 17 patients, $p < 0.05$) in another trial.[15]

• In a double-blind, randomised study involving 16 patients with type 1 diabetes receiving 2.0

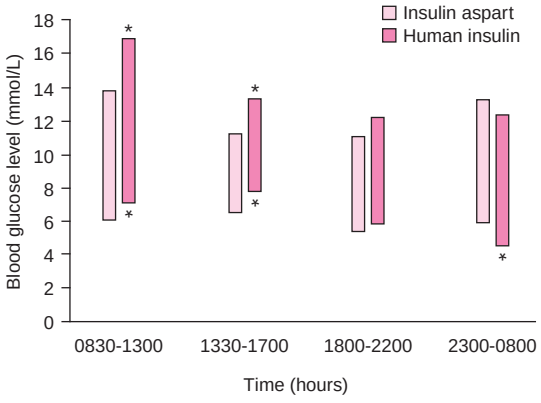



**Fig. 2.** Mean increase in plasma glucose levels in 11 patients with type 1 diabetes after pre-meal treatment with either insulin aspart or human insulin. Doses were individually adjusted throughout a 1 day study period in this randomised, double-blind, sequential study.[17] *p < 0.05 versus insulin aspart.

mU/kg/min of either human insulin or insulin aspart (a dosage selected to induce hypoglycaemia), it was shown that the sympatomatic and physiological responses to hypoglycaemia induced by the 2 insulins did not differ significantly. Heart rate, systolic blood pressure, hypoglycaemia symptoms and counterregulatory hormone levels were similar in each case.[18]

• The total number of hypoglycaemic events was similar after both insulins in a randomised, double-blind trial including 90 patients with type 1 diabetes given insulin at doses intended to optimise blood glucose control (mean dose 40.9 æ 13.6 U/day insulin aspart; 39.7 ± 13.5 U/day human insulin) before each main meal for 4 weeks. However, there were significantly fewer major hypoglycaemic episodes (in which the patient required help from a third party) with insulin aspart than with human insulin (20 events in 16 subjects *vs* 44 events in 24 subjects, $p < 0.002$). Furthermore, the incidence of hypoglycaemic events during the last 2 weeks of the study with insulin aspart was half that with human insulin (11 *vs* 22 events, $p < 0.05$).[17]

• In the above study, 81 adverse events (excluding mild to moderate hypoglycaemia) were reported with insulin aspart compared to 66 adverse events with human insulin (no significant difference). Of these only 5 and 8 of the reported events with insulin aspart and human insulin, respectively, were assessed as bearing some relationship to insulin. With insulin aspart these included fatigue, anorexia, vomiting, pyrexia and hypoglycaemia with convulsions, whereas after human insulin, serious adverse events included confusion and hypoglycaemia with convulsions. Measurements of insulin antibodies were made in 83 individuals before and after the trial and the difference in change from baseline (i.e., change with insulin aspart minus the change with human insulin) was not significant between treatments (0.4 ± 3.0%).[17]

## 5. Insulin Aspart: Current Status

Insulin aspart is a recombinant analogue of human insulin that is in late phase clinical trials. It has shown clinical efficacy and a faster onset of action in the treatment of type 1 diabetes and may provide better glucose control than normal human insulin. Insulin aspart is well tolerated.

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