Synopsis of the original article ‘Hypoglycaemia frequency and physiological response after double or triple doses of once-weekly insulin icodect vs once-daily insulin glargine U100 in type 2 diabetes: a randomised crossover trial’

Pieber TR, et al. Diabetologia 2023;DOI 10.1007/s00125-023-05921-8

Synopsis created and reviewed by Novo Nordisk
Introduction

This study compared the
• frequency of hypoglycaemia
• time to hypoglycaemia
• recovery from hypoglycaemia
after double or triple doses of icodec vs glargine U100

Furthermore, the
• symptomatic response
• counterregulatory response
to hypoglycaemia were compared
between icodec and glargine U100
Methods

Overall trial design

Randomised
Open-label
Two-period
crossover

43 individuals
with type 2
diabetes

Methods

Hypoglycaemia induction at steady state following double and triple doses

Plasma glucose

5.5 mmol/l

○ Assessment of hypoglycaemic symptoms score, counterregulatory hormones, vital signs and cognitive function

5.5 mmol/l

Constant intravenous glucose (5.5 mg kg⁻¹ min⁻¹)

3.0 mmol/l

2.5 mmol/l
Results – Glucodynamics after double/triple doses

Proportion of individuals with clinically significant hypoglycaemia

<table>
<thead>
<tr>
<th></th>
<th>Double dose</th>
<th>Triple dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icodec</td>
<td>39.5%</td>
<td>52.6%</td>
</tr>
<tr>
<td>Glargine U100</td>
<td>35.7%</td>
<td>70.0%</td>
</tr>
</tbody>
</table>

Proportion of individuals with PG\text{nadir} \leq 2.5 \text{ mmol/l}

<table>
<thead>
<tr>
<th></th>
<th>Double dose</th>
<th>Triple dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icodec</td>
<td>4.7%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Glargine U100</td>
<td>2.6%</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

* p = 0.03

Time to decline from PG\text{5.5 mmol/l} to PG\text{3.0 mmol/l}

- Double dose: 2.9–4.5 h
- Triple dose: 2.2–2.4 h
- No statistically significant treatment difference

Recovery from hypoglycaemia

- Took <30 min for all treatments at a constant i.v. glucose infusion rate of 5.5 mg kg\textsuperscript{-1} min\textsuperscript{-1}

I.v., intravenous; PG, plasma glucose
Results – Physiological response to hypoglycaemia

Participants included in subgroup analysis

<table>
<thead>
<tr>
<th>PG_{nadir} &lt; 3.0 mmol/l</th>
<th>Hypoglycaemic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icodec</td>
<td>20 (46.5%)</td>
</tr>
<tr>
<td>Glargine U100</td>
<td>19 (45.2%)</td>
</tr>
<tr>
<td>Icodec</td>
<td>20 (52.6%)</td>
</tr>
<tr>
<td>Glargine U100</td>
<td>29 (72.5%)</td>
</tr>
</tbody>
</table>

Counterregulatory hormones

- All (glucagon, adrenaline, noradrenaline, cortisol, growth hormone) increased during hypoglycaemia with both insulin products at both dose levels
- Greater response for icodec vs glargine U100 after triple dose:

<table>
<thead>
<tr>
<th>Treatment ratio^{a} [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline at PG_{3.0 mmol/l}</td>
</tr>
<tr>
<td>Cortisol at PG_{3.0 mmol/l}</td>
</tr>
<tr>
<td>Cortisol at PG_{nadir}</td>
</tr>
</tbody>
</table>

Other responses to hypoglycaemia

- No statistically significant treatment differences in hypoglycaemic symptoms score, vital signs and cognitive function

^{a} Icodec vs glargine U100
CI, confidence interval; PG, plasma glucose
Double or triple doses of once-weekly icodextr lead to a similar risk of hypoglycaemia compared with double or triple doses of once-daily glargine U100.

During hypoglycaemia, comparable symptomatic and moderately greater endocrine responses are elicited by icodextr vs glargine U100.

Plasma glucose

3.0 mmol/l

Hypoglycaemic symptoms

Counterregulatory hormone response