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W Crasto,1 J Jarvis,1 E Hackett,1 V Nayyar,1 P G McNally,1 M J Davies,1,2 I G Lawrence1

ABSTRACT

Some patients with type 2 diabetes mellitus (T2DM) are profoundly insulin resistant and require large insulin doses to achieve optimal glycaemic control. However, large volumes of subcutaneous conventional U-100 insulin can cause discomfort at the injection site, resulting in poor concordance with insulin therapy. One therapeutic option is the use of U-500 insulin, thus reducing the insulin volume by 80%. This review will address the practical issues associated with the use of U-500, clinical efficacy and safety aspects of this concentrated insulin, which has an important role in a subgroup of patients with T2DM.

The rising prevalence of obesity is presenting major challenges for chronic diseases such as type 2 diabetes mellitus (T2DM), with a huge impact on healthcare resources. Moreover, there is a considerable burden of disability and morbidity from cardiovascular disease and diabetes related complications. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that early and tight glycaemic control (aiming for a glycosylated haemoglobin (HbA1c) of <7%) can reduce the incidence of complications, though this is rarely achieved in clinical practice.

SEVERE INSULIN RESISTANCE IN T2DM

Average insulin requirements in patients with T2DM are approximately 80 units/day—that is, 0.5–0.8 IU/kg/day. The presence of more pronounced IR increases the insulin requirements to 1–2 IU/kg/day, and exceptionally insulin requirements as high as 566 IU/kg/day have been used in syndromic forms of IR (IR linked to genetic syndromes).14 15 “Severe insulin resistance” is defined as “insulin requirements in excess of 200 units a day for more than 2 days”. However, such large volumes of insulin (for example, 2 ml with a dose of 200 units of U-100 insulin) can be painful, and cause considerable discomfort at the local site of injection. Severe insulin resistance in T2DM can present in a number of conditions:

- Obesity
- Stressful conditions such as severe infection, pregnancy or steroid use
- Endocrine and IR related disorders—polycystic ovary syndrome, haemochromatosis, Cushing syndrome, Werner syndrome, acanthosis nigricans, HAIR-AN syndrome (hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN)), and lipodystrophy (congenital and acquired)
- Genetic defects of the insulin receptor gene (type A syndrome, Leprechaunism, and Rabson–Mendenhall syndrome)
- Insulin receptor antibodies.
Obesity, infections and pregnancy are the most common causes of severe insulin resistance. Clinical experience shows that relatively large doses of insulin are required to keep the blood glucose within near normal ranges in these conditions. Since the definition of insulin resistance adopted in most cases is largely clinical, it is not possible to comment on whether improved glycaemic control is associated with reduction in IR.

INSULIN U-500

Insulin is standardised so that each unit of insulin contains 0.56 μg of insulin. It is available in U-10 strength for paediatric use, whereas there are different strengths and dilutions available for adult usage throughout the world. In the UK, almost all the insulin use is U-100 (that is, 100 units of insulin/ml). In contrast, U-500 insulin contains 500 units of insulin/ml. U-500 Human Actrapid (NovoNordisk) has been recently discontinued, but U-500 Humulin R (Eli Lilly) is available in the UK on a “named patient basis”. Since U-500 insulin is unlicensed in the UK, general practitioners are not obligated to provide it on an ongoing basis. Unfortunately it may therefore be difficult for some patients to collect repeat supplies from the hospital, and hence ongoing care plans and supervision from hospital staff responsible for patients on this insulin formulation is required.

Biosynthesis and pharmacokinetics

Humulin R U-500 is synthesised by genetic modification of Escherichia coli for human insulin production. It consists of zinc–insulin crystals dissolved in a clear fluid. Each ml contains 500 units of human insulin, 16 mg glycerine, 2.5 mg metacresol and sodium hydroxide and/or hydrochloric acid may be added to adjust the pH. Humulin R (U-500) is only available in a 20 ml vials and must be used for subcutaneous injection. Intravenous and intramuscular routes of administration are not advised.

U-500 has an onset of action of 30 min, a peak onset of action of 1–3 h, and duration of action of lasting up to 8 h. In patients with insulin receptor abnormalities this may be further prolonged (lasting up to 24 h) due to problems with insulin degradation.

CLINICAL EFFICACY

The clinical efficacy of U-500 in reported case series is listed in table 1.

Syndromic forms of insulin resistance

In a series of 45 patients with extreme forms of insulin resistance, Cochran and colleagues reported insulin dose requirements from 3 to >500 units/kg per day. Insulin U-500 was used in all cases though individual reports have suggested that novel forms of therapy—that is, use of recombinant leptin in patients with severe lipodystrophy—may have resulted in improved metabolic performance.

Subcutaneous use of U-500 regular pork insulin reduced insulin requirement by one third to one quarter in a patient with insulin resistance. The resistance was not immunologic in this patient but mediated at target organ level due to a receptor/post-receptor defect. In another case report, insulin requirements reduced notably (55–75%) when U-500 insulin was used instead of U-100 insulin in a patient with antibody induced IR.

In T2DM obese patients

Garg et al reported a case series of 16 insulin treated obese T2DM patients describing their experiences with the use of U-500 Human Actrapid. A mean reduction in HbA1c of 2.37% was observed over a 2 year period and 47% achieved HbA1c targets of <7.5%. No significant increases in weight, blood pressure or lipid profiles were seen.

We have recently reported long term follow up of patients on U-500 Human Actrapid. This retrospective audit reviewed 81 patients with T2DM on U-500 Human Actrapid over a mean duration of 30 months. Mean (SD) HbA1c improved from 10.0 (1.5)% to 8.9 (2.0)% (p<0.001), whereas mean insulin doses increased from 311.3 (111.5) vs 368.4 (179.9) units/day and weight increased from 116.2 (27.1) kg vs 121.3 (29.3) kg (p<0.001). However, the number of patients achieving an HbA1c <7.5% increased from 5.1% (4 patients) to 27.5% (23 patients) (p<0.0001). Patients taking U-500 for a longer period (>36 months) showed a greater reduction in HbA1c compared to those who had taken U500 insulin for a shorter period (<36 months): 1.8 (1.5)% vs 0.99 (1.8)% (p<0.05).

CSII

A case series using U-500 insulin via CSII in four patients demonstrated a fourfold decline in insulin doses and associated improved glycaemic control (HbA1c reduction of 3.5% at 6 months) compared with U-100 insulin. A review of six patient records using U-500 in insulin pumps showed a drop in mean (SD) HbA1c from 9.1 (1.8)% to 6.9 (0.9)% (p=0.05) at 6 months. Mean doses of insulin usage decreased and patients lost a mean weight of 6.1 lb (2.8 kg) with no significant hypoglycaemia.

INITIATION, DOSE ADJUSTMENT AND TITRATION OF U-500 INSULIN

Guidelines for the use of U-500 insulin have yet to be written and so it is likely that protocols for starting U-500 insulin differ

<table>
<thead>
<tr>
<th>Study</th>
<th>No of subjects</th>
<th>Duration in months</th>
<th>HbA1c reduction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garg et al</td>
<td>16</td>
<td>24</td>
<td>−2.37% (p&lt;0.001)</td>
<td>Obese T2DM; reduction in insulin doses; modest weight gain</td>
</tr>
<tr>
<td>Nayyar et al</td>
<td>81</td>
<td>30</td>
<td>−1.2% (p&lt;0.001)</td>
<td>T2DM patients on metformin; no significant weight gain; target HbA1c of &lt;7.5% in 22.5%</td>
</tr>
<tr>
<td>Bulchandani et al</td>
<td>6</td>
<td>6</td>
<td>−2.2% (p=0.03)</td>
<td>T2DM patients using U-500 by CSII; weight loss of 6.1 lb (2.8 kg); higher patient satisfaction with U-500 pump therapy</td>
</tr>
<tr>
<td>Knee et al</td>
<td>4</td>
<td>6</td>
<td>−3.5% (p&lt;0.001)</td>
<td>T2DM using U-500 by CSII; subjective improvement in QOL</td>
</tr>
<tr>
<td>Wafa WS et al</td>
<td>15</td>
<td>12</td>
<td>−2.2% (p&lt;0.001)</td>
<td>T2DM patients; weight gain 1.6%; no change in hypoglycaemic events after treatment</td>
</tr>
<tr>
<td>Neal JM et al</td>
<td>20</td>
<td>6</td>
<td>−1.7% (p&lt;0.001)</td>
<td>T2DM patients; no change in insulin doses or BMI</td>
</tr>
<tr>
<td>Ballani P et al</td>
<td>9</td>
<td>6</td>
<td>−2.5% (p&lt;0.001)</td>
<td>T2DM patients; non-significant increase in insulin doses; weight gain 4.7 kg (p&lt;0.01)</td>
</tr>
<tr>
<td>Lane WS et al</td>
<td>9</td>
<td>3</td>
<td>−1.1% (p=0.026)</td>
<td>T2DM patients using U-500 by CSII; weight gain 4.1 lb (1.9 kg) (p=0.078), no significant change in insulin dose (p=0.622); no clinically significant hypoglycaemic episodes</td>
</tr>
</tbody>
</table>

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HbA1c, glycosylated haemoglobin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; QOL, quality of life.
between centres. U-500 insulin is usually started when insulin dose requirements exceed >200 units per day. Ballani and colleagues suggest that patients with an HbA1c of >8.5%, despite dose titration with U-100 and monitoring by a healthcare professional over at least 6 months and high insulin doses as mentioned above, should prompt use of U-500.20

U-500 can be easily introduced in the outpatient clinic by a diabetes specialist (nurse or physician). Clear instructions should be given to the patient and their carers and/or family members at the time of initiation. Since insulin delivery is not possible with the use of insulin pens, patients need to use conventional insulin syringes. Usually 0.5 ml syringes are used. A particular practice with U-500 is to designate 0.01 ml of U-500 insulin as 1 “mark” instead of the conventional 1 “unit”. This correlates to 1 mark on the 0.5 ml insulin syringe and is equal to 5 units of U-100. This potentially helps patients to differentiate between U-500 and U-100 insulin. Patients are reminded that switching to U-500 means that they are on five times their original insulin doses and small incremental changes in a dose of U-500 insulin can potentially cause greater shifts in blood glucose readings.

Once U-500 is initiated, frequent contact with the diabetes team is recommended. Close liaison with the manufacturer and the hospital pharmacy stocking U-500 supplies is needed to ensure continued availability. Alerts on all relevant patient medical records including computerised records is mandatory and should be entered at the initiation visit.

Intensive insulin therapy achieves good glycaemic control not only with timely use of insulin but also titrating insulin doses with regular blood glucose monitoring. Self management skills must be taught to every patient so that they can titrate insulin doses more effectively.

U-500 can be administered in a basal bolus regimen, though this is not generally recommended. One of the reasons for this is because patients can be on exceptionally large doses of background insulin and U-500 can potentially reduce this requirement by offering lower volumes of injection. Therefore, U-500 can be administered four times a day, which also includes a bedtime injection. Alternately, Cochran and colleagues have suggested that for insulin doses between 300–750 units a day, three injections would suffice whereas for doses between 750–2000 units a day, four injections must be given.

SAFETY ASPECTS

To avoid the possibility of drug administration errors, the American Diabetes Association recommends that special precautions should be exercised.15 U-500 insulin should be clearly labelled and stored separately from the conventional strength U-100 insulin.

U-500 has the word “concentrated” marked on the vial and comes in a much larger vial size (20 ml), and this must be explained carefully to the patient and all family members/carers. This is very important particularly in situations when another member within the same household is on U-100 insulin therapy, making it imperative that different storage areas are used at all times. This is of equal relevance when patients are admitted to hospital and the onus falls on hospital staff to exercise great caution.

A recent statement from the Institute for Safe Medication Practices (ISMP) recently emphasised this point. Their recommendations suggest that the word “concentrated” should precede “U-500”, which is yet another measure designed to ensure safety and avoid errors in prescribing.

PRACTICAL ISSUES

Patients need to be instructed regarding their dosage and should be reminded that this formulation requires the administration of a smaller volume of solution than is the case with less concentrated formulations. During hospital admissions patients are advised to take their own “insulin kits” rather than rely on hospital supplies, and explicit care should be taken to store their insulin separately to avoid serious drug administration errors to other patients. An important feature with regards to prescribing U-500 insulin is that the currently marketed formulation which is Humulin R closely mimics the other Humulin insulin formulations which require a letter after the name to identify one type of insulin from another—for example, Humulin S, Humulin I, Humulin R. This may cause potential errors in prescribing.

Experience with the use of U-500 insulin in insulin pumps has been reported in case reports as mentioned above, though important considerations are the potential to cause prolonged and severe hypoglycaemia and the difficulties with accurate “bolus dosing” with U-500 insulin.

WEIGHT GAIN

Weight gain is a potential concern with insulin therapy. This is particularly relevant when patients are treated with intensive insulin regimens to control hyperglycaemia. Literature reports on patients receiving U-500 confirm increases in weight, though some case series have demonstrated that weight gain is modest and probably attributable to the improvement in glycaemic control.

PATIENT SATISFACTION

There are clear benefits to using U-500—for example, smaller volumes of insulin, injections that are not as painful as standard insulin, and better glycaemic control. So it is assumed that patients will be more concordant with treatment recommendations though no formal studies on patient satisfaction with U-500 have been carried out.

COST IMPLICATIONS

Cost comparisons between insulin preparations with comparisons between the available U-100 formulations and U-500 have been described in the literature.15 21 (For most recent cost comparisons refer to table 2). Similar costs have been noted in patients using a basal bolus regimen with U-500 Human Actrapid and glargine insulin.21

CONCLUSION

The management of insulin therapy in the patient with T2DM and profound IR is a therapeutic challenge, and a number of strategies have been adopted over the years. Lifestyle interventions

Table 2 Cost comparisons between U-500 and U-100 in the UK (costings from 2008)

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Vial size</th>
<th>Price per vial</th>
<th>Price per ml</th>
<th>Price per 10 units</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 aspart</td>
<td>10 ml</td>
<td>£17.27 (£19, US$24)</td>
<td>£1.73</td>
<td>£0.17</td>
</tr>
<tr>
<td>U-100 lispro</td>
<td>10 ml</td>
<td>£17.28 (£19, US$24)</td>
<td>£1.73</td>
<td>£0.17</td>
</tr>
<tr>
<td>U-100 glargine</td>
<td>10 ml</td>
<td>£28.00 (£33, US$36)</td>
<td>£2.60</td>
<td>£0.26</td>
</tr>
<tr>
<td>U-100 detemir</td>
<td>5 x 3 ml cartridges</td>
<td>£39.00 (£43, US$54)</td>
<td>£2.60</td>
<td>£0.26</td>
</tr>
<tr>
<td>U-500 (Humulin R)</td>
<td>20 ml</td>
<td>£52.75 (£68, US$121)</td>
<td>£7.64</td>
<td>£0.15</td>
</tr>
</tbody>
</table>
Key learning points

- U-500 insulin is an acceptable alternative when conventional U-100 insulin dose requirements exceed 200 units per day, in severely insulin resistant, insulin treated patients with T2DM and poor glycaemic control.
- Although the definition of insulin resistance adopted in most cases is largely clinical, severe insulin resistance is defined "insulin requirements in excess of 200 units of U-100 insulin a day for 2 days".
- U-500 insulin is concentrated insulin (500 units/ml), smaller injection volumes are needed, and injections are not as painful as standard insulin with improvements in glycaemic control.
- U-500 Humulin R (Eli Lilly) is unlicensed in the UK; however, it is used at many diabetes centres in the UK on a "named patient basis" and can be easily commenced by a hospital specialist (nurse or physician) on an outpatient basis.
- Practical considerations while using this insulin are potential prescribing errors, hypoglycaemia, delivery with conventional insulin syringes rather than insulin pens and limited knowledge among health professionals.

including weight reduction and exercise should be recommended, but may be difficult to implement for the patient with long-standing morbid obesity and poor mobility, and a small number of patients continue to experience poor glycaemic control despite escalating doses of conventional U-100 insulin.

In our retrospective audit of subcutaneous use of U-500 Human Actrapid via MDII (unpublished data) in 19 patients with T2DM, a substantial improvement in glycaemia occurred, and by 24 months, mean HbA1c of 8.17 (1.87)% (range 5.3–11.3%) within 3 months. A further gradual improvement in glycaemia occurred, and by 24 months, mean HbA1c was 7.81 (1.23)% (p = 0.0004). A reduction in HbA1c of 3.15% is impressive in any setting, and it is noteworthy that 42.1% of patients remaining on U-500 Human Actrapid achieved and maintained an HbA1c <7.5%, which is the target glycaemic control for the Diabetes National Service Framework in England.28 This audit was of routine clinical practice, and quality of life questionnaires were not undertaken; however, many patients described a notable improvement in well being.

In summary, U-500 insulin is an acceptable alternative to the use of large doses of conventional U-100 insulin in severely insulin resistant, insulin treated patients with T2DM and poor glycaemic control. The mechanism of improved glycaemic control with the use of U-500 insulin is likely to be due to a composite of both optimisation of insulin therapy and improved concordance. U-500 insulin is only available in vials and thus needs to be given via a syringe and needle; however, the reduction of insulin volume by 80% results in a substantial reduction in injection site discomfort, and hence potentially improved concordance. It is important that this insulin continues to be available as a therapeutic tool to achieve glycaemic targets, which will potentially contribute to reducing the incidence of diabetes related complications in this difficult group of patients.

Competing interests: None declared.

REFERENCES


Key references