

# Clinical use of Humulin R U-500 insulin in the UK: results of the first Association of British Clinical Diabetologists' U-500 audit

UMESH DASHORA,<sup>1</sup> ANDREW MACKLIN,<sup>2</sup> BOB RYDER,<sup>3</sup> ERWIN CASTRO,<sup>1</sup> ABCD NATIONWIDE U-500 AUDIT CONTRIBUTORS<sup>4</sup>

## Abstract

**Human soluble insulin Humulin R U-500 has been in use worldwide for marked insulin resistance but is not specifically licensed in the UK. The Association of British Clinical Diabetologists conducted a nationwide audit of Humulin R U-500 to understand its use in the UK. The results show that 67 out of 119 clinicians who responded to the survey are using U-500R. The commonest indication for using it was a high daily insulin dose. These results are the first glimpse of the practical usage of high strength insulin in the UK and may help our approach to patients with high insulin resistance and the use of newly available higher concentration insulins.**

*Br J Diabetes* 2016;**16**:185-187

**Key words:** U-500, insulin, type 2 diabetes, weight, hypoglycaemia, ABCD

## Introduction

Humulin™ R regular U-500 (U-500) has been in use worldwide for many years and is generally used in patients with high insulin resistance to reduce the volume and number of injections. There are no data on its use in the UK, where it is not currently licensed for use.

The activity profile for U-500 is shorter in onset, with a delayed but prolonged peak and extended duration compared with human soluble insulin U-100 (U-100).<sup>1,2</sup> Efficacy studies of U-500 have already been published.<sup>3,4</sup> In a retrospective database analysis, U-500 was found to be more economical in pharmacy and overall cost and compliance but with a slightly higher rate of hypoglycaemia compared with U-100.<sup>5</sup> Variability in absorption from day to day and from different parts of the body appears to be

lower than for U-100.<sup>6</sup> The onset, peak action and duration is more similar to neutral protamine Hagedorn (NPH) insulin than to human soluble insulin and the effect can last for 24 hours or more.<sup>6,7</sup> The recommended doses are therefore twice daily, unless the requirement is very high when a third dose or administration via an insulin pump may be considered.<sup>8-10</sup> U-500 can reduce mean HbA<sub>1c</sub> with fewer injections, but the body weight, insulin dose and hypoglycaemic episodes increase.<sup>11,12</sup> There is an added risk of error with U-500 as there is no dedicated device for administration. The use of syringes calibrated for U-100 insulin means that the dose indicated does not match the number of units delivered, increasing the chance of user error. As this insulin remains unlicensed in the UK, there are issues of funding and responsibility for treatment within the NHS structure.

## Concentrated insulin for insulin pump

Concentrated insulins in insulin pumps have not been adequately studied. None of the pumps are calibrated for dosing concentrated insulin and the risk of errors in dosing mirror those of using a syringe. U-500 dose rates and ratios may be converted either by dividing or multiplying by 5 for continuous subcutaneous insulin infusion (CSII).<sup>13-15</sup> U-500 in insulin pumps has been evaluated in small retrospective studies and one prospective study, as well as a few case reports.<sup>13-16</sup>

## Methods

Members of the Association of British Clinical Diabetologists (ABCD) were invited to participate in a nationwide audit of U-500 to understand its use in the UK (see Appendix 2 for survey questions distributed by SurveyMonkey, available online at [bjd-abcd.com](http://bjd-abcd.com)). Responders were self-selected after recruitment approaches delivered by social media and direct mailing. The survey was deliberately simple to complete and was based on recall and perception rather than asking for concrete data. This was intended to increase engagement while aiming for a reasonable assessment of the scope and magnitude of U-500 insulin use in the UK.

## Results of the ABCD audit

Fifty-two of the 119 clinicians who contributed to the survey had no patients on U-500. Those who used U-500 were not evenly distributed geographically across the UK (see map in Figure 1), with no responders from Wales and a geographical gradient

<sup>1</sup> Diabetes and Endocrine Centre, Conquest Hospital, Hastings, UK

<sup>2</sup> Diabetes Centre, Dorset County Hospital, Dorchester, UK

<sup>3</sup> Diabetes and Endocrine Unit, City Hospital, Birmingham UK

<sup>4</sup> see Appendix 1, available online at [bjd-abcd.com](http://bjd-abcd.com)

**Address for correspondence:** Dr Umesh Dashora  
Diabetes and Endocrine Centre, Conquest Hospital, The Ridge,  
St Leonards on Sea, East Sussex TN37 7RD, UK

Tel: +44 (0)1424 755255

E-mail: [u.dashora@nhs.net](mailto:u.dashora@nhs.net)

<http://dx.doi.org/10.15277/bjd.2016.098>

**Figure 1.** Geographical distribution of use of U-500 in the UK**Table 1** Prevailing U-500 use in the UK

Number of patients on U-500	Number of responder clinicians	% (of total responders)
0	52	43.7
1–5	46	38.7
6–10	11	9.2
11–20	8	6.7
21–50	2	1.7

favouring the south of England.

The audit showed that the use of U-500 in the UK is quite variable. Most centres are using it in very few patients, but some centres are using it more frequently (Table 1).

Funding for U-500 is difficult as it is not a licensed product in the UK. CCG/GP-based funding for U-500 was not associated with perceived indications for U-500. Hospital-based funding was associated with the indication for use being higher insulin doses (generally in excess of 200 units per day as a total daily dose). Interestingly, private funding did not correlate with the indication being patient choice. The reason might be that funding decisions were based on the licence for U-500 and therefore were restricted for all patients, regardless of the indication for use or patient choice (Table 2).

Belief in dose errors correlated with the perceived risk of hypoglycaemia and weight gain but not expected HbA<sub>1c</sub> benefit. It was also unrelated to the number of patients being treated by the clinician (Box 1).

**Table 2** Indication for using U-500 (multiple answers permitted)

Number of patients	Daily dose >200	Individual dose >70	Other indication	Patient choice	Total
1–5	35/46 (76%)	7/46 (15%)	8/46 (17%)	6/46 (13%)	46
6–10	9/11 (82%)	1/11 (9%)	2/11 (18%)	2/11 (18%)	11
11–20	8/8 (100%)	1/8 (13%)	1/8 (13%)	1/8 (13%)	8
>20	2/2 (100%)	0/2	0/2	0/2	2

**Box 1.** Comments about other indications for which clinicians have used U-500

- We use in CSII regime for patients with marked insulin resistance and very high total insulin dose
- Daily dose greater than 300–400 units and poor control
- Case-by-case basis
- Increasing problems with injection site reactions with patients on high dose single injections
- Doses >250 of basal insulin in a basal bolus regime after all oral options exhausted and GLP-1/bariatric surgery considered
- Used during pregnancy
- Works fine in pumps too

### Challenges of high strength insulin and the potential solutions

Using high strength insulin is associated with the potential for error. This may be mitigated by a structured system of patient education, alert triggers on hospital systems identifying these patients and clear understanding amongst health professionals and patients about the insulin concentration being used.

Administration of U-500 dose by volume using a tuberculin syringe is the technique that has been recommended by the Institute for Safe Medication Practices.<sup>17</sup> These syringes are only available with larger needles, are not covered by most insurers and are rarely available in pharmacies. These difficulties may delay the initiation and appropriate use of this medication.

Recently, additional high strength insulins have become available for use in patients with high insulin requirement. Insulin degludec 200 units/ml (IDegU200) is available with a pen, but with the same brand name as insulin degludec 100 units/ml (IDegU100). The problem of misunderstanding units is mitigated to a large extent by the dose counter window for IDegU200 displaying doses in actual units. Each click is equivalent to a two-unit increment in dose. The dose delivered is therefore what you see on the dial.

Insulin glargine 300 units/ml (IGlarU300) has a different brand name (Toujeo™ rather than Lantus™), which would also

mitigate the chance of confusion and error.<sup>18</sup> The pen for IGlU300 is SoloSTAR which can only go up to 80 units in one dose, adding another layer of safety.

Another way to avoid confusion could be to use tables for conversion and wallet cards.<sup>19,20</sup> The European Medicine Agency is consulting on guidance to minimise the risk of error with the use of insulin in high concentration alone (U-200, U-300 and others) or in combination with other medicines.<sup>21</sup>

### Conclusions

U-500 is being used with mixed indications and mixed results throughout the UK. The factors limiting its uptake may well relate to the fact that it is being used 'off licence', clinician experience and familiarity varies significantly, different hospital trusts and health authorities have different funding policies, administration is difficult, there is no simple dedicated delivery device and the evidence of efficacy and adverse effects are somewhat mixed. It will be interesting to see how it fares as new insulin strength products come onto the market backed by more trial data, smart pen devices and better marketing.<sup>22</sup>

**Conflict of interest** None.

**Funding** None.

### References

- De la Pena A, Riddle M, Morrow LA, et al. Pharmacokinetic and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. *Diabetes Care* 2011;**34**:2496–501. <http://dx.doi.org/10.2337/dc11-0721>
- De la Pena A, Ma X, Reddy S, Ovalle F, Bergenstal RM, Jackson JA. Application of PK/PD modelling and simulation to dosing regimen optimisation of high-dose human regular U-500 insulin. *J Diabetes Sci Technol* 2014;**8**:821–9. <http://dx.doi.org/10.1177/1932296814532326>
- Jones P, Idris I. The use of U-500 regular insulin in the management of patients with obesity and insulin resistance. *Diabetes Obes Metab* 2013;**15**:882–7. <http://dx.doi.org/10.1111/dom.12094>
- Reutrakul S, Wroblewski K, Brown RL. Clinical use of U-500 regular insulin: review and meta-analysis. *J Diabetes Sci Technol* 2012;**6**:412–20. <http://dx.doi.org/10.1177/193229681200600229>
- Eby EL, Wang P, Curtis BH, et al. Cost, healthcare resource utilization, and adherence of individuals with diabetes using U-500 or U-100 insulin: a retrospective database analysis. *J Med Econ* 2013;**16**:529–38. <http://dx.doi.org/10.3111/13696998.2013.772059>
- Binder C, Brange J. Insulin chemistry and pharmacokinetics. In: Porte D Jr, Sherwin RS (eds). *Ellenberg's and Rifkin's Diabetes Mellitus*. 5th ed. Stamford, CT: Appleton & Lange, 1997, 689.
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–53. [http://dx.doi.org/10.1016/S0140-6736\(98\)07019-6](http://dx.doi.org/10.1016/S0140-6736(98)07019-6)
- Knee TS, Seidensticker DF, Walton JL, Solberg LM, Lasseter DH. A novel use of U-500 insulin for continuous subcutaneous insulin infusion in patients with insulin resistance: a case series. *Endocr Pract* 2003;**9**:181–6. <http://dx.doi.org/10.4158/EP.9.3.181>
- Lalej-Bennis D, Selam JL, Fluteau-Nadler S, et al. Extreme insulin resistance: clinical management by external subcutaneous insulin infusion. *Diabetes Metab* 1997;**23**:533–6.



### Key messages

- There is considerable variation in the use of U-500 insulin in the UK
- The commonest indication is insulin resistance requiring high doses
- A number of concentrated insulin preparations like U-200, U-300, U-400 and U-500 provide additional options in these patients

- Nathan DM, Axelrod L, Flier JS, Carr DB. U-500 insulin in the treatment of antibody-mediated insulin resistance. *Ann Intern Med* 1981;**94**:653–6. <http://dx.doi.org/10.7326/0003-4819-94-5-653>
- Boldo A, Comi RJ. Clinical experience with U500 insulin: risks and benefits. *Endocr Pract* 2012;**18**:56–61. <http://dx.doi.org/10.4158/EP11163.OR>
- Eby EL, Curtis BH, Gelwicks SC, et al. Initiation of human regular U-500 insulin use is associated with improved glycemic control: a real-world US cohort study. *BMJ Open Diabetes Res Care* April 30, 2015 3:e000074. <http://dx.doi.org/10.1136/bmjdr-2014-000074>
- Lane WS. Use of U-500 regular insulin by continuous subcutaneous insulin infusion in patients with type 2 diabetes and severe insulin resistance. *Endocr Pract* 2006;**12**:251–6. <http://dx.doi.org/10.4158/EP.12.3.251>
- Bulchandani DG, Konrady T, Hamburg MS. Clinical efficacy and patient satisfaction with U-500 insulin pump therapy in patients with type 2 diabetes. *Endocr Pract* 2007;**13**:721–5. <http://dx.doi.org/10.4158/EP.13.7.721>
- Lane WS, Weinrib SL, Rappaport JM, Przestrzelski T. A prospective trial of U500 insulin delivered by Omnipod in patients with type 2 diabetes mellitus and severe insulin resistance. *Endocr Pract* 2010;**16**:778–84. <http://dx.doi.org/10.4158/EP10014.OR>
- Lane WS, Weinrib SL, Rappaport JM, Hale CB, Farmer LK, Lane RS. The effect of long-term use of U-500 insulin via continuous subcutaneous infusion on durability of glycemic control and weight in obese, insulin-resistant patients with type 2 diabetes. *Endocr Pract* 2013;**19**:196–201. <http://dx.doi.org/10.4158/EP12226.OR>
- Institute for Safe Medication Practices (ISMP). As U-500 insulin safety concerns mount, it's time to rethink safe use of strengths above U-100. 31 October 2013. In: Acute Care ISMP Medication Safety Alert. Horsham, PA: ISMP. <https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=62>
- Sanofi. Sanofi receives FDA approval of once-daily basal insulin Toujeo® 2015. <http://www.news.sanofi.us/2015-02-25-Sanofi-Receives-FDA-Approval-of-Once-Daily-Basal-Insulin-Toujeo>
- Cochran E. U-500 insulin: when more with less yields success. *Diabetes Spectrum* 2009;**22**:116–22. <http://dx.doi.org/10.2337/diaspect.22.2.116>
- Segal AR, Brunner JE, Burch FT, Jackson JA. Use of concentrated insulin human regular (U-500) for patients with diabetes. *Am J Health Syst Pharm* 2010;**67**:1526–35. <http://dx.doi.org/10.2146/ajhp090554>
- Medicines and Healthcare Products Regulatory Agency. High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error. *Drug Safety Update* 2015:3.
- Grant P, Chowdhury TA. Drug therapies in diabetes: delivering individualised treatment. *Clin Med* 2016 (in press).

## Appendix 1: Contributors to the audit

Kate Allen	Malcolm Littley
Marga Mara	Douglas
Alison Stewart	Krishnan Amutha
Karen Tait	Stuart Ritchie
Charles Williams	Keith Sands
Gordon Dere	Geraldine Brenna
Fiona Green	Nick Morrish
Ken Darzy	Jonathan Webber
Mahajan Tripti	Chris Baynes
Deborah Bosman	Paula Chattington
Andrew Macleod	Kate Hunt
Rahul Nayar	Tahseen Chowdhury
S.C Bain	Stella George
Jesse Kumar	Mujahid Saeed
J.P.H Wilding	Ralph Abraham
David Jenkins	C. Bodmer
Simon Eaton	Alexandra Ward
D Barnes	Anna Brackenridge
Ruth Mac	Jackie Elliott
Yuyu Kyaw	Kokswee Gan
Nigel Huston	Richard Paisey
Erwin Castro	Mahesh Sathivageeswaran
Umesh Dashora	Jane Dale
Rob Gregory	Helen Partridge
Philip Newland-Jones	Julia Platts
Chinnusamy Ravikumar	Alex Bickerton
Rajbhandaro Satyan	Menon Ravik
Rob Moisey	Andrew Macklin
D Hopkins	Susana Gonzalez

## Appendix 2: U 500 questionnaire

1. My indications for using U500 insulin are:

- I don't use U500 insulin to treat my patients  
 Daily insulin dose > 200 units  
 Individual insulin doses > 70 units  
 Patient Choice

Other reasons (please specify)

2. How many patients under your care are taking U500 insulin?

- 0  
 <5  
 5-10  
 10-20  
 20-50  
 >50

3. Your impressions of U500:

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
U500 reduces HbA1c significantly	<input type="checkbox"/>				
U500 causes significant weight gain	<input type="checkbox"/>				
U500 causes more hypos than U100	<input type="checkbox"/>				
U500 is associated with more dosing errors	<input type="checkbox"/>				

4. The U500 prescriptions are funded by:

- Hospital/department funding  
 Individual Treatment application, approved by CCG  
 Ongoing scripts provided by patient's GP (without needing individual funding agreed)  
 Private prescription

Other (please specify)

5. To give us a sense of the geographical variation in use please give the location & first part of the postcode for your hospital.

City/Town:

Postal Code:

6. I would be willing to be contacted to provide hard data for a further study, to back up my impressions. My email address is:

Email Address: