Continuous subcutaneous insulin infusion for the treatment of diabetes Appraisal Consultation Document

Comments

[redacted] **Co-Chair, Insulin Dependent Diabetes Trust Clinical Effectiveness,**

Point 4.1.1

This states that the Assessment Group concluded that MDI based on long-acting insulin analogues is more efficacious than MDI therapy based on older insulins and therefore analogue-based MDI was used as a comparator for CSII therapy. I question whether this is a correct comparator for children. In young children under 6 years trials have not been carried out to demonstrate the safety or efficacy of insulin analogues in young children and whether it is appropriate in older children where only small trials of relatively short duration have been carried out.

In addition, the background of many studies state that the DCCT [1991] showed that intensive treatment with MDI results in better glycaemic control as measured by the HbA1c test but this study was carried out in highly selected adults with Type 1 diabetes and its findings cannot be extrapolated to children. Again this raises the question of whether it is correct to only compare only MDI with CSII, should a comparison with free mix twice daily also be compared with CSII?

There are two recently published studies that have investigated effects the effects of different regimes and insulins over 10 year periods in children that warrant inclusion and support the above concerns.

[1] Prevailing therapeutic regimes and predictive factors for prandial insulin substitution in 26,687 children and adolescents with Type 1 diabetes in Germany and Austria. Diabetic Medicine, October 2007.

In 26,687 children and adolescents treated from 1995 to 2005 in 152 clinics, 87% were treated with MDI or CSII and while this percentage increased over the period of the study, the HbA1c remained constant ie it did not improve. In addition, those using insulin analogues received up to 11% higher insulin doses per day compared with those treated with human insulin.

[2] Continuing stability of centre differences in pediatric diabetes care: do advances in diabetes treatment improve outcome? Diabetes Care, Vol 30, number 9, September 2007

21 paediatric diabetes centres investigated the influence of changes in insulin regimes, and other factors over 10 years, on HbA1cs, hypoglycaemia and ketoacidosis. 85.3% of the 2,269 children/adolescents were on one of 5 insulin regimes - the remaining 309 were on regimes that could not be classified. The HbA1c results for the different regimes were as follows:

Regime	HbA1c 8.2	Insulin dose [by body weight]
Miscellaneous	8.2	0.66
Twice daily premix	8.6	1.01
Twice daily *free* mix	7.9	1.00
Thrice daily	8.2	1.24
Basal bolus	8.2	1.03
Pumps	8.1	0.92

Despite many changes over the past 10 years including increased use of insulin analogues, basal bolus regimes [4 injections + a day] and CSII those using twice daily *free* mix of soluble/regular plus NPH [intermediate-acting] and had lower HbA1cs than all other groups. HbA1cs on CSII were not significantly different from the total group even in centres where considerable numbers of patients were using them. The researchers concluded that despite major and continuing changes in insulin and insulin regimes, glycaemic control has not improved over a decade in these 21 international centres.

Both these studies suggests that the so-called conventional regimes may be superior to modern intensive regimes and indeed CSII but also highlight the need to compare CSII with twice daily free mix soluble and NPH regimes.

Point 4.3.2 while agreeing that the lack of RCTs and lack of RCTs of longer duration requires evidence from observational studies, the statement that Committee *'was persuaded that the few, small trials [RCTs] of relatively short duration could not be relied on alone to capture the benefits of CSII therapy'* is biased. It assumes that there will be benefits of CSII if more and larger trials are carried out when this may or may not be the case in all categories of people with type 1 diabetes.

Bias

It is important that the final guidance does not mislead people and therefore I think stronger comment should be made about the possible/ probable bias of the studies involved in reaching these recommendations, Firstly, the selection bias in that studies are carried out in people who agree/want CSII treatment because they believe it to be a better form of treatment. Secondly, that people on CSII therapy generally receive better, more comprehensive and ongoing education on diet, exercise and adjusting insulin compared to people on MDI or twice daily injections and therefore the studies are not comparing like with like.