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(54) Title: TREATMENT OF VERY LOW BIRTHWEIGHT (VLBW) INFANTS BY INCREASING BLOOD INSULIN LEVELS

(57) Abstract: Treatment of Very Low Birthweight (VLBW) Infants by Increasing Blood Insulin Levels This invention relates to the treatment of very low birthweight (VLBW) infants by increasing blood insulin levels in said infant during the first few days of life, for example using insulin or insulintropic agents, and maintaining said increased levels for an extended period. This treatment leads to improved weight gain and overall improvement in outcome for this high-risk population, including a reduced risk of retinopathy of prematurity (ROP). Methods of treatment and uses of insulin and insulintropic agents in such methods are provided.



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Treatment of Very Low Birthweight (VLBW) Infants by Increasing
Blood Insulin Levels

This invention relates to methods and means for treating very
5 low birthweight (VLBW) infants to reduce the risks of
associated medical problems.

In all human newborns, the disruption of the intrauterine
delivery of nutrients via the placenta results in an acute
10 phase of profound catabolism with a weight loss that is
restored only after the establishment of regular postnatal
feeding. Although data from human infants are sparse, data
from animal studies indicate that this catabolism relates to
beta cell apoptosis immediately after birth, which is followed
15 by renewal of beta cells, reflecting the change from a
prenatal state of continuous and parenteral delivery of
nutrients to a postnatal state of discontinuous and enteral
delivery. Thus, this catabolic phase reflects transient
insulin deficiency followed by restoration of normal insulin
20 secretion related to enteral feeds.

In the term neonate, the catabolic phase is transient and may
be considered to be physiological, given that term human
newborns have large fat stores (on average, 12% of the body
25 weight of a term human newborn is fat) and lipolysis can be
readily activated. In very low birthweight (VLBW) neonates,
however, the catabolic phase may be prolonged, for example
because of delay in instituting normal enteral feeding or
because of the immaturity of the gut and pancreas. The
30 prolonged catabolism which occurs in these infants results in
insulin resistance and hyperglycaemia that, in turn, enhances
the risk of infection. Overall, prolonged catabolism leads
to poor weight gain and brain growth, and low levels of IGF-
1, which have been implicated in the pathogenesis of
35 retinopathy of prematurity (ROP).

Longitudinal data from VLBW and/or SGA infants suggest that an early failure to provide the anabolic drive for catch-up growth has long-term consequences in terms of brain growth, height gain, and body composition in early childhood, and may thereby affect intellectual performance and disease risk in adult life.

The present inventors have discovered that early continuous insulin intervention improves glucose control during the first week of life and prevents the pronounced hyperglycaemia that may be evident in some babies, particularly on day 2 through 3. This intervention prior to hyperglycemia is more efficient than intermittent or continuous insulin therapy in response to hyperglycemia and may lead to improved weight gain and overall improvement in outcome of this high-risk population.

An aspect of the invention provides a method of treating a very low birth weight (VLBW) infant or preventing or attenuating neonatal catabolism in a VLBW infant or preventing or attenuating the development of hyperglycemic insulin resistance in a VLBW infant or reducing the risk of mortality and morbidity in a VLBW infant, the method comprising; increasing blood insulin levels in said infant and maintaining said increased levels for an extended period.

Insulin levels may be increased or elevated in said infant from within 24 hours of birth, more preferably from within 4, 8 or 12 hours of birth. Insulin levels may be increased relative to levels in the untreated infant.

Increased blood insulin levels are preferably maintained for up to 7 days after birth. For example, increased blood insulin

levels may be maintained for 3 or more, 4 or more, 5 or more or 6 or more days up to about 7 days.

Preferably, the infant is treated in accordance with the present methods until the end of the neonatal catabolic phase and the establishment of enteral feeding.

A VLBW infant is an infant weighing less than 1500g at birth. A VLBW infant may be premature or may be a full term infant who is small for gestational age (SGA).

In some preferred embodiments, a VLBW infant suitable for treatment as described herein is non-hyperglycaemic. In other words, the VLBW infant has blood glucose levels of less than 10 mmol/l.

Methods described herein may be useful in preventing or attenuating neonatal catabolism and the development of hyperglycemic insulin resistance, and may therefore be useful in reducing the risk of mortality and morbidity in VLBW infants, in particular the risk of infection, retinopathy of prematurity (ROP), intracranial haemorrhage and/or necrotising enterocolitis. A method of reducing the risk of retinopathy of prematurity in a VLBW infant may comprise; increasing blood insulin levels in said infant and maintaining said increased levels for an extended period, as described herein.

Methods described herein may facilitate induction of anabolism and may have beneficial effects on long-term growth, brain development and neuropsychological outcomes as well as reducing the risk of long-term disease associated with being born premature and/or small for gestational age (SGA).

Blood insulin levels may be increased by introducing exogenous insulin to the infant (i.e. insulin not produced by the

infant) or by stimulating an increase in the production of endogenous insulin by the infant.

In some embodiments, insulin levels may be increased by administering insulin to the infant. Aspects of the invention provide insulin for use in the treatment of a VLBW infant as described herein and the use of insulin in the manufacture of a medicament for use in a method of treating a VLBW infant. Preferably, the VLBW infant is a non-hyperglycaemic VLBW infant.

As is well known in the art, insulin is a 51 amino acid polypeptide hormone of 5.7 kD which is secreted by islet cells within the pancreas and is an important regulator of carbohydrate metabolism.

Insulin may include animal-derived insulin, for example pork, fish or beef insulin, or, more preferably, recombinant human insulin or derivatives and analogues thereof. A human insulin analogue or derivative may have an amino acid sequence that differs from the human insulin by the addition, substitution or deletion of 1, 2, 3, 4 or 5 amino acids and may have improved properties such as onset, peak, and duration of action relative to wild-type human insulin.

Many clinically approved insulins are commercially available and may be used in accordance with the invention, including, for example, short acting insulins such as soluble insulin (Actrapid®, Humulin®) and insulin analogues (Humalog® (Lispro), Novolog® (Aspart)).

In some preferred embodiments, insulin is continuously administered to the VLBW infant to increase insulin levels and maintain the increased levels. Continuous administration may be especially suitable for short-acting insulins.

Methods and means of continuous administration of therapeutic agents are well known in the art. Insulin may, for example, be administered continuously by infusion, in particular intravenous infusion.

Medical practitioners are familiar with the administration of insulin, which is preferably in a "therapeutically effective amount", this being sufficient to show benefit to the individual without elicited undesirable side effects. The actual amount of insulin administered, and rate and time-course of administration, will depend on the particular circumstances and is within the responsibility of medical practitioners.

In some embodiments, 0.01 units/kg/hour to 0.1 units/kg/hr of insulin may be administered, more preferably 0.02 units/kg/hr to 0.075 units/kg/hr. For example, doses of about 0.025 units/kg/hr or about 0.05 units/kg/hr may be administered.

In other embodiments, blood insulin levels may be increased by stimulating an increase in the production and secretion of endogenous insulin by the infant. This may be achieved, for example, by administering an insulinitropic agent to the infant.

Insulinitropic agents include peptides such as incretins, which promote insulin secretion and beta cell development. Incretins include glucagon-like peptide-1 (GLP-1) (P01275 GI:45644939 residues 7 to 36 or 37), glucose-dependent insulinitropic polypeptide (GIP) (P09681 GI:121194 residues 52 to 93) and derivatives or agonists of these peptides, including exendin 3 (P20394 GI:119677), exendin 4 (AAB22006.1 GI:248418) (Xu G et al 1999; Tourrel et al 2001) NN2211 (Rolin B et al 2002).

Commercially available GLP-1 agonists include Exendin (Lilly), GLP-1 I.N.T. (Transistion Therapeutics), Byetta (Amylin), Liraglutide (Novo) and AVE0010 (Aventis).

Other insulinotropic agents include DPP-IV inhibitors.

5 Commercially available DPP-IV inhibitors include Vildagliptin (Lilly), Saxagliptin (BMS) and Sitagliptin (Merck).

Insulinotropic peptides may be synthesized by conventional means as detailed below, such as solid-phase peptide
10 synthesis. Solid phase peptide synthesis is described in J. M. Stewart and J. D. Young, Solid Phase Peptide Synthesis, W. H. Freeman Co. (San Francisco), 1963 and J. Meienhofer, Hormonal Proteins and Peptides, vol. 2, p. 46, Academic Press (New York), 1973.

15 Insulinotropic peptides may also be produced through the use of recombinant DNA technology (for example, see Sambrook "Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press 3rd Edition (2001), and Ausubel *et al.*,
20 Current Protocols in Molecular Biology, John Wiley and Sons, (1994)).

The insulinotropic activity of an agent may be determined by providing a compound to animal cells, or injecting a compound
25 into animals and monitoring the release of immunoreactive insulin (IRI) into the media or circulatory system of the animal, respectively. The presence of IRI may be detected, for example, through the use of a radioimmunoassay which specifically detects insulin.

30 Administration of an insulinotropic agent may be continuous or periodical. The frequency of administration may depend on the active half-life of the agent. For example, a short acting

agent may be administered continuously, while a long acting agent may be administered periodically, for example daily.

In some embodiments, the insulinotropic agent is continuously administered to the infant to increase production and secretion of insulin, thereby increasing blood insulin levels and maintaining the increased levels. Methods and means of continuous administration of therapeutic agents are well known in the art and are described in more detail above. An insulinotropic agent may be administered continuously by infusion, for example intravenous infusion

In other embodiments, long-acting insulinotropic agents may be administered periodically, for example daily, to increase blood insulin levels in the VLBW infant and maintain these increased levels.

Other aspects of the invention provide an insulinotropic agent for use in the treatment of a VLBW infant as described herein and the use of an insulinotropic agent in the manufacture of a medicament for use in a method of treating a VLBW infant.

The insulinotropic agent may be administered from within 24 hours of the birth of said infant and may be administered for up to seven days after birth.

In some embodiments, a method of treating a VLBW infant may comprise administering insulin and an insulinotropic agent to said infant.

Related aspects of the invention relate to the combination of insulin and an insulinotropic agent in the treatment of a VLBW infant and the use of insulin and an insulinotropic agent in the manufacture of a medicament for use in the treatment of a VLBW infant.

Insulin and insulintropic agents are described in more detail above.

5 Blood glucose levels may be measured and/or monitored in the VLBW infant during the treatment described herein. Preferably, blood glucose levels in the infant remain between 4 and 8 mmol/l when the blood insulin level is increased in accordance the methods described herein.

10 In cases in which the blood glucose level drops below a threshold value, typically 4.0 mmol/l, during the treatment (hypoglycaemia), glucose may be administered to the infant. For example, glucose, conveniently in the form of a solution
15 comprising up to about 20% dextrose, may be administered by infusion.

Techniques for monitoring blood glucose levels are well-known in the art and include, for example, the use of a glucose
20 sensor, such as the MiniMed Glucose Sensor.

Various further aspects and embodiments of the present invention will be apparent to those skilled in the art in view of the present disclosure. All documents mentioned in this
25 specification are incorporated herein by reference in their entirety.

The invention encompasses each and every combination and sub-combination of the features that are described above.

30 Certain aspects and embodiments of the invention will now be illustrated by way of example and with reference to the figures described above and tables described below.

Figure 1 shows blood glucose levels in VLBW infants treated within the first 24 hours with insulin as described relative to controls.

5 Figure 2 shows the proportion of time spent in normo-glycaemic condition by VLBW babies subjected to insulin treatment in the first 24 hours relative to controls.

Figure 3 shows the timing of hyperglycaemia in VLBW babies
10 subjected to early insulin treatment relative to controls.

Figure 4 shows the ratio of glucose to insulin in VLBW babies subjected to early insulin treatment relative to controls.

15 Figure 5 shows the amount of IGF-1 in VLBW babies subjected to early insulin treatment relative to controls.

Figure 6 shows the amount of IGFBP-1 in VLBW babies subjected to early insulin treatment relative to controls.
20

Table 1 shows patient demographics of VLBW infants randomised to receive either a continuous insulin infusion over the first seven days of life or intermittent insulin therapy as dictated by blood glucose levels (i.e. more than 10 mmol/l).
25

Table 2 shows growth and hormone data during the whole 7-day study period by treatment group. Median (IQ Range).

Table 3 shows pilot data from neo-natal insulin replacement
30 studies on numbers with retinopathy of Prematurity (RoP) (Chi-square p 0.03).

Examples

Sixteen very low birth weight infants (less than 1500 g)
35 were randomised to receive either a continuous insulin

infusion over the first seven days of life or intermittent insulin therapy as dictated by blood glucose levels (i.e. more than 10 mmol/l). Details of the infants studied are summarised in Table 1.

5

The early introduction of insulin therapy was observed to result in more stable blood glucose control over the seven-day period, as illustrated by data collected with the MiniMed Glucose Sensor shown in Figure 1. Normal blood glucose levels were achieved in the active treatment group by additional infusions of glucose and, overall, the babies treated with continuous insulin infusion spent a much longer part of the first week with normal glucose levels than those treated with intermittent insulin therapy dictated by blood glucose levels (Figure 2).

15

The hyperglycaemia that was evident in many of the control babies over the first week of life was abolished in those babies given continuous insulin therapy from day one (Figure 3). Infants in the control arm received insulin therapy because of the high blood sugars and, in fact, the amount of insulin given over the seven days in the two groups was not significantly different. However, in the control babies the insulin failed to prevent further episodes of hyperglycaemia, probably because of the development of insulin resistance. The glucose-insulin ratios based on daily measurements in the two groups of babies are illustrated in Figure 4 and suggest an altered relationship between insulin and glucose between the groups. The early introduction of continuous insulin therapy was shown to attenuate or prevent the catabolism and insulin resistance which was evident in the control babies.

20

25

30

Early continuous insulin delivery was also observed to result in higher IGF-1 and lower IGFBP-1 levels (Fig 5, 6): IGF-1 bioavailability was thus increased by the treatment.

- 5 Insulin-like growth factor (IGF-1) bioactivity provides the best assessment of bioavailability of IGF-1 in the newborn. The IGF-1 Kinase receptor activation assay (KIRA) based on cells transfected with the human *IGF1R* gene was used to determine the effect of early continuous insulin delivery.
- 10 The bioassay has been validated and is highly sensitive and specific (Chen et al 2003).

Infants treated with insulin from day 1-7 were observed to have a 2.4 fold increase in IGF-1 bioactivity compared with

15 controls (P 0.005 Table 2, Fig 7).

Since low IGF-1 in VLBW infants has been associated with the development of ROP (Hellstrom et al 2001, Hellstrom et al 2002, Hikino et al 2001), these results are indicative that

20 early insulin treatment may prevent or reduce this complication in the newborn.

The incidence of RoP in infants treated with insulin from day 1-7 was assessed in relation to a control group. Early

25 continuous insulin delivery was observed to result in a reduced incidence of RoP in VLBW infants (Table 3).

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	Control	Insulin
Number	8	8
Males : Females	5;3	4;4
Gestational Age	26.9 (23.29-29.8)	26.13 (23.7-29.8)
Birth Weight	733 (584-1094)	789 (611-1387)
Birth Weight SDS	-1.37	-0.86

Table 1

	Elective insulin	Controls	P-value
Change in Weight (g)	+0.3 (-6.6 to +8.9)	-42.0 (-13 to -64)	0.06
Change in Leg length (mm)	+0.74 (+0.37 to +1.37)	-0.38 (-1.46 to +1.02)	0.049
Mean insulin level (pmol/l)	101.2 (71.9 to 118.7)	71.1 (47.2 to 142.9)	0.3
Mean proinsulin level (pmol/l)	7.9 (6.7 to 28.6)	12.0 (7.8 to 13.6)	0.7
Mean IGF-I level (ng/ml)	10.00 (5.5 to 14.3)	10.00 (7.8 to 13.0)	0.8
Mean IGFBP-1 level (ng/ml)	149 (78 to 307)	385 (165 to 775)	0.046
Mean IGF-I/BP-1 molar ratio	0.048 (0.023-0.261)	0.022 (0.014-0.150)	0.2
Mean IGF-I bioactivity (KIRA ug/l)	0.243 (0.173-0.307)	0.103 (0.094-0.118)	0.005

Table 2

	Standard	Early insulin
RoP	9	2
No RoP	23	27

Table 3

Claims:

1. A method of treating a very low birth weight (VLBW)
5 infant comprising;
increasing blood insulin levels in said infant and
maintaining said increased levels for 3 or more days.
2. A method according to claim 1 therein the infant is non-
10 hyperglycaemic.
3. A method according to claim 1 or claim 2 wherein said
insulin levels are increased in said infant within 24 hours of
birth.
15
4. A method according to any one of claims 1 to 3 wherein
said increased levels are maintained for up to 7 days.
5. A method according to any one of claims 1 to 4 wherein
20 blood insulin levels are increased by administering insulin to
said infant.
6. A method according to claim 5 wherein said insulin is
administered at 0.01 to 0.1 units/Kg/hour.
25
7. A method according to claim 6 wherein insulin levels are
increased by continuously administering insulin to said
infant.
- 30 8. A method according to claim 5 wherein insulin is
administered by infusion.
9. A method according to any one of claims 5 to 8 further
comprising administering an insulinotropic agent to said
35 infant.

10. A method according to claim 9 wherein the insulinotropic agent is an incretin or a derivative or agonist thereof.

5 11. A method according to claim 10 wherein the insulinotropic agent is selected from the group consisting of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), exendin 3, exendin 4, and NN2211.

10 12. Use of insulin in the manufacture of a medicament for use in a method of treating VLBW infants according to any one of claims 1 to 11.

13. Use of insulin in the manufacture of a medicament for the
15 treatment of a non-hyperglycaemic VLBW infant.

14. Use of a combination of insulin and an insulinotropic agent in the manufacture of a medicament for the treatment of a non-hyperglycaemic VLBW infant.

20

15. A method according to any one of claims 1 to 6 wherein blood insulin levels are increased by administering an insulinotropic agent to said infant.

25 16. A method according to claim 15 wherein the insulinotropic agent is an incretin or a derivative or agonist thereof.

17. A method according to claim 16 wherein the insulinotropic agent is selected from the group consisting of glucagon-like
30 peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), exendin 3, exendin 4, and NN2211.

18. A method according to any one of claims 15 to 17 wherein insulin levels are increased by continuously administering the
35 insulinotropic agent to said infant.

19. A method according to claim 18 wherein the insulinotropic agent is continuously administered by infusion.

5 20. A method according to any one of claims 15 to 17 wherein insulin levels are increased by periodically administering the insulinotropic agent to said infant.

10 21. Use of an insulinotropic agent in the manufacture of a medicament for use in a method of treating VLBW infants according to any one of claims 1 to 6.

15 22. Use of an insulinotropic agent in the manufacture of a medicament for the treatment of a non-hyperglycaemic VLBW infant.

20 23. Use according to claim 21 or claim 22 wherein the insulinotropic agent is an incretin or a derivative or agonist thereof.

24. Use according to claim 23 wherein the insulinotropic agent is selected from the group consisting of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), exendin 3, exendin 4, and NN2211.

25 25. A method according to any one of claims 1 to 11 or 15 to 20 comprising monitoring blood glucose levels in said infant.

30 26. A method according to claim 25 comprising administering glucose to said infant to maintain stable blood glucose levels between 4 and 8 mM/l.

35 27. A method according to claim 26 wherein said glucose is administered as a solution comprising up to 20% dextrose.

Insulin

Controls

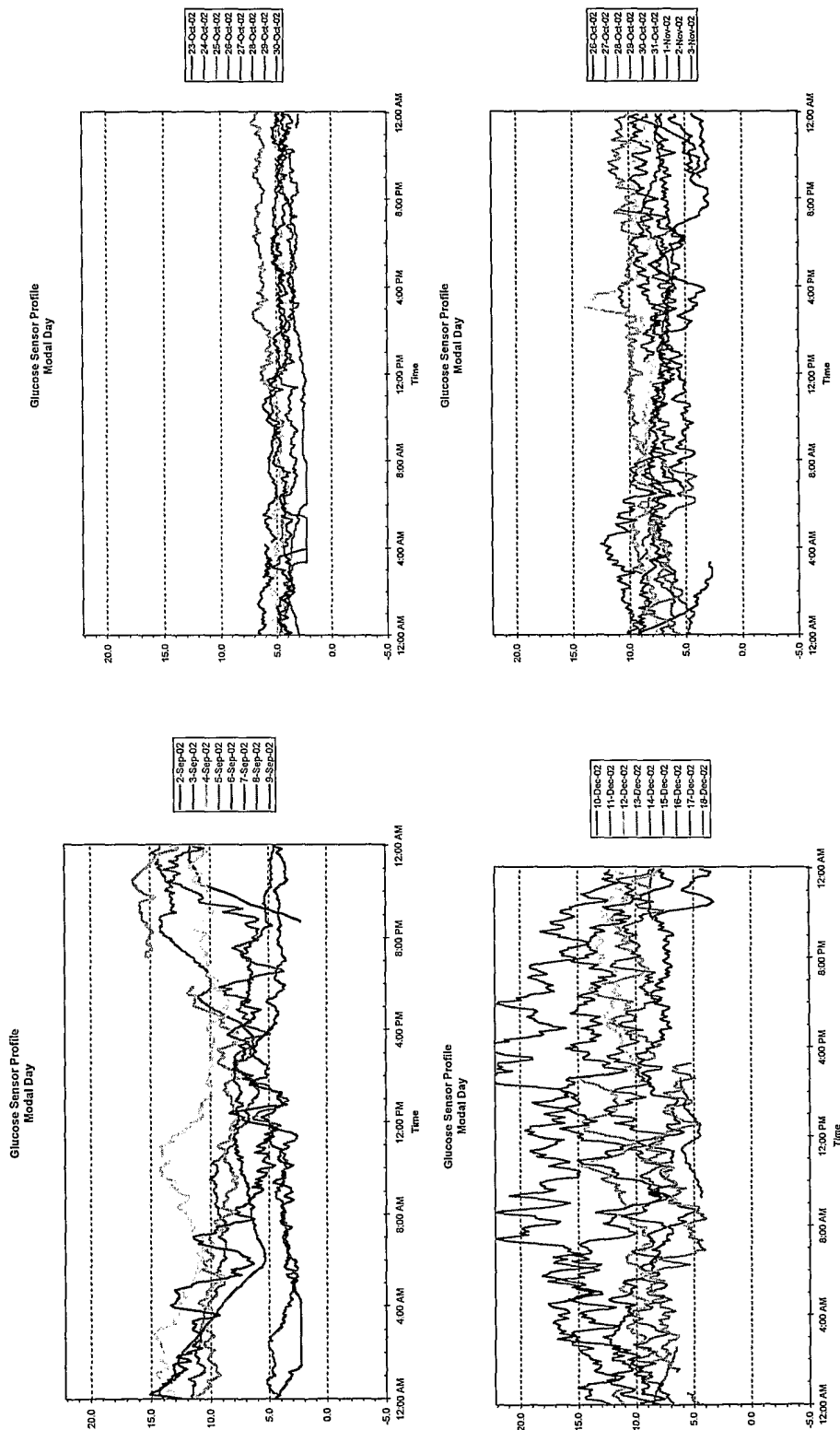


Figure 1

5

Insulin Effects on Glucose Control

10

15

20

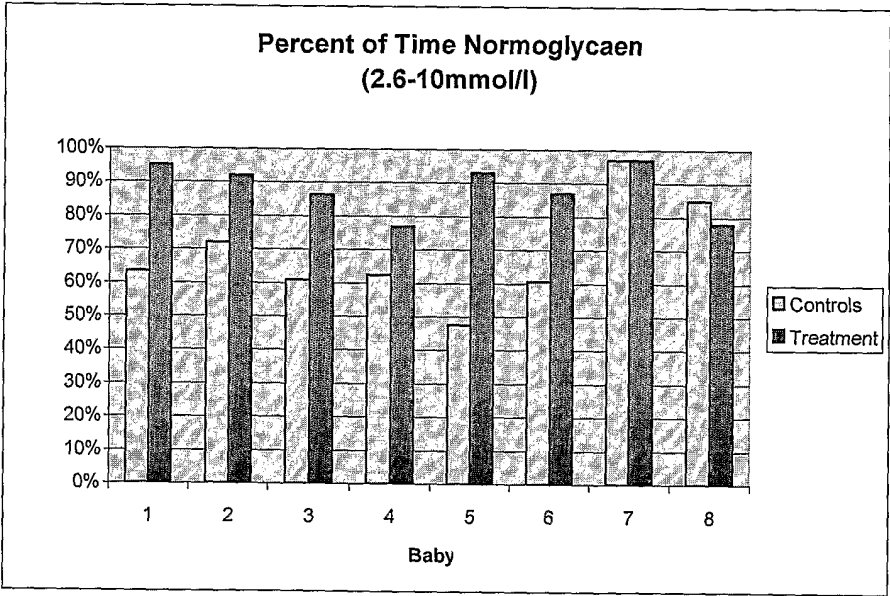


Figure 2

25

Timing of Hyperglycaemia

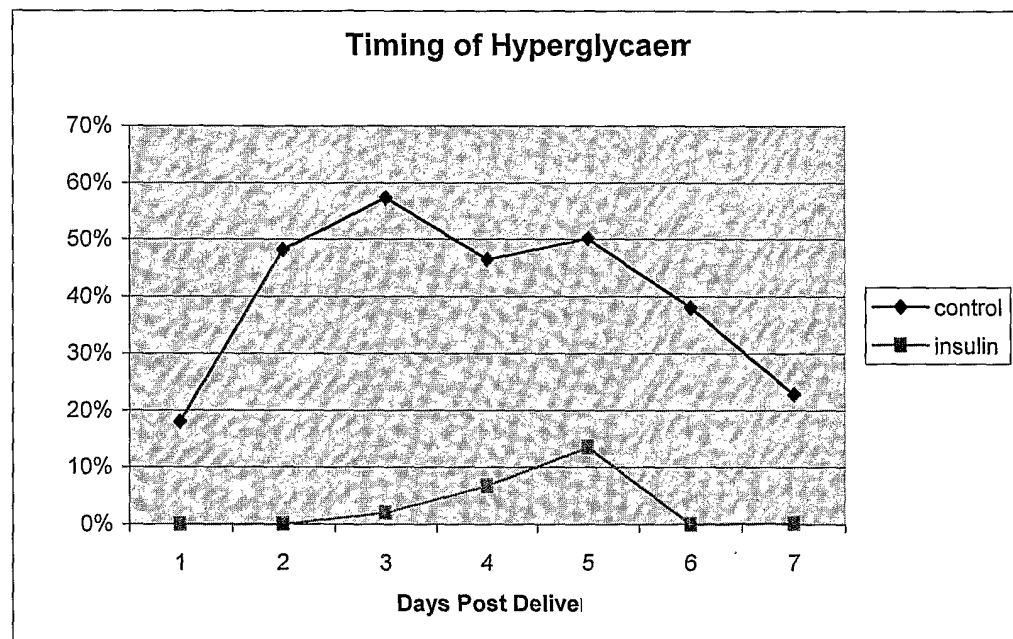


Figure 3

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Insulin Resistance: Glucose/insulin ratio

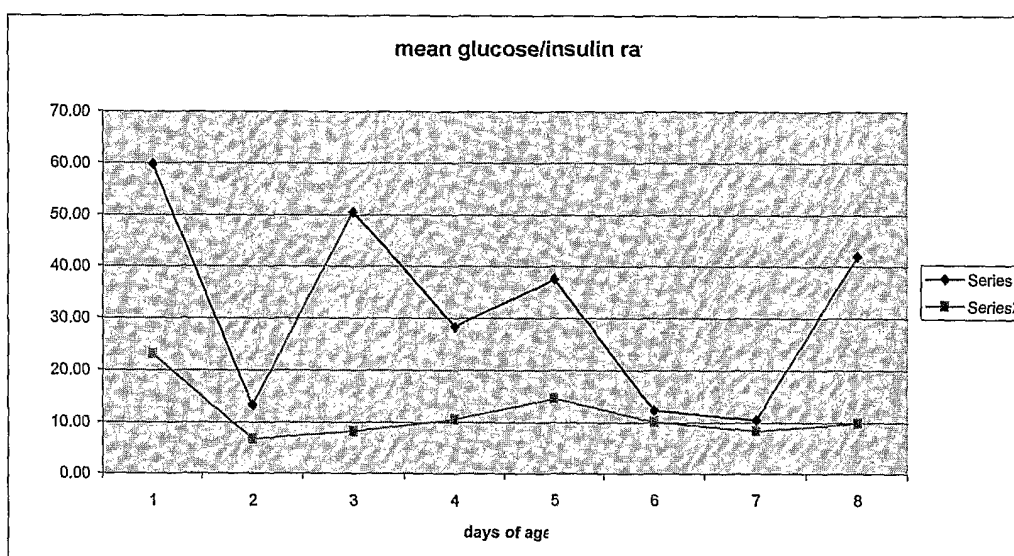


Figure 4

5/7

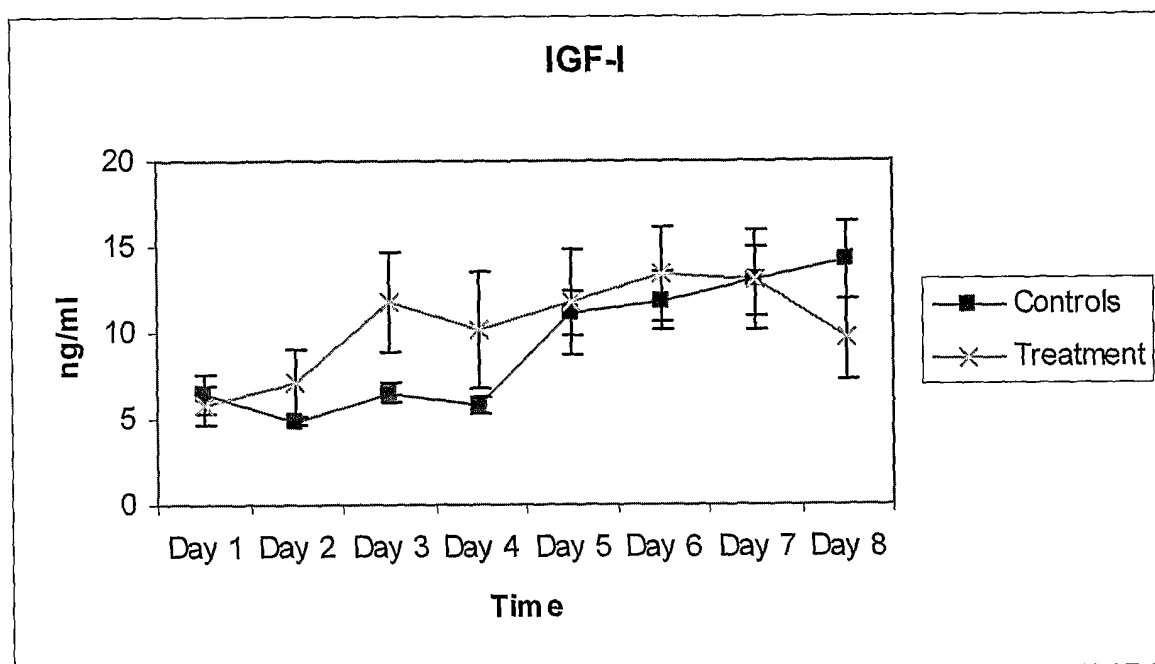
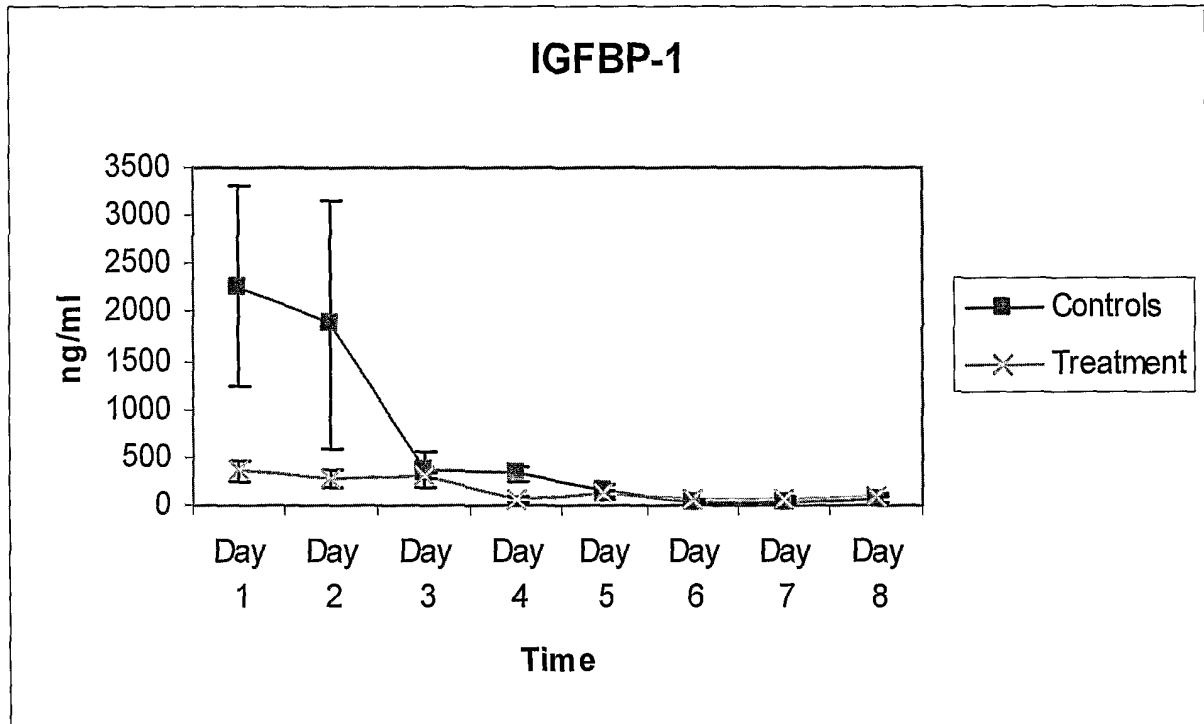


Figure 5

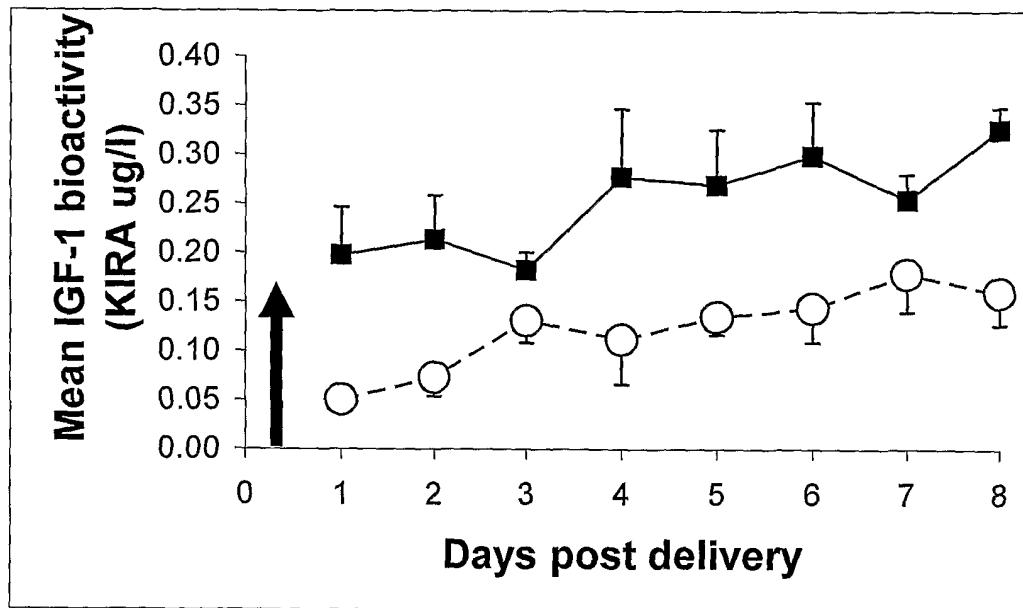
6/7



5

Figure 6

7/7



- ↑ Onset of insulin infusion in cases
- Continuous insulin
- Controls

Figure 7

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference NRSCP6355127	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/GB2006/000480	International filing date (day/month/year) 10/02/2006	(Earliest) Priority Date (day/month/year) 10/02/2005
Applicant CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
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☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☒ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/000480

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/28 A61K38/18 A61P5/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THABET F ET AL: "Continuous insulin infusion in hyperglycaemic very-low-birth-weight infants receiving parenteral nutrition." CLINICAL NUTRITION (EDINBURGH, SCOTLAND) DEC 2003, vol. 22, no. 6, December 2003 (2003-12), pages 545-547, XP002384156 ISSN: 0261-5614 abstract last paragraph of text ----- -/-	1-27

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

7 June 2006

Date of mailing of the international search report

28/06/2006

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/000480

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MENA ET AL: "Insulin homeostasis in the extremely low birth weight infant" SEMINARS IN PERINATOLOGY, W.B. SAUNDERS, GB, vol. 25, no. 6, December 2001 (2001-12), pages 436-446, XP005406530 ISSN: 0146-0005 abstract -----	1-27