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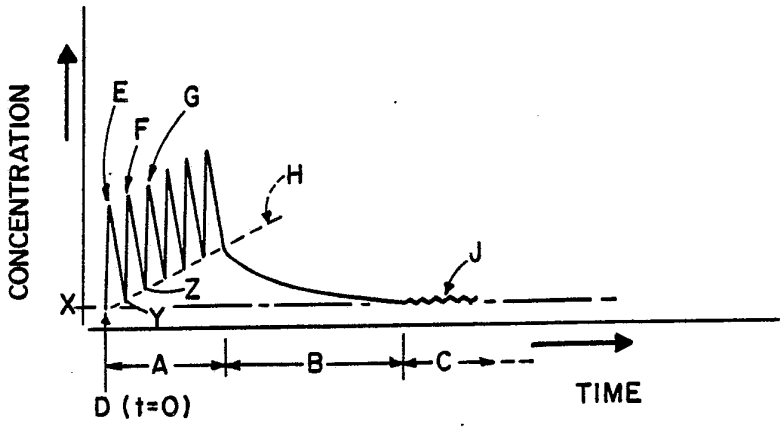

(57) Abstract

A method and apparatus for treating a diabetic or traumatized subject with impaired dietary fuel processing systems which includes establishing an elevated carbohydrate concentration in the subject's metabollic system and activating the dietary carbohydrate processing capabilities of the subject's body tissues, particularly liver and muscle, by administering insulin to increase the 'free' insulin concentration in the subject's metabolic system during at least part of the period when the carbohydrate concentration is elevated, such insulin being administered in pulses to produce a series of peaks in such 'free' insulin concentration. An external programmable insulin pump (10), having a microprocessor (12), pump section (14), and infusion catheter (16), is provided for delivering such pulses of insulin to produce the series of peaks in 'free' insulin concentration.

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INSULIN DELIVERY ALGORITHM

Related Application

This application is a continuation-in-part of my copending U. S. application Serial No. 562,435, filed December 6, 1983.

Background of the Invention

This invention relates to timing the administration of insulin and various fuels (carbohydrates, proteins, and fats) to individuals whose fuel processing (i.e., oxidation, storage, and conversion to other substrates) capabilities are chronically abnormal (e.g., diabetic subjects) or acutely disrupted (e.g., accidentally or surgically traumatized patients).

The normal fuel processing capabilities of the body, such as of the liver and other tissues, e.g., muscle, can be disrupted by disease (e.g., diabetes) and by trauma (accidental or surgical).

Insulin is often administered in large quantities to diabetic subjects, surgical patients or accident (especially burn) victims in attempts to restore normal fuel processing capabilities and to prevent the breakdown of muscle protein. Since massive doses of insulin lower blood sugar levels, glucose may also be infused.

Established treatment programs for diabetic patients administer insulin to control blood glucose concentrations. Insulin infusion patterns based directly on measured blood glucose levels are disclosed in Aisenberg et al., U.S. Patent No. 3,387,339; Klein, U.S. Patent No. 4,206,755; Edelman, U.S. Patent No. 4,073,292; and Chem. Abstracts, 92:135345m. Insulin infusion patterns based on projected blood glucose levels and expected changes in blood glucose levels, calculated using measured blood glucose levels,

are disclosed in Albisser et al., U.S. Patent No. 4,245,634; Schindler et al, U.S. Patent No. 4,253,456; Clemens, U.S. Patent No. 4,151,845; Clemens et al, U.S. Patent No. 4,055,175; and Chem. Abstracts, 89:39926u. In programs of the above types, both the amount of insulin infused and the duration of the infusion are dependent on measured glucose concentrations. That is, when measured glucose concentrations and/or projected concentrations arise to a certain prescribed limit, insulin is administered. Insulin infusion then continues until such glucose concentrations approach or fall below a certain level.

In addition to these patterns of insulin infusion based on concurrently-measured glucose levels, insulin-administering devices have been developed which can infuse insulin according to a predetermined profile of the patient's insulin requirements. For example, Franetzki et al, U.S. Patent No. 4,482,872, discloses such a device wherein a base rate of insulin is continuously infused and the predetermined program (stored in a microprocessor), which typically administers a larger amount (pulse) of insulin, can be called up by the patient when needed. Haerten et al, U.S. Patent No. 4,077,405, likewise discloses a device which can administer pulses of medication (e.g., insulin) over a constant baseline in response to pre-programmed or manually-controlled signals. These devices administer insulin in patterns which, like the above-mentioned methods which respond to concurrently-measured glucose concentrations, are a function of and are designed to directly control the actual concentration of glucose

in the blood stream.

Summary of the Invention

In general, the invention features a method of treating a diabetic or a traumatized subject which includes the steps of 1) establishing an elevated carbohydrate concentration in the subject's metabolic system and 2) activating the dietary carbohydrate processing capabilities of the subject's liver by administering insulin to increase the "free" insulin concentration in said subject's metabolic system during at least part of the period when the carbohydrate concentration is elevated, with said insulin being administered in pulses to produce a series of peaks in said "free" insulin concentration.

In preferred embodiments the changes in the free insulin concentration are effected by administering time-varying quantities of insulin, the elevated carbohydrate concentration is established by the ingestion or infusion of carbohydrates, the administering step is initiated coincident with the establishing step, the insulin is administered in pulses, a primary series of insulin pulses which produces sharp peaks over a gradually increasing interpeak concentration is followed by an interval during which no insulin is administered to allow the insulin concentration to return to that concentration which existed prior to the administration of the primary series of pulses (the baseline concentration), the interval is followed by the administration of a secondary series of insulin pulses to produce an insulin concentration which oscillates about the baseline

concentration which maintains the fuel processing system in an active state, the average amount of insulin in the pulses of the secondary series is less than the average amount of insulin in the pulses of the primary series, and the secondary series continues during the entire period between carbohydrate ingestions or infusions.

Further in preferred embodiments the time-varying quantities of insulin are administered using an external or implantable programmable insulin infusion pump.

The program of changes in insulin concentrations of the present invention activates and maintains processing capabilities for body fuels such as carbohydrates (glucose, fructose, sucrose, galactose, starches, and related analogs and derivatives), amino acids, and lipids of a diabetic or a traumatized patient's system. In diabetic patients, the method of insulin administration indirectly controls blood glucose concentrations by addressing the underlying problem of diabetes, namely the absence of autoregulation of glucose concentrations by the metabolic system, by rapidly and efficiently activating and maintaining the metabolically-dormant dietary carbohydrate processing system, in particular the liver but including muscle.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiment thereof, and from the claims.

Description of the Preferred Embodiment

We first briefly describing the drawings.

Drawings

Fig. 1 shows the concentrations of "free" insulin achieved by the preferred embodiments of the invention.

Fig. 2 is an enlargement of Section A of Fig. 1.

Fig. 3 is an enlargement of Section C of Fig. 1.

Fig. 4 is a schematic block diagram of an external programmable insulin pump programmed to deliver insulin according to the present invention.

Fig. 5 is a schematic block diagram of an implantable programmable insulin pump programmed to deliver insulin according to the present invention.

Description

The present program of insulin concentration changes is directed to coordinating elevated carbohydrate concentrations in body tissues, for example due to the ingestion of a carbohydrate-containing meal or due to a carbohydrate (e.g., glucose) infusion, with the insulin concentrations resulting from the program so that they may act together to activate and maintain the body's fuel processing capabilities. In particular, the program is designed to coordinate elevated liver and portal vein glucose concentrations with the aforementioned insulin concentrations so as to activate the dietary carbohydrate processing system which, based on investigations into the enzymes involved in the metabolism of glucose and the distribution of exogenous and endogenous glucose in the metabolic system, is believed to be primarily in the liver and to a lesser extent in muscle. Both the amount of insulin infused and the duration of the administration of the insulin pulses are independent of prevailing blood glucose levels.

Due to the binding of insulin to antibodies in persons

who has received insulin (e.g., insulin-taking diabetic subjects), the concentration of insulin which is available to interact so as to regulate fuel processing capabilities, in particular to regulate blood glucose concentrations, is typically much lower than the total concentration of insulin in the system. The concentration of insulin which is so available is referred to as the "free" insulin concentration.

The initial portion of the program is designed to activate the body's fuel processing capabilities, in particular the dietary carbohydrate processing system. In order to activate the system, the body's tissues, in particular the liver (but including muscle), must see (i.e., be subject to) sharp changes in the "free" insulin concentration as well as a gradual overall increase in the interpeak "free" insulin concentration, at the same time that the concentration of glucose in the liver and portal vein is high, e.g., after ingestion of a carbohydrate-containing meal or after an infusion of carbohydrates. Section A of Fig. 1 and Fig. 2 show the necessary pattern of "free" insulin concentrations. The combination of these three factors, i.e., rapid changes in "free" insulin concentration superimposed over a gradually increasing "free" insulin concentration in the presence of a high intra-liver or portal vein glucose concentration, will cause the liver (and to a lesser extent muscle) to synthesize and activate the enzymes responsible for metabolizing glucose.

After the system is activated, it may be maintained by administering time-varying quantities of insulin to produce a "free" insulin concentration which oscillates

near or about the baseline concentration, i.e., that concentration of insulin which existed prior to administering the initial portion of the program. Section C of Fig. 1 and Fig. 3 show the oscillating "free" insulin concentrations.

The time-varying quantities of insulin are preferably pulses of insulin, i.e., injections or infusions which start and stop within a short period of time (on the order of seconds). However, any time-varying quantities which produce the necessary pattern of "free" insulin concentrations may be used.

The administration of a primary series of pulses of insulin spaced closely enough such that the effect of one pulse (i.e., a "free" insulin concentration peak) has not been completely dissipated before the next pulse is administered will result in the necessary sharp changes in "free" insulin concentration over an increasing interpeak insulin concentration. Referring to Figs. 1 and 2, a carbohydrate-containing meal is ingested or a carbohydrate infusion is initiated at D, or time =0, when the "free" insulin concentration is X. X represents the concentration of "free" insulin present in the patient's system prior to the administration of the insulin pulses of the primary series, and is herein referred to as the baseline concentration. For example, in a diabetic patient X would be the lowest "free" insulin concentration in the patient's system following the last insulin injection of a typical treatment program. Typical baseline "free" insulin concentrations are from 5 to 15 micro-Units of insulin per milliliter of serum (μU/ml).

Coincident with or shortly following the establishment of an elevated carbohydrate concentration, the first pulse of the primary series of the present insulin delivery program is administered, which will result in peak E. The pulse is an amount of insulin sufficient to cause the peak "free" insulin concentration in the blood to reach from 50 to 3000 μU/ml, preferably 100 to 2000 μU/ml. When the "free" insulin concentration decreases by about 90% to Y (i.e., to about 10% over the "free" insulin concentration at the time of administering the first pulse) the second pulse of the primary series is administered, which will result in peak F. When the "free" insulin concentration again decreases by about 90% to Z, or to about 10% over the "free" insulin concentration at the time of administering the second pulse, the next pulse of the primary series is administered, which will result in peak G. Repetition of this process will result in the increasing interpeak "free" insulin concentration denoted by line H. In the primary series of insulin pulses the amount of insulin injected per pulse may be constant or may vary provided the peak "free" insulin concentratin achieved after each pulse is from 50 to 3000 μU/ml, preferably 100 to 2000 μU/ml. The interpulse duration also may be constant or may vary, provided the next subsequent pulse is administered before the insulin concentration resulting from the previous pulse has returned to that concentration which existed prior to administering the previous pulse, so that the interpeak "free" insulin concentration increases by 10 to 500 μU/ml from one pulse to the next. The duration of the primary series administered with each meal or

carbohydrate infusion does not exceed three hours and generally falls within the range of about 6 to 180 minutes. Particularly effective results have been obtained with a series of 10 pulses, administered six minutes apart, over an interval of 56 minutes. Since it is desirable to administer the least amount of insulin consistent with activation of dietary fuel processing system, and since the amount of insulin required to activate a system will vary from patient to patient or even from day to day in the same patient, a rigid length or duration cannot be assigned to the primary series.

After completion of the pre-determined primary insulin pulses--carbohydrate meal/infusion sequence, pulse administration is suspended to allow the "free" insulin concentration to return to the baseline concentration, as shown in Section B of Fig. 1.

When the free insulin concentration is at or near the baseline concentration, a secondary series of smaller insulin pulses is administered to produce a concentration of "free" insulin which oscillates about or near the baseline concentration, as shown by curve J in Section C of Fig. 1 and in Fig. 3. The pulses of insulin of the secondary series are of an amount sufficient to result in peak "free" insulin concentrations of 10-300 μU/ml. The pulses (single or paired) are spaced so as to maintain a relatively constant interpeak "free" insulin concentration of 5 to 15 μU/ml between discrete pulses or pulse pairs. That is, the effects of one pulse (or pair of pulses) are allowed to dissipate before the next pulse (or pulse pair) is administered.

Administration of this secondary series will (1)

together with the primary series, maintain in an active state the body's fuel processing capabilities, in particular the dietary carbohydrate processing system, and (2) permit cycling of hepatic glucose output and hepatic glucose uptake in the period between carbohydrate ingestions or infusions. That is, as the "free" insulin concentration increases above the baseline the glucose-producing function of the activated liver is inhibited and the liver will take up glucose; as the "free" insulin concentration falls towards or below the baseline the activated liver will produce and release glucose.

Once the fuel processing system has been activated and maintained for a period of time (from one to four days) by the primary and secondary series of the insulin infusion program, it is enabled to function in a normal manner. In diabetic patients, repetitive administration of the primary and secondary series over this period enables the liver (and muscle) to function normally to autoregulate body glucose concentrations. While in insulin-dependent diabetic patients a permanent cessation of insulin injections or infusions is not possible, it is anticipated that once the program has been administered for about one to four days the activated dietary fuel processing system would only require a "tune-up" every seven to 30 or more days. Between "tune-ups" the diabetic subject would be returned to a standard conventional therapy (e.g., subcutaneous insulin, oral hypoglycemic agents, diet) in order to maintain basic levels of insulin in the metabolic system. However, with an activated fuel processing system coupled to standard conventional therapy, the diabetic subject would be less

subject to wide fluctuations in blood sugar levels and would need a less restrictive American Diabetes Association diet. Alternatively, the system may be maintained indefinitely by administering the primary series with meals and the secondary series during the nighttime.

An insulin infusion program which conforms to the present invention would involve, for example, administering a primary series of insulin pulses (e.g., intravascularly (including the portal vein), intraperitoneally, or subcutaneously) immediately following the ingestion of a mixed meal containing 10-100 g of dietary carbohydrate of alteratively 10-100 g of glucose or its equivalent (e.g., Sustacal), or the infusion of an equivalent synthetic combination of fuels. The pulses of the primary series, administered every six to thirty minutes over a 6 to 180 minute period, may be of equal or variable amounts with the average amount of the pulses being between 0.01-0.05 Units of insulin per kilogram of body weight (U/kg), and preferably 0.02 to 0.04 U/kg. As previously stated, it is desired to use the least amount of insulin required to obtain the desired therapeutic effect. These pulses will produce a corresponding series of peaks in the "free" insulin concentration having a peak amplitude of 50-3000 μU/ml, preferably 100-2000 μU/ml, in arterial blood or in arterialized venous blood at six to thirty minute intervals. Coincident with these "free" insulin peaks the interpeak "free" insulin concentration will increase by 10-500 μU/ml at six to thirty minute intervals, achieving a maximum interpeak "free" insulin concentration

of 60-1000 μU/ml at 6 to 180 minutes. Insulin administration is then suspended for an amount of time (e.g., 90-120 minutes) sufficient to allow the "free" insulin concentration to gradually return to the baseline "free" insulin concentration of 5-15 μU/ml. Following achievement of baseline "free" insulin concentrations, equal or variable insulin pulses of an average amount between 0.001-0.02 U/kg are administered every two to ninety minutes in order to achieve peak "free" insulin concentrations in arterial or arterialized venous blood of 10-300 μU/ml with a periodicity of two to ninety minutes. This secondary pulse format is continued during the entire period between carbohydrate ingestions or infusions.

The described sequence is repeated with each meal or infusion. The meals are ingested or the infusions are initiated frequently, e.g., from two to eight times a day. Meals and infusions may be administered in any combination, e.g., exclusively meals, exclusively infusions, or meals alternating with infusions in a regular or irregular pattern.

In 8 to 96 hours a significant improvement in the respiratory quotient and carbohydrate oxidation rate should be observed following the ingestion of a carbohydrate-containing meal or an equivalent carbohydrate infusion, observations which are comparable to those seen in normal subjects following ingestion of an equivalent carbohydrate-containing meal or initiation of a comparable infusion.

The primary and secondary series of the described insulin delivery program can be infused using a standard

external programmable insulin pump, such as shown schematically in Fig. 4. An external pump configuration would be preferable for use in clinical situations, for example, on an out-patient treatment basis (e.g., for "tune-ups"), for accidentally or surgically traumatized patients, or to bring a patient's metabolic system under control prior to surgery. Referring now to Fig. 4, external programmable pump 10 has a programmable microprocessor 12, pump section 14, and infusion catheter 16. Programmable microprocessor 12 includes programming keyboard 18 and display 20, for example an LCD or LED display. Pump section 14 includes pump mechanism 22 and insulin reservoir 24. Infusion catheter 16 extends from pump mechanism 22 and is inserted into the patient to deliver insulin intravascularly (including the portal vein), intraperitoneally, or subcutaneously. For example, in this configuration programmable microprocessor 12 would be programmed (1) to deliver the insulin pulses of the primary series every six to thirty minutes for 6 to 180 minutes, (2) to suspend insulin infusion for 90-120 minutes, and (3) to deliver the smaller insulin pulses of the secondary series until the next primary series is initiated. Initiation of the primary series can be automatically controlled, e.g., programmed to coincide with pre-set carbohydrate infusions, or can be manually controlled, e.g., by pressing the appropriate key on keyboard 18 when a meal is ingested. Alternatively, microprocessor 12 can be programmed to deliver only the primary series (under either manual or automatic control).

Glucose levels can be independently monitored using

fingersticks, venipuncture, or glucose sensors. A glucose sensor or analyzer could also be incorporated into the external programmable pump and arranged so as to sound an alarm when glucose levels reach certain pre-set limits as is known in the art, for example, in artificial β-cells. In this configuration, however, the glucose sensor would not control the initiation or rate of insulin infusion, but would at most be used to suspend insulin infusion if glucose levels reach a pre-set lower limit. Simultaneously with the suspension of insulin infusion, an alarm would alert the patient (or attendant); the insulin infusion program (primary series) could then be manually restarted, if desired, along with the administering of carbohydrates.

The described program can also be administered using a standard implantable programmable insulin pump, such as shown schematically in Fig. 5. The implantable pump configuration would be preferable for long-term self-care by diabetic patients. Referring to Fig. 5, implantable pump assembly 26 includes an external transmitter/receiver unit 28 and the implantable pump unit 30. External transmitter/receiver unit 28 includes programmable microprocessor 32, having programming keyboard 34 and display 36, for example, an LCD or LED display, and telemetry unit 38 which transmits control signals received from microprocessor 32 to implantable unit 30 and transmits informational signals received from implantable unit 30 to microprocessor 32. Implantable pump unit 30 includes power supply 40, programmable microprocessor 42, receiver/transmitter 44 which transmits informational signals received from microprocessor 42 to external unit

28 and transmits control signals received from external unit 28 to microprocessor 42, pump mechanism 46, and insulin reservoir 48. Infusion catheter 50 extends from pump mechanism 46 and terminates intravascularly (including the portal vein), intraperitoneally, or subcutaneously. Insulin reservoir 48 can be refilled using syringe 52. Implantable pump unit 30 can be initially programmed to administer the primary and secondary insulin series as described for the external insulin pump configuration. Using external transmitter/receiver unit 28, the insulin delivery pattern can then be initiated and/or changed, for instance, to deliver only the primary series whenever desired.

Glucose levels can be independently monitored as with the external pump configuration using fingersticks, venipuncture, or glucose sensors. Glucose sensors may also be incorporated into the implantable insulin pump and arranged so as to transmit glucose levels to the external unit 28, as is well known in the art. The external unit could merely sound an alarm when glucose levels reach a pre-settable limit, or could be programmed to suspend insulin infusion (as with the external pump configuration) and sound an alarm simultaneously. It is important to note that in both the external and implantable configurations, the glucose-level-triggered alarm is used primarily for informational purposes and would not independently initiate insulin or glucose infusions.

It should also be noted that administering carbohydrates so as to induce elevational levels sufficient to work in combination with the described insulin-infusion

pattern runs directly contrary to standard treatment regimens for diabetic patients. Further, although the pulses are timed to coincide with the anticipated elevated portal vein glucose concentrations following the ingestion of carbohydrate-containing meals or following the initiation of carbohydrate infusions, the pattern of insulin infusion and the resulting insulin concentrations of the present invention differ significantly from those which occur in normal man and from those which occur in diabetic patients on a typical treatment program.

The program of insulin infusion described can be used in diabetic subjects for rapid and efficient primary activation of the fuel processing system, in particular, the dietary carbohydrate processing system, or, for maintenance of the system by the administration, immediately prior to or following the ingestion of meals, of defined intravenous pulses of insulin of smaller magnitude than that used for primary activation. This insulin delivery pattern could also be effective in preserving and/or restoring fuel (e.g., glucose, amino acids, lipids) processing capabilities of hepatic and other tissues (e.g., muscle) in both diabetic and non-diabetic subjects in acute care situations, i.e., traumatized individuals (surgical patients, accident victims) or patients on hyperalimentation.

Other embodiments are within the following claims. For example, the interprandial (including night-time) "free" insulin concentration may be maintained at or near the baseline level by substituting standard insulin therapy for the secondary series, for example, using

long-acting (NPH) insulin or using continuous low-level insulin infusion, administering the primary series of pulses with meals; and the primary and/or secondary series could be administered intravenously (including the portal vein), intraperitoneally, or subcutaneously by using multiple oscillatory insulin injection regimens.

The Claims

1. A method of treating a diabetic or traumatized subject comprising the steps of

establishing an elevated carbohydrate concentration in said subject's metabolic system; and

activating the dietary carbohydrate processing capabilities of the subject's body tissues, particularly liver and muscle, by administering insulin to increase the "free" insulin concentration in said subject's metabolic system during at least part of the period when said carbohydrate concentration is elevated; said insulin being administered in pulses to produce a series of peaks in said "free" insulin concentration.

2. The method of Claim 1 wherein said insulin is administered to produce said peaks in said "free" insulin concentration over a progressively increasing interpeak "free" insulin concentration.

3. The method of Claim 2 wherein said pulses of insulin are administered over a period of up to three hours.

4. The method of Claim 3 wherein said pulses of insulin are administered for 6 to 180 minutes.

5. The method of Claim 4 wherein said pulses comprise a primary series and wherein there is a secondary series of pulses following said primary series; said secondary series of pulses of insulin being arranged to produce oscillations in said "free" insulin concentration

about a baseline concentration in such a way as to maintain said dietary carbohydrate processing capabilities of said subject's body tissues, particularly liver and muscle, in an active state.

6. The method of Claim 5 wherein said baseline concentration is that "free" insulin concentration which existed prior to administering said primary series; said program further comprising an interval following said primary series and prior to said secondary series during which said "free" insulin concentration is allowed to return to said baseline concentration.

7. The method of Claim 6 wherein said secondary series continues until the next subsequent establishment of an elevated carbohydrate concentration.

8. The method of any of Claims 1, 2, 3, 4, 5, 6, or 7 wherein said activating step is coincident with said step of establishing an elevated carbohydrate concentration.

9. The method of any of Claims 1, 2, 3, 4, 5, 6, or 7 wherein said activating step is performed from 2 to 8 times a day.

10. The method of any of Claims 1, 2, 3, 4, 5, 6, or 7 wherein said elevated carbohydrate concentration is established by ingesting carbohydrates.

11. The method of any of Claims 1, 2, 3, 4, 5, 6, or 7 wherein said elevated carbohydrate concentration is established by infusing carbohydrate into said subject's bloodstream.

12. The method of any of Claims 1, 2, 3, 4, 5, 6, or 7 wherein said elevated carbohydrate concentration is established by administering from 10-100 g of dietary carbohydrate.

13. The method of any of Claims 1, 2, 3, or 4 wherein said insulin pulses each fall within the range of about 0.01-0.05 U/kg.

14. The method of Claim 13 wherein said insulin pulses each fall within the range of about 0.02-0.04 U/kg.

15. The method of Claim 13 wherein said pulses are administered every six to thirty minutes.

16. The method of any of Claims 5, 6, or 7 wherein the insulin pulses of said secondary series each fall within the range of 0.001-0.02 U/kg.

17. The method of Claim 16 wherein said pulses of said secondary series are administered every two to ninety minutes.

18. The method of Claim 16 wherein the average amount of said insulin pulses of said primary series is between 0.01-0.05 U/kg.

19. The method of Claim 18 wherein the average amount of said insulin pulses of said primary series is between 0.02-0.04 U/kg.

20. The method of Claim 16 wherein said pulses of said primary series are administered every six to thirty minutes.

21. The method of Claim 7 wherein said insulin pulses of said primary series comprise 0.01-0.05 U/kg; said insulin pulses of said secondary series comprise 0.001-0.02 U/kg; said pulses of said primary series are administered every six to thirty minutes; said pulses of said secondary series are administered every two to ninety minutes; said elevated carbohydrate concentration is established from two to eight times a day by administering 10-100 g of dietary carbohydrate; and said administering of said primary series is initiated coincident with the administering of said dietary carbohydrate.

22. A programmable insulin infusion pump comprising a programmable microprocessor; a pump mechanism controlled by said microprocessor; an insulin reservoir feeding into said pump mechanism; and a catheter extending from said pump mechanism capable of terminating in a subject intravascularly, intraperitoneally, or subcutaneously; said microprocessor being programmed to effect changes in the free insulin concentration of the metabolic system of a diabetic or traumatized subject during at least part of a period in which an elevated carbohydrate concentration is established in said subject's metabolic system in such a way as to activate the fuel processing capabilities of said subject's body tissues; said pump administering insulin

in pulses to produce a series of peaks in said "free" insulin concentration while said carbohydrate concentration is elevated.

23. The pump of Claim 22 wherein said microprocessor, said pump mechanism, and said insulin reservoir are external to said subject.

24. The pump of Claim 22 wherein said microprocessor, said pump mechanism, said catheter, and said insulin reservoir comprise an implantable unit, said implantable unit being implanted subcutaneously in said subject, said microprocessor comprising a first microprocessor, said pump further comprising an external transmitter/receiver unit, said external unit comprising a second programmable microprocessor, means for receiving control signals from said second microprocessor and transmitting said control signals to said implantable unit, and means for receiving informational signals from said implantable unit and transmitting said informational signals to said second microprocessor, said implantable unit further comprising a power supply, said power supply powering said first microprocessor and said pump, means for receiving said control signals from said external unit and transmitting said control signals to said first microprocessor, and means for receiving said informational signals from said first microprocessor and transmitting said informational signals to said external unit.

25. The pump of any of Claims 22, 23, or 24 further comprising a glucose sensor and an audible or visual alarm, said sensor arranged so as to measure said subject's blood glucose level and to activate said alarm and suspend said program of insulin administering when said measured glucose level reaches a pre-set level.

26. The pump of any of Claims 22, 23, or 24 wherein said effecting step comprises administering a program of time-varying quantities of insulin.

27. The pump of any of Claims 22, 23, or 24 wherein said time-varying quantities are arranged to produce peaks in said free insulin concentration over an increasing interpeak free insulin concentration.

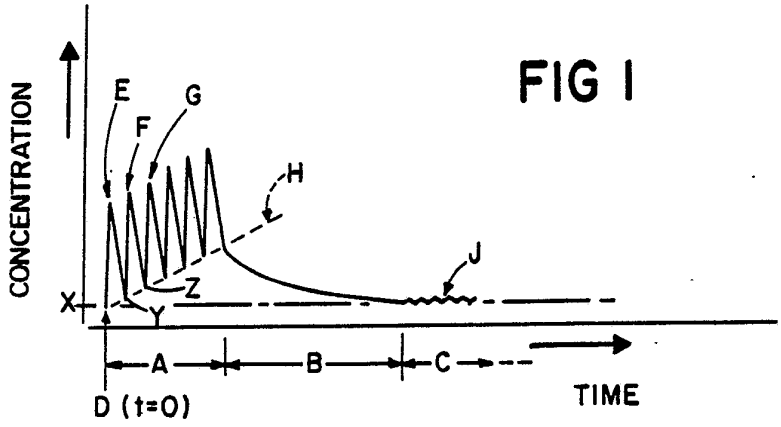


FIG 1

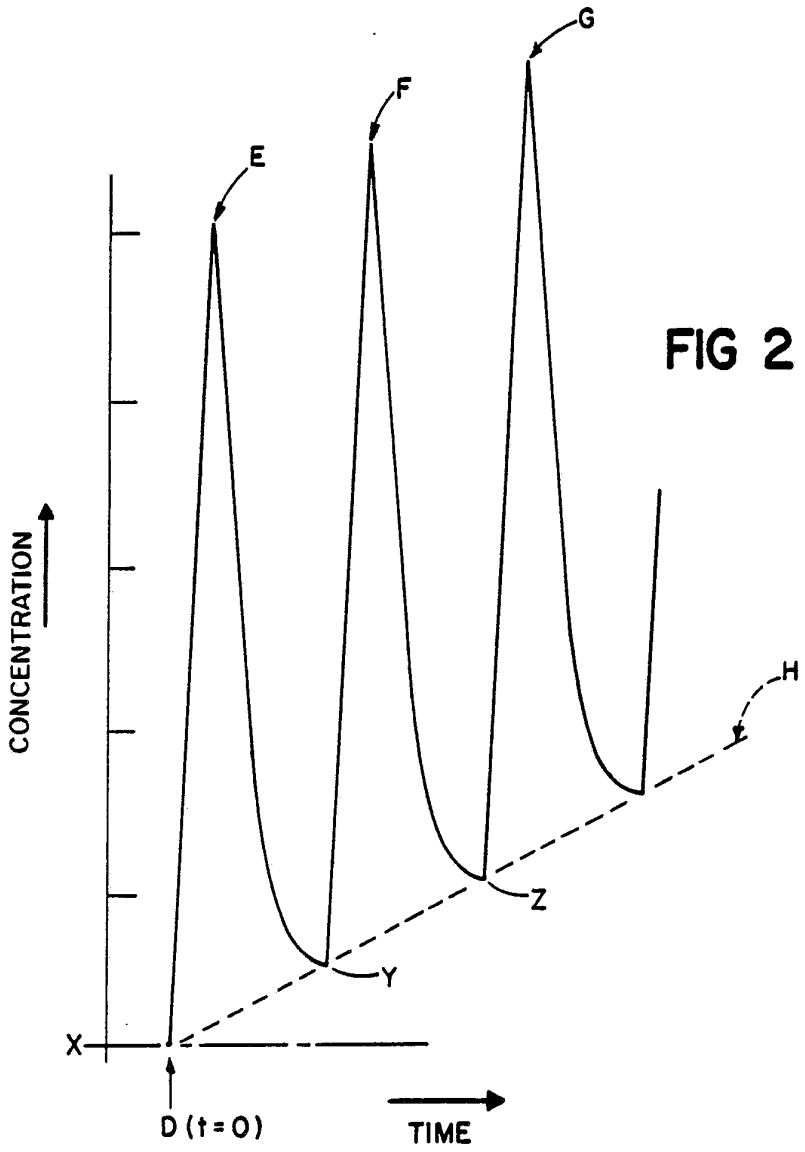


FIG 2

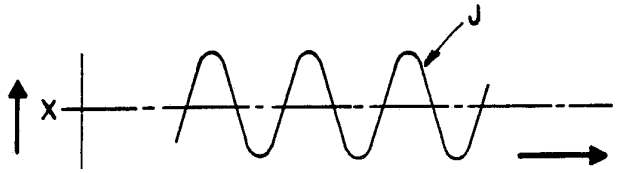
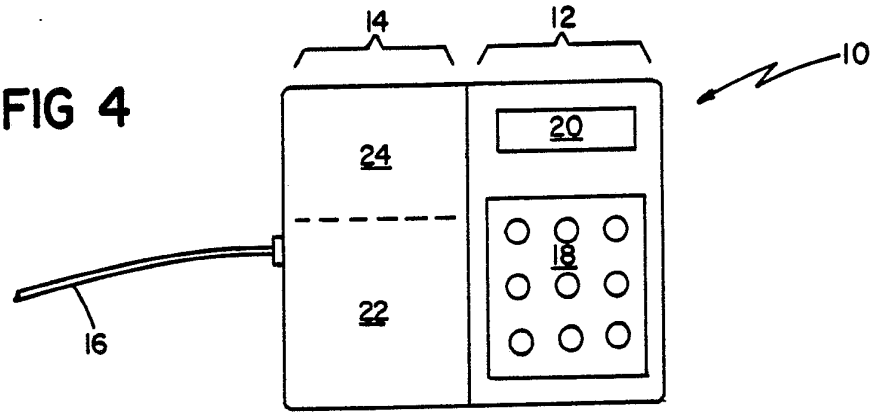


FIG 3

FIG 4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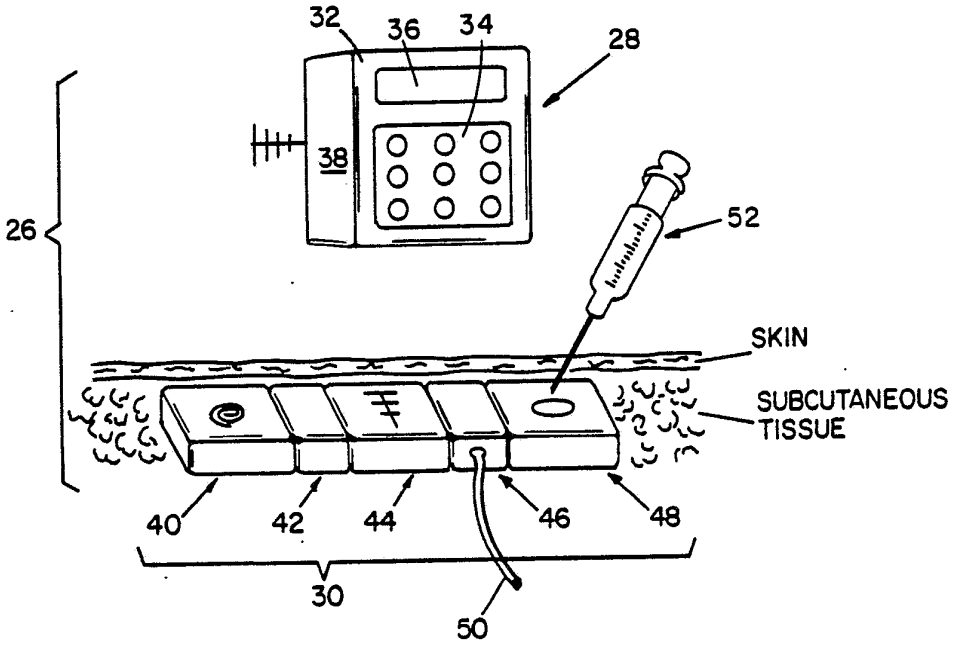
32
36
34
28
38
26
52
SKIN
SUBCUTANEOUS TISSUE
40
42
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46
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FIG 5

INTERNATIONAL SEARCH REPORT

International Application No PCT/US84/02020

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] A61K 37/26; B67 D 5/48
U.S. Cl 424/178; 604/65; 604/67

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	424/178; 604/65; 604/67

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A 4,253,456 Published 3 March 1981, Schindler et al.	1-27
X,P	US, A 4,472,385 Published 18 September 1984, Brange et al.	1-27
X,E	US, A 4,498,843 Published12 February 1985, Schneider et al	1-27
X	N, Diabetologia Vol. 19 issued 1980, W.D. Lougheed et al., "Insulin Aggregation in Artificial Delivery Systems" See pages 1-9	1-27
X	N, Diabetes Vol. 32 issued May 1983, W.D. Lougheed et al, "Physical Stability of Insulin Formulations", See pages 424-432	1-27
X	N, Diabetes, Vol. 30 issued January 1981, Jacques Bringer et al, "Prevention of Insulin Aggregation By Dicarboxylic Amino Acid During Prolonged Infusion", See pages 83-85	1-27

* Special categories of cited documents: [15]

"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

"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.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
22 February 1985	01 MAR 1985
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/USA	Frederick E. Waddell

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	US, A 4,055,175 Published 25 October 1977, Clemens et al.	1-27
X	US, A 4,245,634 Published 20 January 1981, Albisser et al.	1-27
X	US, A 4,282,872 Published 11 August 1981, Franetzki et al	1-27
X	N, Diabetes Vol. 31, No. 1 issued 1 January 1982, Foss et al, "Restoration of Glucose Homeostasis in Insulin-Dependent Diabetic Subjects", An Inducible Process, See pages 46-52	1- 27

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers....., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.