CLINICAL RESEARCH

Insulin bolus given by sprinkler needle: effect on absorption and glycaemic response to a meal

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Abstract

Two studies were conducted investigating the effect of injecting short acting insulin subcutaneously by means of a sprinkler needle; this needle has 14 small holes in the wall but is sealed at the tip. In the first study absorption of 8 U iodine-125 labelled Actrapid HM injected subcutaneously at two separate sites in the abdominal wall was measured in 10 patients. One injection was given with the sprinkler needle and the other with a conventional needle. The initial dose absorbed during the first 30 minutes was significantly higher with the sprinkler needle. In the second study 10 U Actrapid HM was given to 11 other patients (all negative for C peptide and with low insulin binding antibody titres) on two separate days immediately before a standardised breakfast either by the sprinkler needle or by a conventional needle (random order). Plasma free insulin increased more rapidly and to higher concentrations with the sprinkler needle and the glycaemic response was considerably diminished.

The sprinkler needle improves both the insulin absorption rate and the glycaemic response to a meal and may reduce the 30 minutes or so before meals that diabetics must inject to minimise postprandial hyperglycaemia.

Introduction

In non-diabetic subjects a steep increase in the plasma insulin concentration occurs in response to a meal and between meals concentrations are low and comparatively stable.¹ In an effort to mimic this "normal" pattern an increasing number of diabetic patients now follow a regimen of injecting fast acting insulin before the main meals and long or intermediate acting insulin at bedtime (the so called basal-bolus regimen).^{2,3} Compared with the insulin

peaks induced by meals in non-diabetics, however, those in insulin treated diabetics show a less steep rise and fall and the maximum concentration is lower. A possible explanation may be that maximum insulin absorption takes place only after the injected insulin has achieved diffusion equilibrium in the tissue.^{4,6}

We decided to see whether subcutaneous injection of short acting insulin by means of a special needle containing 14 small holes in the wall but sealed at the tip (sprinkler needle) might improve the absorption rate of insulin and hence diminish the glycaemic response to a meal.

Materials, subjects, and methods

The sprinkler needle is an ordinary 25 mm multi-injection needle with an inner diameter of 0.5 mm but with 14 holes set in the wall 5-15 mm from the tip, which is sealed. The total square area of the 14 holes is equal to the square area of the original outlet. For comparison as a "conventional" needle a similar but unmodified needle was used. For all injections, which were given at an angle of 45 degrees, the whole length of the needle was inserted. The sprinkler needle is experimental and has been used only in our studies. Figure 1 shows the action of the needle.

ABSORPTION STUDY

Ten patients (three women, seven men) with a history of insulin dependent diabetes mellitus for a mean of 18 years (range 1-28 years) participated in the absorption study. Their mean age was 32.2 years (range 19-50), height 176.8 cm (range 156-188 cm), and weight 68.9 kg (range 55-84 kg). After an overnight fast and abstinence from smoking the patients took their normal breakfast followed by 200 mg potassium iodine to block the thyroid. Eight units of iodine-125 labelled insulin (Actrapid HM 40 U/ml, specific activity 0.056-0.074 MBq/ml) was injected subcutaneously at two separate sites in the abdominal wall roughly 5 cm distal to the umbilicus and 7 cm from the midline. One injection was given with the conventional needle and the other with the sprinkler needle, the injection sites being chosen at random. All injections were given at an angle of 45 degrees.

Emission of γ rays was measured continuously with two stationary gammacounters (5x5 cm Na-I scintillation detectors), readings being taken initially every five minutes and later every 10 minutes for up to eight hours after the injections or until the residual activity was less than 5-10% of the initial value. All counts were corrected for background activity and the

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FIG 1—Action of sprinkler needle.

FIG 2—Mean percentage residual radioactivity at injection site compared with percent of initial.

residual activity at a given time expressed as a percentage of initial values and plotted semilogarithmically. From these data we calculated the percentage of the initial dose absorbed during consecutive 30 minute periods. Before the insulin injection and hourly thereafter blood glucose was measured to ensure a stable concentration between 6 and 12 mmol/l. If the concentration rose above 12 mmol/l 4 U fast acting insulin (Actrapid HM) was injected subcutaneously in another region. If the glucose concentration fell below 6 mmol/l the patient was given apple or orange juice.

MEAL TEST STUDY

Eleven other patients with insulin dependent diabetes mellitus (four women, seven men; mean duration of disease 14 years (range 5-30)) participated in the meal test study. Their mean age was 43.4 years (range 26-69), height 171.6 cm (range 161-189 cm), and weight 67 kg (range

52-83 kg). The patients had a plasma C peptide concentration of less than 0.05 pmol/l six minutes after 1 mg glucagon intravenously, and their mean concentration of insulin binding antibodies was low (0.361 U/l; range 0.017-1.967 U/l). None of the patients had diabetic nephropathy, two had symptoms of peripheral neuropathy, and seven had background retinopathy. Before the study five patients were having two insulin injections daily, one a single injection daily, and five were using insulin pumps; the mean daily insulin dose was 38.2 U (range 20-52 U). The mean glycosylated haemoglobin value was 8.8% (range 6.2-9.7%; normal range 4.1-6.1%).

Patients were admitted to hospital the day before testing. None had received intermediate acting insulin for 36 hours or long acting insulin for 48 hours before the study. Blood glucose concentration was kept between 8 and 12 mmol/l during these periods by repeated injections of 4-8 U fast acting insulin. At 7 am next morning a cannula was inserted and at 8 am

FIG 3—Mean percentage of initial insulin dose absorbed during consecutive 30 minute periods (calculated from data in fig 2).

(immediately before a standardised breakfast) 10 U insulin (Actrapid HM 100 U/ml) injected subcutaneously in the abdomen either by the sprinkler or by the conventional needle. Blood samples were drawn for estimation of blood glucose and plasma free immunoreactive insulin concentrations at -60, -15, 0, 15, 30, 45, 60, 75, 90, 105, and 120 minutes. The aim was to keep the blood glucose concentration between 8 and 12 mmol/l for the rest of the day by repeated injections of small doses of fast acting insulin. The same procedure was repeated the next morning with the other needle. On the two days of the meal tests fasting blood glucose and plasma free insulin concentrations were equal.

Blood samples were drawn into chilled heparin tubes containing 500×10^6 kallidinogenase inactivating units of aprotinin per l blood and plasma stored at -25°C for later analysis of glucose⁷ and free insulin.⁸ All individual samples were run in the same assay in order to avoid interassay errors.

ETHICS AND DATA HANDLING

All patients gave informed consent to the study, which was approved by the local ethics committee.

Data from the absorption study were presented as mean values (figs 2 and 3) and data from the meal test study as means and SEM (figs 4 and 5). In both studies significance was tested by the paired Wilcoxon rank sum test. Differences resulting in p values below 0.05 were considered to be significant. The residual activity after injection plotted in figure 2 was measured at five minute intervals.

Results

The sprinkler needle gave rise to significantly lower residual activity from 20 to 70 minutes after the insulin injection (fig 2; $p < 0.05$). Calculation of the

TABLE I—Timing of significant differences in increase in plasma insulin and blood glucose values between the two methods of injection

Case No	Increase in plasma insulin (pmol/l)						Increase in blood glucose (mmol/l)	
	15 min		45 min		60 min		60 min	
	Sprinkler needle	Conventional needle	Sprinkler needle	Conventional needle	Sprinkler needle	Conventional needle	Sprinkler needle	Conventional needle
1	320	95	500	375	410	355	1.35	1.3
2	245	50	575	285	560	365	3.15	3.2
3	90	105	270	180	270	165	4.35	7.6
4	140	245	285	370	395	395	3.15	2.75
5	235	0	515	330	485	270	5.95	7.35
6	160	80	305	240	225	200	2.3	2.25
7	35	70	200	255	195	270	5.3	6.55
8	175	110	750	520	650	545	1.45	1.6
9	60	-10	290	220	355	285	6.4	8.4
10	95	-85	295	225	525	335	7.6	8.9
11	175	110	510	455	415	460	-4.4	0.05
Mean (SEM)	157.27 (25.93)	70.00 (25.50)	408.64 (51.34)	314.09 (32.18)	407.73 (42.88)	331.36 (33.38)	3.33 (0.99)	4.54 (0.98)
z Value	-2.0449		-2.2672		-2.0896		-2.1339	
p Value	0.0409		0.034		0.0367		0.0329

FIG 4—Mean (SEM) changes in plasma free insulin concentrations during intake of standardised breakfast preceded by subcutaneous injection of insulin by sprinkler or conventional needle.

TABLE II—Areas under insulin and glucose curves with the two methods of injection

Case No	Area under curve (0-120 min)			
	Insulin (pmol/l/min)		Blood glucose (mmol/l/min)	
	Sprinkler needle	Conventional needle	Sprinkler needle	Conventional needle
1	43.800	36.565	66	56
2	50.250	31.568	309	342
3	23.925	17.438	615	746
4	33.863	38.288	225	177
5	54.413	36.375	632	651
6	25.163	19.575	244	256
7	20.288	27.300	389	440
8	54.375	44.438	112	123
9	32.063	23.588	546	797
10	40.463	30.038	647	827
11	37.988	41.925	-422	16
Mean (SEM)	37.870 (3.640)	31.550 (2.690)	305.73 (92.21)	402.82 (92.47)
z Value	2.2228		2.3117	
p Value	0.0262		0.0208	

percentage of the initial dose absorbed during consecutive 30 minute periods showed absorption in the first period to be significantly faster with the sprinkler needle than with the conventional needle (fig 3; $p < 0.02$).

FIG 5—Mean (SEM) changes in blood glucose concentrations during intake of standardised breakfast preceded by subcutaneous injection of insulin by sprinkler or conventional needle.

In the meal test study plasma free insulin increased more rapidly and to higher concentrations when the sprinkler needle was used as compared with the conventional needle, differences being significant at 15, 45, and 60 minutes after injection (table I, fig 4; $p < 0.05$). When the sprinkler needle was used the area under the insulin curve from time zero to 120 minutes (38 SEM 3.6) pmol/l/min was significantly greater than that when the conventional needle was used (32 (2.7) pmol/l/min) (table II; $p < 0.05$). The glycaemic response was considerably diminished when insulin was injected with the sprinkler needle (306 (SEM 92) mmol/l/min) as compared with the conventional needle (403 (92) mmol/l/min) (table II; $p < 0.05$). The increase in blood glucose showed a significant difference only 60 minutes after the injection (table I, fig 5; $p < 0.05$).

Discussion

This study shows that the initial absorption of short acting insulin is faster when insulin is injected with a sprinkler needle compared with injection by a conventional needle.

Previous studies have shown that after subcutaneous injection of fast acting insulin transport in the interstitial space and thus absorption are subject to the rate limiting effects of diffusion conditions and distance.⁴ Absorption from the depot during the first 15 to 60 minutes after injection is comparatively slower than during the later phase.⁵ An explanation for this so called lag phase phenomenon may be that after injection diffusion equilibrium must occur before constant and maximal insulin absorption can take place. This is supported by the lag phase that occurs in the initial stage of a continuous subcutaneous insulin infusion but which disappears when the infusion is stopped.⁶ Thus we have found that by spreading the injected insulin in the tissue with the aid of a sprinkler needle the insulin absorption rate is increased.

To examine the clinical importance of our finding we carried out a meal test. The results showed that plasma free insulin increased more rapidly and reached higher concentrations when using the sprinkler needle as compared with a conventional needle and that the glycaemic response to a meal was significantly smaller when the sprinkler needle was used.

The initial absorption rate of insulin may also be increased by employing jet injection devices, which produce a more rapid increase in plasma free insulin than after injection with a conventional needle.⁹⁻¹¹ Jet injection devices, however, need regular maintenance, are inconvenient to carry, and are expensive; hence they are not widely used.⁹⁻¹²

The sprinkler needle is as easy to use as a conventional needle and may reduce the 30 minutes or so before meals that diabetic patients must inject¹³ to minimise postprandial hyperglycaemia.

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(Accepted 27 March 1987)

100 YEARS AGO

Another Report of the evidence collected by the Royal Commission on Education has been issued, and, though it consists of over 1,000 pages, it contains nothing beyond the evidence taken down to April 6th and the syllabus of points for inquiry. The latter is concerned with many matters of great importance to school-boards and the teaching profession, such as the state of laws, codes, and grants, the consideration of cost and grievances.

The good of the child as an individual and as a unit in society is the object which national education should seek to attain, and we look in vain for any special attention given by the Commissioners to ascertaining from competent authorities the actual condition of health, strength, and growth of our school-population. The reason of this omission is not far to seek when we look at the lists of Commissioners and witnesses, for no member of the medical profession appears among those concerned in compiling the volume. It is very desirable that, before the Commission has concluded its work, some direct and impartial evidence should be collected as to the condition of the children as seen in our primary schools. A good deal of evidence is published about the teaching of science to the children; and it may be presumed that those who desire this kind of instruction to be given are possessed of scientific training, and they ought, therefore, to be able to see the propriety of instituting a scientific inquiry as to the actual condition of the children, to be made by those who would be competent to observe for themselves, and not be dependent entirely upon the opinions of teachers.

Two important references in the points given for inquiry remain without satisfactory answer in evidence thus far. "Is it (that is, the quantity of knowledge demanded) such as to cause over-pressure? Definition of over-pressure." Here we come upon a question of great importance, a problem that requires the best skill of the medical profession. This term, "over-pressure," which we so often meet with in the evidence, is not a medical term; but the physical effects of too much school work, or anything else that exhausts and deprives of strength, may be determined by observation. Before witnesses are questioned as to whether over-pressure exists in their schools, the Commission should define what is meant by this condition, and how other people can see it when they look at children in schools.

Another disadvantage, which flows from the unfortunate mistake which the Committee has made, in taking only the opinion of teachers on the

condition of the children, is that any defects found in them are likely to be attributed to some of those conditions only which the teacher sees. The condition of many children in our schools, besides those "over-pressed," demands attention; the blind and the dumb are to some extent cared for, but what pains are taken by the Education Department to train the badly made feeble brains, to check the development of myopia, to ascertain whether intelligent children—who suffer from frequent headaches, as many do, or who occasionally have a fit—are educated or excused attendance at school on account of ill-health, to their own disadvantage and the public loss? The evidence of many school teachers shows abundantly, what is well known, that a hard-and-fast rule for educating children is not what will produce the best effects. Teachers and Her Majesty's Inspectors seem to differ in methods of diagnosing the child's condition, but both are apt to think that they can recognise the child's state of health by instinct and practice, whereas the real condition of the child can only be determined by scientific observation. (*British Medical Journal* 1887;ii:30.)

The House of Lords has taken a step of great public importance in appointing a Select Committee on the subject of the abatement of the smoke nuisance. It is to be hoped that the Committee will at once proceed to take evidence. We all want to know what further resources in the way of abating this nuisance are actually available. Since the question was inquired into thirty years since by Lord Palmerston's Committee, no official report has been made on the subject. It is, however, well known that enormous progress has been made in all practical as well as scientific details, and even principles connected with the economic and smokeless consumption of fuel both for domestic and manufacturing purposes. Very little of this available knowledge is, however, largely utilised, or, indeed, adequately apprehended either by private individuals or manufacturing firms. It is monstrous that where so much can be done so little is done. In 1887 we are but little ahead in common practice of 1853. The mere taking of evidence and focussing existing information in an official publication would itself be of great public service. (*British Medical Journal* 1887;ii:32.)