

Parenteral absorption of insulin from the lung in diabetic children

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Abstract Semi-synthetic human insulin was delivered via a novel nebulizer to the respiratory tracts of six diabetic children. Blood glucose control obtained was at least as good as a control day when they received their usual dose of subcutaneous insulin.

Systemic absorption of insulin given by aerosol into the respiratory tract was first described by Gaensslen in 1925.¹ Wigley *et al.* repeated these experiments 46 years later using diabetic subjects.² The potential to give diabetic subjects their daily requirement of insulin via this route appeared slight, as the percentage of the delivered dose that was absorbed systemically was very small, the reproducibility of the dose thought to be poor, and the animal insulins used could produce allergic reaction when given over the long-term.

A delivery system was developed which overcomes in part the first two problems. Semi-synthetic human insulin was used to diminish the risk of the third.

THE NEBULIZER

This machine consists of a standard Hudson nebulizer which is driven by a battery powered air pump. A 200 ml chamber is filled with aerosolized insulin by operation of the pump for a predetermined time. The patient inhales this 'mist' during the very first phase of inspiration through a mouthpiece. The duration of inspiration and expiration (usually 3 s each) is cued by a green and red light, or additionally a tone signal. The mist chamber is filled again during exhalation. The number of successful breaths completed is recorded on a visual display. Breaths not conforming to the preset pattern trigger an alarm, and are not counted (Fig. 1). Using this system, the amount of aerosolized insulin (Actrapid, semi-synthetic, human U500) delivered is very uniform (approximately $\pm 5\%$). The actual dose per breath is determined by setting the running time of the pump usually to deliver 2 μ l/breath. The patents for this machine are currently held by the Development Finance Corporation.

METHODS

Diabetic children with the characteristics shown in Table 1 were recruited into the trial. Their parents gave informed consent.

On Day 1 the children received their usual subcutaneous doses of insulin and their usual carbohydrate controlled diet at approximately 0830, 1030, 1230, 1530, 1800 and 2100 h.

Blood samples were collected from an indwelling venous line before insulin dosage and breakfast, at half-hourly intervals for

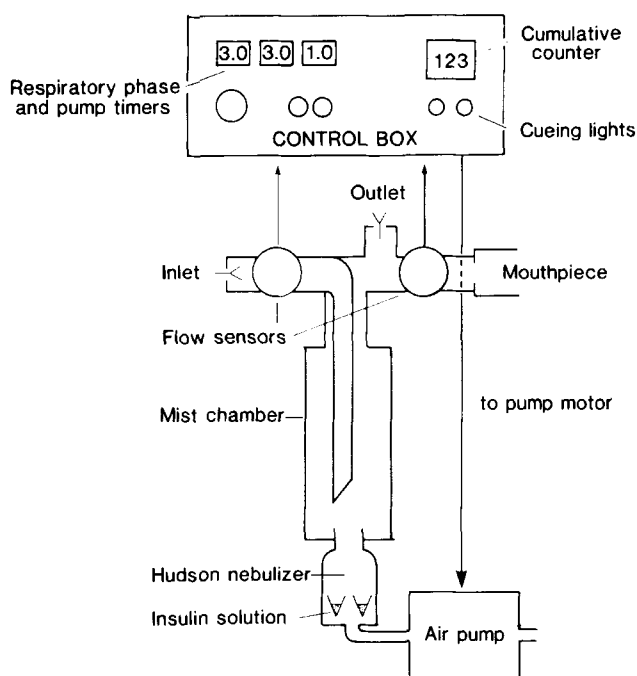


Fig. 1 Diagram of patient-activated nebulizer.

Table 1 Characteristics of diabetic patients

Patient	1	2	3	4	5	6
Age (years)	9	8	10	12	10	15
Duration of diabetes (years)	2	4	1	5	1	3
Usual insulin (U; dose/day per kg)	0.37	0.78	0.63	1.0	0.39	0.49
Presence of residual β cell function (24 h urinary C-peptide creatinine ratio > 0.2 nmol/mmol)	+	—	+	—	+	+
Presence of anti-insulin antibodies (titre >1:2)	—	+	+	+	—	—

2 h and thereafter hourly until mid-afternoon. The blood samples were analysed for plasma glucose, and 'free insulin' (by radio-immunoassay after PEG precipitation using a modification of the method of Kuzuya *et al.*³). During this sampling period the patient received 50 breaths of aerosolized insulin diluent, and

Table 2 Changes in pulmonary function tests

Pulmonary function results (% of expected normal values)	Patient number	Before study	Time of lung function testing			
			After diluent inhaled	After insulin inhaled	After 3 days of insulin inhalation	10 days after insulin inhaled
VC	1*	90	90	92	91	86
FVC		95	96	92	90	91
FEV ₁		97	95	89	88	89
MMFR		119	118	120	129	127
FRC		83	88	94	89	102
RV		73	84	70	75	129
TLC		89	93	87	87	99
VE Max 50% VC		66	62	67	64	60
VE Max 25% VC		77	69	80	74	65
VC	2†	101	111	101	107	103
FVC		104	111	105	110	109
FEV ₁		84	94	72	89	102
MMFR		59	72	33	63	94
FRC		107	109	114	—	101
RV		107	97	129	—	90
TLC		103	106	109	—	104
VE Max 50% VC		48	35	65	—	44
VE Max 25% VC		27	37	87	—	29
VC	3*	94	92	96	97	96
FVC		97	96	99	101	100
FEV ₁		100	98	103	104	99
MMFR		142	134	118	125	135
FRC		79	80	75	91	—
RV		68	96	80	93	—
TLC		91	96	94	98	—
VE Max 50% VC		70	73	68	70	—
VE Max 25% VC		69	74	75	65	—
VC	4	93	88	92	—	—
FVC		95	94	91	—	—
FEV ₁		91	92	84	—	—
MMFR		121	121	115	—	—
FRC		102	103	102	—	—
RV		106	124	120	—	—
TLC		95	98	96	—	—
VE Max 50% VC		60	55	52	—	—
VE Max 25% VC		67	65	67	—	—
VC	5	82	85	85	86	83
FVC		87	87	85	87	90
FEV ₁		82	80	79	79	78
MMFR		103	89	83	78	69
FRC		97	86	100	80	78
RV		109	103	133	81	90
TLC		91	90	95	85	89
VE Max 50% VC		22	35	38	32	33
VE Max 25% VC		41	31	34	28	28
VC	6	108	109	106	—	—
FVC		108	106	109	—	—
FEV ₁		102	93	98	—	—
MMFR		105	86	76	—	—
FRC		122	119	114	—	—
RV		108	124	104	—	—
TLC		107	111	107	—	—
VE Max 50% VC		41	38	37	—	—
VE Max 25% VC		45	36	39	—	—

*These two subjects continued to use the nebulizer for a further 3 days after the original experimental day. †Patient apprehensive.

lung function (Table 2) was measured before and 15 min after.

On Day 2 the procedure was repeated, substituting nebulized insulin immediately before each meal. The dose was prescribed

empirically on the basis of earlier pilot studies in normals and other diabetic children. Lung function was tested during this morning and again 3 days later. Two children subsequently took the machine home for 2 days and attempted to control

their diabetes with it entirely. They measured blood glucose using BM Glycemic 20-800 strips and a Reflolux meter before each meal.

In normal individuals suppression of fasting C-peptide concentrations is a biological effect of exogenous insulin. This phenomenon was used in five adults in an attempt to quantitate the efficiency and reproducibility of absorption via the transpulmonary route compared with a control day when subcutaneous insulin was given. Baseline fasting plasma C-peptide was measured at -15, -5 and 0 min before the insulin was given by each route on 2 successive days.⁴ Subcutaneous Actrapid insulin was given in a dose of 0.1 unit/kg on Day 1, a dose of 4-5 times this via the nebulizer on Day 2. On a third day no insulin was given. Plasma C-peptide was remeasured at the time intervals shown in Fig. 4. Biological effect on C-peptide levels was used, as insulin levels represent the sum of exogenous and endogenous contributions. For ethical reasons, excessive lowering of blood glucose as an index of insulin effect in normal fasting volunteers could not be used, limiting the amount of insulin delivered.

The measurement of depression of C-peptide levels in response to exogenous insulin, rather than a rise in serum insulin levels, was adopted as it is not possible to differentiate between the contributions of endogenous and exogenous insulin to the total serum insulin level.

RESULTS

Flow parameters of lung function were sometimes altered by the insulin diluent and the insulin over the study period (Table 2). The overall effect of insulin with diluent was not appreciably greater than the diluent alone, but was variable between patients. Patients 1, 2 and 4 appeared to have significant functional alterations, although patient 2 was difficult to test because of apprehension. The diluent consists of water buffered to neutrality and contains the antiseptic methyl parahydroxybenzoate, sodium acetate and sodium chloride.

The individual results of blood glucose and insulin are shown in Fig. 2. In all children the control day showed poor blood glucose control, possibly attributable to their relative inactivity in the laboratory. On the second day all but one showed considerably improved blood glucose and free plasma insulin responses with similar activity levels and identical diet. The exceptions related to machine malfunction due to a blocked nebulizer unit. The responses between patients were variable and individual calibration was necessary. Within patients the rise in free plasma insulin concentrations for a given nebulized dose was variable (Fig. 2) indicating either differences in efficiency of absorption from time to time or some other biological variable such as variable antibody binding or insulin removal rate.

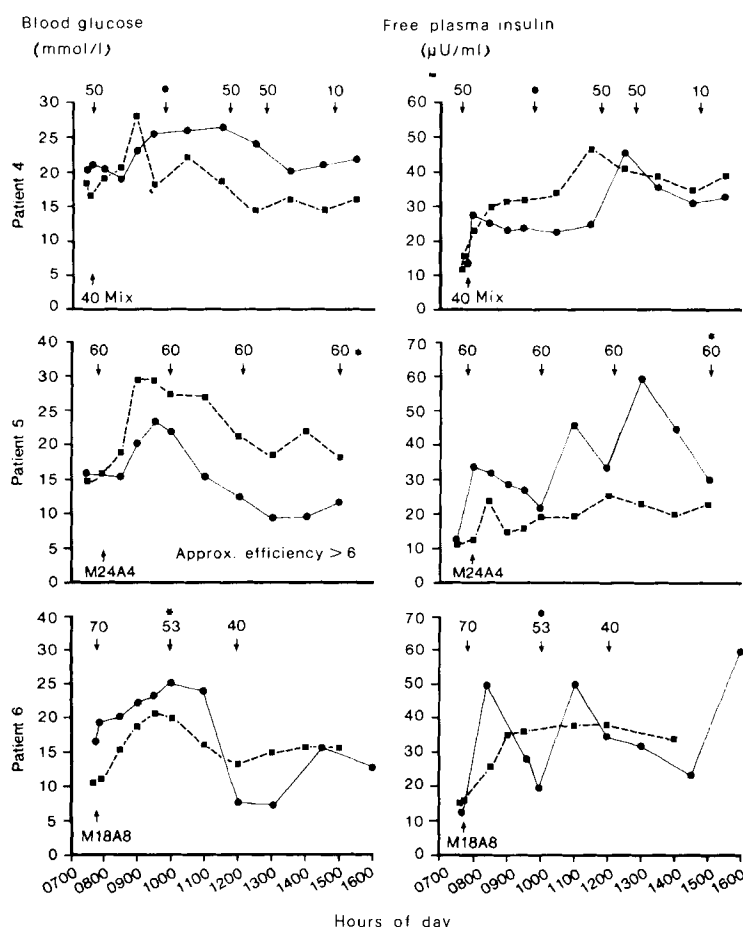


Fig. 2 Blood glucose and insulin results. Figures in upper part of panel are number of breaths taken. Figures in lower part of panel are doses of SC insulin; M = Monotard; A = Actrapid; mix = Mixtard. *Machine malfunction.

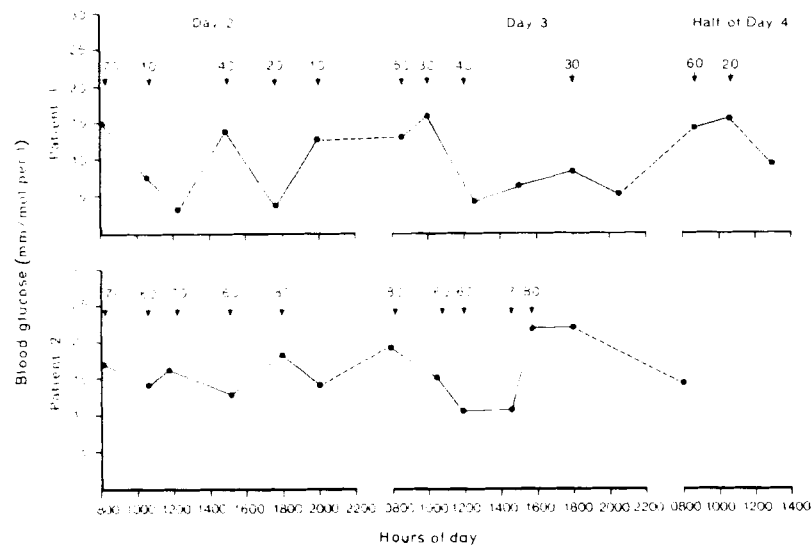


Fig. 3 Longer term blood glucose responses to nebulized insulin. Figures in upper part of panel represent the number of breaths of insulin taken (4500).

In the two children who continued with the machine at home for 2 further days, similar control of blood glucose was experienced (Fig. 3).

The absorption kinetics of insulin through the lung in normals appears to be little different to that of subcutaneous Actrapid insulin (Fig. 4). The efficiency of absorption in normals ($n = 5$) was between 20 and 25% as judged by *in vivo* C-peptide responses. The reproducibility of biological effect in a normal subject is shown in Fig. 5.

The efficiency of absorption in the diabetics was difficult to calculate because of poor matching of the results on the day subcutaneous insulin was given compared with the day insulin was delivered by nebulizer. The presence of insulin antibodies also makes measurement of absorption kinetics different to those in normals.

DISCUSSION

It is possible to control diabetes in children with insulin delivered by the transpulmonary route using a novel patient-activated

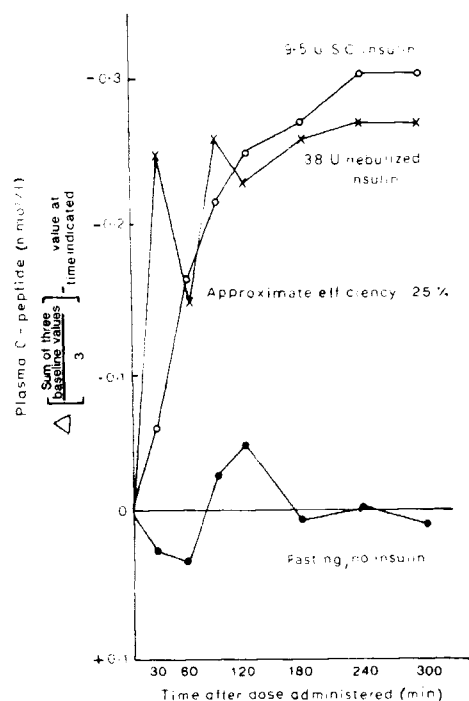


Fig. 4 Depression of fasting plasma C-peptide in response to subcutaneous and nebulized insulin.

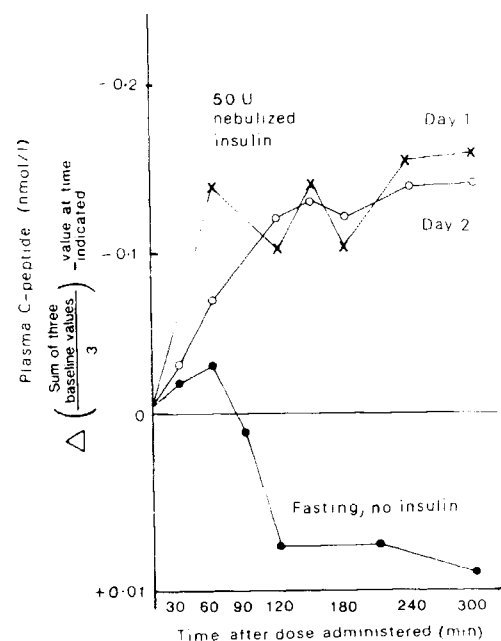


Fig. 5 Reproducibility of biological effect of nebulized insulin in a normal subject.

nebulizer. The efficiency of absorption compared with the subcutaneous route is relatively low (20–25%) but the predictability of biological response to a given dose is sufficient in the same individual for a degree of control of blood glucose at least as good as with subcutaneous insulin to be obtained. With further modifications such as optimizing compressor flow rates and degree of filling of the nebulizer bowl to obtain optimal particle size nebulae and regularizing depth and duration of inspiration, it should be possible to increase the efficiency of absorption and reproducibility of biological effect. The long-term effects on the respiratory tissues are not known; longer clinical trials are being undertaken with caution. A portable machine has been constructed so that these trials can be conducted at home or at school.

ACKNOWLEDGMENTS

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