LOW DOSE INSULIN THERAPY FOR TREATMENT OF DIABETIC COMA AND PRECOMA — SINGAPORE EXPERIENCE

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SYNOPSIS

Twenty-five consecutive patients admitted to Toa Payoh Hospital with severe uncontrolled diabetes mellitus were treated with small hourly intramuscular doses of soluble insulin. The regime was effective in bringing down blood glucose in 23 patients. The two non-responders were "insulin resistant". Three patients died of causes not attributable to this form of therapy.

INTRODUCTION

Since Sonksen et al (1972) showed that small doses of insulin were adequate in the treatment of severe uncontrolled diabetes mellitus, different small-dose insulin regimes have been used in the treatment of diabetic ketoacidosis and hyperosmolar non-ketotic diabetic 'coma' (Alberti et al, 1973, Page et al, 1974, Kidson et al, 1974, Semple et al, 1974). We chose the small dose intramuscular insulin regime of Alberti et al, 1973, for the treatment of patients admitted to our hospital with severe uncontrolled diabetes mellitus. The regime is simple and easily carried out in a general medical ward. Our aim was not only to determine its effectiveness, but also to see if it was feasible to cut down the number of blood glucose estimations to relieve our laboratory services of some work load.

MATERIAL AND METHODS

Twenty-five consecutive patients admitted to Toa Payoh Hospital, Singapore, with severe uncontrolled diabetes mellitus were treated with this regime. Of these, 18 were Chinese, 4 Malays and 3 Indians. Clinical details are given in Table I. There were 11 males and 14 females. The ages ranged from 14 to 71 years (mean 52.8 years). Of the 25 patients, 22 were ketoacidotic and 3 were in non-ketotic hyperosmolar 'coma'. On admission 17 patients were drowsy but obeyed commands, 3 were in precoma, stuporose and responding to pain and

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TABLE I — Clinal Details

Number Of Patients — 25			
Males — 11		Females — 14	
Mean Age (Yrs) — 52.8 (Range 14-71)			
Keto-Acidotic — 22		Hyperosmolar — 3	
Drowsy — 17	Prcoma — 3	Coma — 2	Conscious — 3

loud noises, 2 in. deep coma (totally unresponsive), and 3 were fully conscious but dehydrated. Precipitating factors and previous therapy are set out in Table II. There were five cases of pyelonephritis, four of pneumonia, four of gangrene, one of cellulitis with septicaemia and one of myocardial infarction. In three cases inadequate insulin was the cause of the coma and no obvious cause was found in seven cases.

Biochemical data on admission are shown in Table III. Mean blood glucose in the ketoacidotic group was 788.37 ± 62 mg/dl (range 474-1208 mg/dl), in the hyperosmolar non-ketotic group 1041 mg/dl (range 894-1250 mg/dl). Mean arterial pH, arterial PCO_2, base excess, standard bicarbonate, and serum sodium were significantly lower in the ketoacidotic group than in the non-ketotic hyperosmolar group, while mean serum potassium was higher in the ketoacidotic group. Mean blood urea was higher in the non-ketotic hyperosmolar group.

TABLE II — Precipitating Factors And Previous Therapy

PRECIPITATING FACTORS		PREVIOUS DIABETIC THERAPY	
Pyelonephritis	— 5	Insulin	— 17
Pneumonias	— 4		
Gangrene	— 4		
Cellulitis With Septicaemia	— 1	Oral Hypoglycaemic Agents	— 2
Myocardial Infarction	— 1		
Inadequate Insulin Therapy	— 3		
None Found	— 7	New Cases	— 6

Blood glucose was measured, using a Beckman glucose analyser, in all patients on admission and subsequently at hourly intervals until the blood glucose had decreased to less than 250 mg/dl. Arterial blood gas estimations were performed using Astrup method, and serum sodium and potassium by flame photometry. In eight patients who did not receive insulin therapy previously, plasma insulin was measured before the commencement of insulin therapy and hourly for five hours by radioimmunoassay using a charcoal separation technique and RHISA (Ames).

Treatment was carried out according to a schedule based on the regime of Alberti et al (1973). Intravenous fluids were commenced as soon as the diagnosis was made. For initial rehydration normal saline was used in the ketoacidotic group and half-strength normal saline for the hyperosmolar non-ketotic group. When the blood sugar had fallen to less than 250 mg/dl, the infusion was changed to 4 per cent dextrose in o.18 per cent saline in both groups. Insulin was commenced only after the results of blood sugar were known and by this time

TABLE III — Biochemical Data On Admission

	KETOACIDOTIC — 17 CASES		HYPEROSMOLAR NON-KETOTIC — 3 CASES	
	MEAN	RANGE	MEAN	RANGE
Blood Glucose (mg/dl)	788.37 ± 62	474 — 1208	1041	894 — 1250
Arterial pH	7.17 ± 0.03	6.80 — 7.34	7.41	7.38 — 7.42
Arterial PCO_2 mm of Hg	25.74 ± 4.3	20 — 38	40.31	37 — 43
Base Excess	-16.46 ± 5.1	-22 — -4	-4.33	-2 — -6
Std. Bicarbonate (mEq/Litre)	9.8 ± 5.1	6.2 — 14.1	19.3	16.8 — 22.8
Serum Sodium (mEq/Litre)	131.15 ± 2.2	118 — 137	158	154 — 161
Serum Potassium (mEq/Litre)	4.96 ± 0.6	3.4 — 7.2	4.1	3.8 — 4.4
Blood Urea (mg/dl)	98.26 ± 8.7	72 — 117	147.26	135 — 163

most patients would have had one and a half to two litres of intravenous fluids. Twenty-two patients with initial blood glucose above 500 mg/dl received a loading dose 20 units soluble insulin intramuscularly each and three patients with initial blood sugar less than 500 mg/dl received a loading dose of 10 units soluble insulin intramuscularly each. Thereafter all patients received hourly intramuscular doses of 5 units soluble insulin until the blood sugar had fallen to less than 250 mg/dl, after which soluble insulin was given subcutaneously six hourly on a sliding scale according to urine sugar, commencing six hours after the last intramuscular dose of insulin. Intravenous potassium was commenced with the first insulin dose except in three cases whose ECGs on admission showed tall T-waves, and in these patients intravenous potassium was commenced three hours after the first insulin dose. Eight patients with arterial blood pH less than 7.1 were each given 100 mEq of sodium bicarbonate intravenously and nine patients with arterial blood pH between 7.2 to 7.3 each received 50 mEq of sodium bicarbonate intravenously. Five patients with arterial blood pH above 7.3 did not receive any bicarbonate therapy. Antibiotics were administered wherever indicated.

RESULTS

The regime was effective in bringing down the blood glucose in 23 of the 25 patients (Table IV). Mean duration required for blood glucose to come down to less than 250 mg/dl was 5.93 ± 1.6 hours. Mean rate of fall of blood glucose was 109.6 ± 55.4 mg/dl per hour. This was variable hour to hour even in the same patient and hence not predictable. There was no hypoglycaemic episode in any of the patients. The level of consciousness improved in 21 of the 23 patients who responded to therapy. Two patients remained comatose after the control of blood sugar, correction of dehydration and acidosis, one due to cerebral thrombosis and the other due to cerebral oedema.

TABLE IV — Results

Total Number Of Cases	— 25
Responded	— 23
Mean duration (hrs) to achieve glucose < 250 mg/dl	— 5.93 ± 1.6
Mean rate of fall of glucose	— 109.6 ± 55.4
Hypoglycaemia	— 0
Failed	— 2
Mortality	— 3

Two ketoacidotic patients did not respond to this regime, blood glucose still rising at the end of four hours and the regime was abandoned at that stage; one was a middle aged Indian female with pyelonephritis and the other an elderly Chinese female with bronchopneumonia. Both were later treated with large intravenous bolus doses of soluble insulin. Although the blood glucose came down and the conscious state improved after a few hours in both patients, they subsequently required more than 300 units per day of conventional bovine soluble insulin for diabetic control. They were both considered insulin resistant and treated with steroids and porcine soluble insulin. Their insulin requirement came down after a few days and they were finally stabilised on moderate doses of porcine semilente insulin. We did not find a single case of insulin resistance in our case records of patients admitted for diabetic ketoacidosis in the previous five years.

Three patients died in the first week of admission; one due to extensive myocardial infarction, another due to cerebral thrombosis. The third death was that of a Chinese girl aged 21 years admitted with severe cellutitis and septicaemia following the excision of a carbuncle one week prior to admission. She was in diabetic ketoacidotic coma and although her blood sugar came down with this regime, she remained comatose and died. Her cerebrospinal fluid pressure was raised during life and we suspected her death was due to cerebral oedema, a well known albeit rare complication of diabetic ketoacidosis. There was no hypoglycaemic episode in any of the patients.

The mean plasma insulin over the first five hours of insulin therapy in the eight patients in whom insulin levels were measured are given in Table V. This was always in the range 20-200 u units/ml necessary for glucose metabolism (Sonksen et al, 1972).

CONCLUSION

Low-dose intramuscular insulin regime was effective in bringing down blood glucose in 23 of 25 patients in this series. We agree with Alberti et al (1973) that the regime is simple and easily carried out especially by junior doctors. However, the rate of fall of blood glucose in the individual patient was

TABLE V — Serum Insulin During Therapy In 8 Patients

	TIME (hour) AFTER START OF INSULIN					
	0	1	2	3	4	5
Mean Serum Insulin u/ml	6.8 ± 1.2	48.2 ± 3.2	53.7 ± 5.1	68.3 ± 3.7	61.7 ± 7.4	48.9 ± 2.8
Mean Insulin (units) Administered	20	5	5	5	5	5

variable and unpredictable. Hence repeated blood glucose estimations are still necessary to monitor the response to therapy, but the frequency of such estimations could be cut down. In our experience, if the initial blood sugar was above 500 mg/dl, a repeat blood sugar estimation is not necessary until four hours after the initial insulin dose. Subsequently two-hourly blood glucose estimations are necessary until the blood glucose has fallen to less than 250 mg/dl. If there has been no significant reduction in blood glucose after four hours of this therapy, the regime should be stopped and large doses of insulin should be given. The greatest advantage of the low dose regime over the large dose regime is that the risk of hypoglycaemia is virtually eliminated. We encountered two cases of insulin resistance amongst 22 ketoacidotic patients treated with this regime, unlike the experience of Kitabchi et al (1976) who did not encounter a single case of insulin resistance in 24 of their ketoacidotic patients treated with low dose intramuscular insulin. We await await with interest reports of insulin resistance from other centres using this regime. Three patients died of causes not attributable to this form of therapy.

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