Usage of Insulin

(Updated and consensus about some practical problems)

In a multinational study sponsored by the World Health organisation, data on profile of diabetes was analysed from 14 populations of age group 35-55 years with widely different characteristics and environmental circumstances, the diversity in therapeutic approach was abundantly clear. While centres in Europe prescribed insulin in 40-60% of the diabetics, in Asia it has been used only in half of this percentage of diabetics. Table 1 amplifies the actual data from each population.

TABLE-1
Multinational Study on Vascular Disease in Diabetes : Type of treatment
(Diabetics screened-total 6006).

Centre	Men			Women		
	Insulin injections (%)	Oral agents (%)	Diet only (%)	Insulin Injections (%)	Oral agents (%)	Diet only (%)
United Kingdom	56.3	28.3	15.4	61.3	30.5	8.2
Switzerland	51.8	38.5	9.7	60.5	32.0	7.4
Belgium	51.0	24.2	24.8	46.0	25.2	8.3
USSR	59.1	30.9	10.0	51.0	42.0	7.0
Poland	58.1	38.2	3.7	60.8	31.8	7.3
East Berlin GDR	42.5	30.2	27.4	50.2	26.2	23.6
Yugoslavia	40.5	37.4	22.1	33.3	45.0	21.7
India	23.2	66.9	9.9	14.3	73.0	12.7
Hong Kong	38.4	59.6	2.0	29.5	65.2	1.3
Japan	29.8	43.0	27.2	32.5	49.0	18.5
Cuba	29.0	55.0	15.7	24.2	64.2	11.5
Oklahoma	21.0	54.2	24.8	19.8	52.0	28.2
Pima	28.0	36.0	36.0	29.6	33.3	37.0
Bulgaria	46.9	44.9	8.2	55.9	39.2	5.0

group for the different regimens followed (Jarrett et al 1979). The mode of therapy in diabetics has been related to the age distribution of population, frequency of heavy manual work, standard of living, access to insulin, the physicians attitude to oral hypoglycaemic agents and demands on the quality of treatment by the community.

Indications for use

Objectively speaking, insulin is indicated whenever deficiency of insulin leads to metabolic disorders that threaten life or when optimum restoration of metabolism cannot be achieved by increasing the production of endogenous insulin or the peripheral tissue sensitivity to insulin.

Consensus from a proforma circulated to the experts in this field in our country indicates unanimous advice on use of insulin therapy in following cases :

(a) All diabetics who have acetonuria (ketotic diabetes).

(b) Young diabetics with onset of disease at age 30 years or less.

(c) Diabetics undergoing surgery or during pregnancy.

Absolutely high blood sugar or loss of weight were also considered by majority as indications for insulin therapy. More than 50% of respondents indicated that proportion of diabetics under their care to be on insulin therapy was 20-40%.

Physiological aspects

The international unit of insulin is defined as the amount required to lower the blood glucose of a fasting 2 kg. rabbit from 120 to 45 mg/100 ml. when injected intravenously. The international reference material has an activity of 22 units/mg. Now there are sensitive methods available for studies of insulin secretion and' metabolism. These employ either radioimmunoassays or in vitro bioassays.

For the normal insulin secreted, the biological half life is about 10 minutes and in a normal person the concentration of insulin in the fasting or post-absorptive phase is about 25 U/ml plasma by immunoassay, rising as much as five times this level after glucose load. In spite of rapid rate of clearance from the circulation, its effects may be apparent for hours. (6-8 hrs)

Absorption from subcutaneous tissues can be erratic. Binder (1967) measured the disappearance of radioactive Lente insulin from the subcutaneous tissue in the same patient on different days. The coefficient of variation was 35%. This absorption is also affected by nature of injected insulin and state of physical activity. Again, only a small proportion of injected insulin ever reaches the liver.

It is well known that of the normal insulin released by beta cells about 60% gets inactivated during intraportal circulation. Integral metabolic effects of insulin is thus not possible unless exogenous insulin is injected intra-portally. One should, therefore, realise that injected insulin in conventional manner is not a simple physiological replacement therapy for a variety of reasons.

Daily dose

The daily dose of insulin, especially initiating the treatment and for weight recovery is 2 units/kg/day (Cathro 1980). However, after stabilization, the maintenance dose may be 0.2 units/kg/day.

In many insulin dependent diabetics (juvenile diabetics) C-peptide assays have shown presence of C-peptide (equimolar to insulin) and this in turn determines the actual insulin requirements of diabetes. Needless to say that a number of metabolic events also alter this daily need. Insulin antibodies appear to influence the 24 hour insulin dose. It has been demonstrated that adult patient with normal weight treated from the onset with highly

purified porcine NPH insulin (6% formed antibodies) had a significantly lower insulin requirements than patients who had been treated initially with pig NPH insulin which was not highly purified (75% formed antibodies) Deckert, et al, (1974).

In common practice, sliding scale of regular insulin is prescribed based on urine glucose tests (urine 4+, 0.5 units/kg/dose to urine trace 0.1 units/kg/dose) and similar are the other convenient working rules. One must profess that one need to individualise treatment schedule as much as possible and use optimum criteria of control for the dose of insulin prescribed in each diabetic. Variation in individual dosage is common and initial dose which patient requires may need to be reduced depending on daily activity and food habits. One should remind onself that frequent hypoglycaemia is as pernicious as frequent orange reduction in urine and optimization be sought in treatment of diabetes. Insulin requirement increase especially during the last trimester of pregnancy. Immediately post-partum insulin requirement again returns to the original daily dose.

Many oestrogen containing oral contraceptives reduce the insulin sensitivity and so insulin dose has to be adjusted in many diabetics on oral contraceptives. Intercurrent disease, especially febrile illness, increase the insulin requirement. It is customary to recommend an increase of 25% of dose of insulin for each degree of temperature rise above 37.5°C. If this is not complied with, there is increased risk of ketoacidosis.

UGDP Trial, Fixed dose vrs. Varied dose regime

Interpretation of the data of UGDP is -beset with many difficulties and raises doubts on the validity of its usage for the adult onset non-ketosis prone diabetic patients. Insulin therapy has been followed in two different manners in the UGDP study.

(i) Standard dose schedule-Mean dose of 15 units/day.

(ii) Variable insulin schedule-this increased from 10 units per patient per day to 47 units per patient per day.

The blood glucose was >150 mg/dl only 7% of the time for the variable group as compared to 23% in the diet alone group. In contrast to the difference in blood glucose control, there was no significant difference in mortality rates among these treatment groups, cardiovascular mortality being 14.1 % in diet alone group, 12,9% in insulin standard group and 14.2% in the insulin variable group (Prout, 1978). Reanalysis of the data by Kilo et al (1978) excluding those who died or dropped out in the first year of the programme or were unavailable for the follow up for 4 consecutive quarterly examinations or were unduly biased with high risk (age >70 years FBS >150 mg/ or DBP>110 mm Hg) then cardiovascular deaths were 4 times as frequent in placebo group as in IVAR group (placebo 12/74 vr. IVAR 3/69).

The results of UDGP study had no influence on the therapeutic practice of Indian diabetic experts and there was no undue change over to insulin therapy instead of sulphonylureas following these reports in the literature.

How many injections daily ?

There is a trend evolving that insulin administration twice or thrice daily provides better regulation of blood glucose in the insulin dependent diabetics. Studies of normal insulin profile pari passu glycaemia, indicate sharp peaks after meals (peak after evening meal being lower despite higher glucose concentration (Hansen and Johansen, 1970), so multiple injections of insulin given intramuscularly or even subcutaneously or a continuous infusion of insulin intravenously seem imperative. With currently available techniques for continuous infusion of insulin, it has been observed that it is not sufficient to maintain the blood glucose within physiological limits. Here infusion providing variable dose achieves this objective more smoothly.

For practical purpose, twice daily mixture of short acting and intermediate insulin seem optimal way of maintaining this therapy and has been conventionally accepted in practice of diabetes in most of the countries including by the Indian. physicians who responed in the consensus questionnaire.

Current methods of assessment of control

The usual practice is to monitor the blood glucose levels and the urine testing. Though for very long, blood glucose profile (3-4 values/day in relation to fasting or postprandial phases) and quantitative urine sugar values have been accepted as realistic or accurate, with availability of auto-analyzers and close loope techniques, more elaboration has been sought to establish authencity of blood glucose values and factors that promote excursion in these values. Some of the attempts are. summarized herewith.

1. SchlichtKrull et al (1965) evolved formula M value in which 5-7 values of blood glucose daily were evaluated using the ratio :

$$M=10\ (\log \frac{\text{Glycaemia}^3)}{120}$$

2. Molnar et al (1968) Mayo Clinic calculated MBG (mean blood glucose) whereby continuous blood glucose monitoring was carried, blood glucose analysed every 5 minutes over 48 hours and mean values calculated. In the normal control values were 80 mg%, stable diabetes 112 mg%, brittle diabetes 188 mg%.

3. Mirouze et al (1974) calculated blood glucose/hr/day and then divided the value by 24. In good control, value was <18, fair <31 and poor >31.

4. Another parameter referred was MAGE (Service et al, 1970) (mean amplitude of glycaemic excursions). This referred to rate of difference between the peak blood sugar and succeeding minimum; blood sugar, value in normal being 60, 40, 21 mg. stable diabetes 67, 82, 79 mg/dl, and in brittle diabetes 119, 154, 169, 184 and 200 mg/dl.

From the values are calculated :

$$\text{RBGP} = \frac{\text{Peak BG-Baseline BG mg/100 ml}}{\text{Time at Peak BG-Time at baseline BG (min.)}}$$

1.1± 0.1 mg/min/100 ml blood.

$$\text{\& RBGF} = \frac{\text{Peak, BG\_-Return BG}}{\text{Time at lower BG-Time at peak BG (min.)}}$$

0.6 ± 0.1 mg/min/m 100 ml.

5. MODD, Mean of daily differences, average the difference between glucose levels at the same points on successive day. (Molnar et al, 1979).

   It is a numerical expression for between blood glucose fluctuations. In normal value is 6.2 to 8.2 mg/dly, is stable diabetes 10.2 to 35.1 mg/dly and in unstable diabetes 36.6 mg-151 .1 mg/dly.

Thus from the recent concepts, it brings out the unreliability of a single value of blood glucose in guiding the control of diabetes. Now haemoglobin A_1C serves as indicator for the integrated blood glucose values, and overall efficiency of various therapeutic regimes. Normal range for HbA_lC is 5-8% of the total haemoglobin concentration. In keto-acidotic patients, the proportion is doubled to 16°/ or more (Paulsen et al, 1976).

Insulin treatment for ketoacidosis

It has now become conventional to institute continuous .intravenous infusion of insulin in instances of diabetic ketoacidotic (DKA) coma. Subcutaneous route will have problems as due to dehydration and hypovolumia and its effects on circulation, rate of absorption cannot be depended upon. Also if IV administration is followed instead 4 hourly, there would be intermittent insulin deficiency state due to its very short biological half life. It is, therefore, usual practice to administer 10-15 units of insulin/hour. This will provide effective serum insulin level of about 80-100 uU/ml and lower blood glucose by 4-5 m Mol/hr (Kidson et al, 1974; Sherwin et al, 1974) (100 IU units of regular insulin dissolved in 1 litre of physiological Saline, containing 0.1 % human albumen (in its absence increase dose by 25%) and deliver 150 ml of this in one hour). If continuous IV infusion is not feasible, 10 IU IM every hour (x 2) and then 2-5 IU/hour can be given. After 48-72 hours, mean is calculated from this dose and given as short acting insulin 4 times a day (Alberti et al, 1973). Approximate maintenance dose is 0.2 0.3 IU/kg.

In India, majority of physicians practise low dose schedule, while few who seem to have elaborate laboratory facilities prefer to individualize this depending on clinical severity and exact blood glucose values. A comparison of closed loop intravenous insulin infusion (i.e. an artificial pancreas), open loop continuous subcutaneous insulin infusion and intensified conventional insulin therapy (preprandial injection of long acting zinc suspension insulin before breakfast, to achieve control of blood sugar (M value) have

been reported by Rizza et al, 1980 from Mayo Clinic. On a short term basis, all three regimes can produce comparable, nearly normal levels of blood glucose in such patients.

Surgery

The diabetic control, dehydration, electrolyte imbalance, acidosis and reduced resistance to infection attribute to poor risk in any emergent surgical condition. Insulin therapy is imperative. Correction of dehydration and electrolyte imbalance should precede any operative procedure. Patient should also be adequately protected against anaerobic or aerobic infections. In elective cases, all diabetics be transferred to insulin and good control achieved, without ketonuria prior to operation. On operation day usual insulin requirement is 50% of the maintenance dose, however, frequent monitoring of blood glucose provides worthwhile dividends and removes many uncertainties and guess work formulae. Continuous infusion of plain insulin (0.07 units/kg/hr) is being advocated during emergency surgery or where available artificial pancrease has been commissioned for covering control of blood glucose.

Pregnancy

Insulin treatment during pregnancy is of importance. Good metabolic control around time of conception avoids chances of abortion or congenital malformations. Control of maternal diabetes determines the perinatal foetal mortality. Insulin treatment should be vigorous, short acting plus intermediate acting insulin may be administered two or more times a day and there should be a weekly checking of glucose values after 20th week of gestation. The avoidance of hypoglycaemia is of equal importance as hyperglcaemia in pregnant diabetics. Potential risk of hypoglycaemia at birth in the new born to such mothers needs recognization.

In renal failure, liver cirrhosis, insulin requirements fall and dosage must be carefully monitored.

Usual problems that cause failure in insulin therapy

a) Dietetic indiscretion.
The insulin dependent diabetic should eat a certain quantity of carbohydrates with each meal and should not change the meal times or miss a meal. Failure of adherence to diet often leads to failure in maintaining control to diabetes,

b) Exercise and irregularities in physical activity. Exercise should be so planned as to prevent hypoglycaemia which could follow if care is not taken as to provide adequate calories for requisite energy requirement. Again, exercise in uncontrolled diabetic can lead to ketosis.

c) Hypoglycaemic induced counter regulation (Somogyi effect). This has been attributed to hormones antagonistic to insulin especially catecholamines.

d) Variations in circulating insulin concentration.
Irregular dissociation of insulin antibody complexes brings in variation in the circulating level of insulin.

e) Administration of relatively high single dose of insulin.
It is commonly observed that those who are on more than 60 units of insulin administered at one single time, cannot be adequately stabilized.
In such a situation divided dosage of 2-3 injections may be more suitable. Actrapid or semi-Retard preparations are preferable.

f) Emotional distress and psychiatric problems can be a major cause for unstable diabetic state. It is necessary to educate, motivate and secure co-operation of the patient in achieving any meaningful success in treating diabetes.

Newer insulins

In order to reduce the immunological and other untoward effects arising from impurities in insulin preparations, Purifications by gel filtration gives single peak insulins (SP) ion exchange chromatography gives monocomponent insulin (MC). In North America, single peak (98% pure insulin) while in Europe monocomponent (99, pure insulin) are now commercially available. Indications for use of such insulins in the country have been elaborated by Kumar & Ahuja (1980).

1. Insulin allergy with localized or generalized manifestations.
2. Insulin resistance due to presence of significant titre of antibodies,
3. Lipoatrophy due to insulin injection.
4. Increased requirements (780 units/24 hours) for insulin in unstable glycaemic states.
5. Indication for insulin is only for a transitory period (pregnancy, surgical intervention).

The following preparations are available :

Actrapid MC :

This has a rapid effect (peak 2-4 hours) and is valuable in the initial stabilization of diabetic patients, in short term therapy including diabetic ketoacidosis, in diabetes undergoing surgery and in pregnant diabetics. It can be used for multiple daily injection and in infusion therapy. It can also be combined with long acting insulins.

Rapitard MC :

It is a combination of quick acting and the long acting MC insulins, one may have to add more Actrapid for stronger initial effect (2-8 hour).

Montard MC :

It is porcine equivalent of Lente MC (2-16 hours). It can be used once or twice a day.

Lente MC :

Its effect is longer (upto 24 hours), can be used once a day. Semi-lente or ultralente are other available preparations of MC insulins.

SIDE EFFECTS

1. Hypoglycaemia

This is the most serious complication and all the physicians must be able to recognise it in its different manifestations.

a) The manifest symptoms are proliferic and one only accepts the situation of hypoglycaemia without symptoms with long years of experiences. This is true especially in patients with long standing diabetes, patients with autonomic neuropathy or in patients on beta blockers or very elderly individuals.

b) Neuroglycopenic syndrome resulting in transiet focal deficit, mental changes visual disturbances and temporal or frontal lobe syndromes may be due to low blood glucose. A number of cardiac manifestations, for example arrhythmia, angina, pulmonary oedema, are related to adrenergic response to hypoglycaemia.

c) Hypoglycaemia during sleep may manifest as nightmares, sweating or a headache on rising in the morning. Again, hypothermia is also considered common during hypoglycaemia and may be helpful as a diagnostic hint in a comatosed patient (Strouch et al, 1969).

2. Local atrophy

Local changes in subcutaneous tissues, such as atrophy, are not common. Rarely hypertrophy also can occur. The lipo-atrophy is attributed to impurities of insulin. This has cosmetic disfigurement and seems that highly purified insulins (such as MC insulins) are devoid of this complication.

3. Generalised reaction due to immunogenicity

(a) Insulin Allergy

This again can be local or generalised, Locally red spots, as bleeding puncture marks and generalised as urticaria or anaphylactic reaction or delayed type of hypersensitivity response is observed. It is now shown that increased IgE is mainly responsible for these reactions.

(b) Insulin antibodies

There seems to be 3 fractions from various components of insulin preparations that can be antigenic ;

(i) Fraction A consists of glucagon, pancreatic polypeptide and VIP (Vasoactive intestinal polypeptide).

(ii) Fraction B consists of mostly pro-insulin and intermediates.

(iii) Fraction C insulin itself.

Various procedures are available to remove impurities. Pork insulin is less antigenic, attempts are continuing to purify this further for still lower immunogenecity.

A correlation between the height of insulin antibodies titre and insulin dose required for stabilisation is suggested (Bloom, 1979). However, it is not universally accepted. In the literature, there are as well some Indications to implicate insulin antibodies in the development of severe vascular complications.

4. Insulin resistance

Earlier definition of insulin resistance as of a "state of non-ketoacidosis in insulin treated person whose daily dose of insulin exceeded 200 IU" is no longer tenable. There is a tendency now to refer to this status when dose of insulin exceeds 100 IU/24 hours for several consecutive days (Paulson et al, 1976). To confirm this status, insulin sensitivity test is suggested, 0.1 unit of plain insulin per kg. body weight is injected i. v. and blood glucose is estimated every 10 minutes. Normally there is fall of glucose to 50% of original value in 30 minutes. In insulin resistance, there is hardly any significant fall. In immunologically conditioned insulin resistance, insulin binding capacity of serum is very high and insulin antibodies are demonstrable.

The treatment consists of replacement of insulin preparation by a highly purified porcine insulin or newer insulin, preferably with continuous infusion technique. In some instances, immunosuppression by steroids or cyclophosphamide or azathioprine may be warranted. Its effects should be manifest within a week.

Other measures to increase endogenous insulin, combination with sulphonylurea, or reduction of catecholamines by beta blocker, etc. should be applicable in mild situations and experience of different centres seems variable on such measures.

EPILOGUE

Insulin has now been in usage for over 50 years. For the scientific knowledge added on this hormone so far three Nobel Prizes have been bestowed. The ultimate goal of treatment in a diabetic with insulin is to restore the physiological effects and normalization of the metabolic status. An attempt to bring euglycaemia and correct other metabolic or hormonal alterations is pursued so as to eliminate or minimize the chronic complications of the disease and thereby to increase the life span of a diabetic. To bring relief to about 50 million of diabetics (estimated world population of diabetics) efforts are continuing unabated as regards purification and newer methods of synthesis of insulin, sophisticated and complicated insulin delivery systems and islet cell transplantation.

On the other hand, in clinical experience, like in other chronic illness, results of long term management, and compliance of therapeutic measures in diabetes indicate success in only 30% of the patients. It is a common experience that many diabetics only follow intermittent therapy.

In the developing countries, the insulin therapy has many additional problems; to enumerate a few, illiteracy, lack of health education and personal hygiene, poor laboratory facilities, lack of proper monitering and the high cost of insulin treatment.

The comparative cost of different modalities of treatment open to a patient are as follows : (i) Lente insulin 40 units/day-Rs. 37.6/month, (ii) Glybenclamide 10 mg/day Rs. 10.5/month and (iii), indigenous drugs-Rs. 5-7.5/month.

This estimate dose not take into account the cost of medical monitering, neither is it indicative of its effectivity on the cost-benefit score.

In our country, the most common insulin preparation being used is Lente. In clinical experience one may achieve a satisfactory control in 85-90% of the instances, remaining 13-15% offer challenge for achieving a uniform metabolic control. For these difficult situations split dosage of regular insulin is the mainstay of treatment. Lately Monocomponent insulins have become available, but restricted supplies and extra cost limit their usage.

Alongwith the continuing research in the field of diabetes, supportive measures for diabetics, e.g. providing health education, subsidising the cost of insulin and provision of clinical care whenever required should be the basis of future health planning in our country.

One must, in pursuing care of a diabetic emphasize on self discipline that would promote the dividends of therapeutic goals in a diabetic.

Acknowledgement

The consensus expressed here relate to information gathered from response to a proforma circulated to Physicians in this country who are specialist in Diabetes and are actively taking care of diabetic clinics. Their co-operation is highly appreciated, inability to include individual names before given.

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