Update Article

PERSPECTIVES FOR CLINICAL TRIALS WITH INDIGENOUS DRUGS FOR CONTROL OF DIABETES

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The essentials for a clinical trial have been standardized as follows (Hill, 1960).

The objective of the trial should be clearly defined and preferably limit itself to answer only very specific information under enquiry.

In its most rigorous form, it demands equivalent group of patients (matched for age, sex, extent or severity of disease) concurrently treated in different ways, one on drug, one on placebo, or the drug with known effect vrs. a new drug under investigation. Number of patients for significant response must be statistically worked out. These groups are constructed by random allocation of patients to one or other treatment group by double blind method. Doctor or patient, both are not aware of the type of medication allocated to patient, code is with a statistician. There are inbuilt methods to check on the compliance of therapy- The treatment schedule must be followed for the total period of trial or the case considered drop out. In measuring the therapeutic effects, objectivity is secured by employing clinical scoring, grading of biochemical measurements or other set laboratory criteria for cure or improvement. The methods of assessment should be remarkably accurate, repeatable and relatively free of observer error. In summary, clinical trials imply, preplanned controlled studies on humans selected according to pre-determined criteria of eligibility and observed for pre-defined evidence.

There is no doubt that there has been wealth of indigenous drugs for effective treatment of many diseases, including diabetes, however, the contribution of the scientists in this field in the present era have not been substantial.

Such preparations have no value at all for insulin dependent diabetics (Type I). Indigenous medicines employed in the treatment of Type II diabetes (NIDDM) have drawn the attention of the physicians in this country and clinical trials are ongoing in this direction. Some aspects of clinical studies on hypoglycaemic drugs are as follows :

A. Case selection

1. Newly diagnosed NIDDM (criteria NDG, 1979) untreated, preferably in age group 35-55 years to avoid overlapping with some indeterminate types of diabetes (MODY/ Glucose intolerance in the aged) should form the case material.
2. Selected cases should be free of any complications that may be considered indicative for insulin therapy.

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3. There should be assurance of compliance, possible patient revisits to same laboratory for follow up for the period of trial.

   Probable exclusions will include : N1DDM who are very underweight, BMI 19 or those with ketosis.

   NIDDM pregnant or lactating.

   NIDDM with established large vessel or small vessel disease, or other organ diseases that would affect metabolism (hepatic/renal).

B. *Preliminary work up* would include complete physical examination, including blood pressure, fundus examination, Blood glucose profile, Hb A_1C, lipid analysis, routine urine examination and serum creatinine should be carried on routinely. A baseline X-ray chest, and ECG examination should be carried on. A complete dietary history should be secured.

C. *The schedule for follow up* be as follows ; In initial period of 4 weeks patient's response to dietary programme advised on basis of body weight, i.e. 25 C/Kg body weight and in proportion CHO 60-65% fat 20-25%, protein 10-15% should be, assessed. Those not responding to diet therapy alone are included in the drug trial. In initial period on drug for 4 weeks, blood glucose (fasting and 2 hours after meals) is monitored fortnightly and later once a month. Weight record is maintained in each visit. Hb A_1C and lipids are done every 3 month.

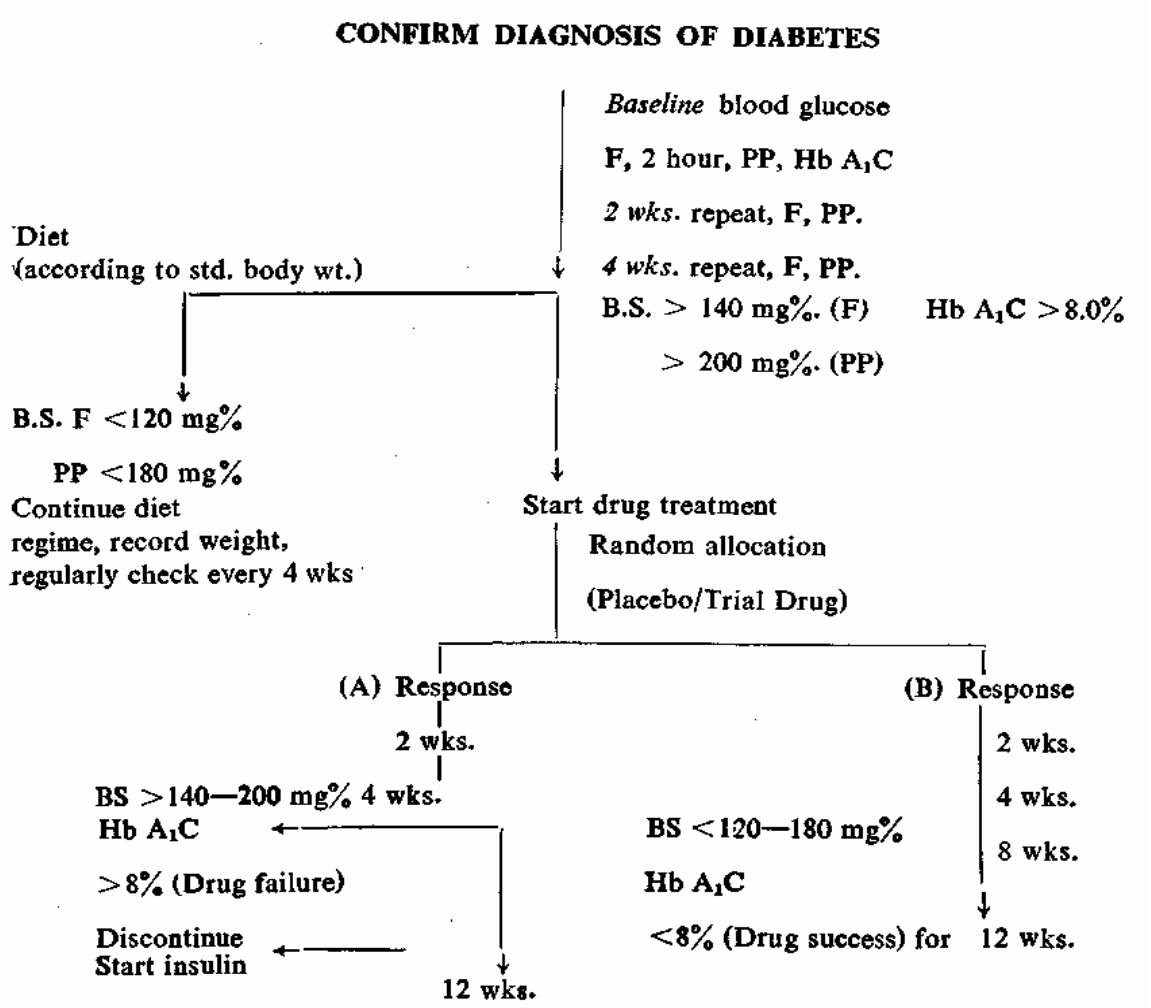
   Case is considered a drop out if the follow up schedule is irregular (less than 75% compliance) or patient has sought additional hypoglycaemic therapy.

   The treatment is considered a failure if an Hb A_1C or blood glucose profile is showing, no response, or patient develops drug related side effects that interfere in daily routine. Drug trial should be for a minimal period of 3 months.

D. *Compliance of drug* is verified by asking the patient to return any amount of drug which has not been consumed during the period before issue of new supply of the drug. In some instances it may also be possible to carry on blood level or urinary excretion of the trial drug.

E. The *data is analyzed* employing statistical methods applying Null hypothesis and P value is calculated on those control drug and compared with those on the trial of indigenous drug. Quantitative parameters should be analysed with Anova tests.

Schematic presentation of suggested schedule is as follows :



The studies at present exclude diabetics with complications though there is recognition that vascular disease is responsible for high degree of morbidity and mortality in such instances. Possible effect of the indigenous drugs, e.g. Elavonoids, Xanthones, quercitrin, quercintion and axillarin as xanthine and aldose reductase inhibitors have not been ever evaluated (De Souze, 1986)[2].

The causes for inconclusive trials in regard to indigenous drugs in diabetic could be stated as follows :

a) Small number of patients recruited in a trial who continue the drug for only a limited period.

b) Very often a fixed drug schedule is being followed and protocols are not designed to permit schedule or dose variation.

c) Criteria for evaluation are limited and based on fasting and post-prandial blood glucose value or OGTT before and after the drug.

d) Comparison for efficacy of hypoglycaemic response is being made with a known very potent drug as sulphonylurea.

e) Often there is no scope incorporated in the design study on possible mechanism of action of particular Drug in humans.

There is failure to appreciate that most of the indigenous drugs are effective only when administered in a combination.

The effectiveness of indigenous drugs is not often immediate, there seems a lag period before any clinical or biochemical alterations are perceived.

As there is heterogeneity in non-insulin dependent diabetes, the drug effective for one type may not have the same response as in another type of diabetes. Clinically, this distinction of types may not only relate to obese and non-obese type but may have other denominators as well.

There is failure to follow biological standardization of the indigenous preparation prior to its clinical use so there map be batch variation.

In Ayurvedic system, equally important steps for success of drug treatment as well include consumption of specific food constituents, changes in some daily habits inclusive of body cleansing or yogic practices and a disciplined pattern of life.

There is need for augmenting the scope of investigation of indigenous preparation and improving the methodology and parameters that would examine comprehensive metabolic homeostasis in a diabetic and not merely evaluate the blood glucose values only.

Mngola (1983)[3] has presented the folkcoric medicinal plants in Africa, Arab and Asian world employed in treatment of Type II diabetes and recommended to W.H.O for strengthening research in this direction.

Clinical validation of the hypoglycaemic agents plant origin should include their preparation and combination as practised by Ayurveda but subject to biological standardization. Criteria for effectiveness should extend beyond blood glucose values and include intermediary metabolites or any alteration in insulin sensivity. Treatment strategy should be inclusive of other components of health care practices advised in the ancient systems.

Blood glucose values are mean of 3 four weekly readings (patient continuing on drug and diet). There should be decoding at this stage (25 patients completing 3 months drug therapy).

In case blood glucose values are intermediate, drug trial modification as change in dosage schedule or combination of indigenous drugs may similarly be studied over next 3 months.

References

1. Hill, A.B. Controlled clinical trials. Blackwell Scientific Publications, Oxford (1960).
2. De Souza, NJ. New strategies for the in vestigation of herbal remedies and plants of potential utility for the treatment of diabetes and diabetes complications. Bull. Delivery of Health Care for Diabetes in Developing Countries, 7, 22, 1986.
3. Mngola, E.N. The use of traditional medi cines for diabetes. In 'World Book of Diabetes in Practise', 1988. Elsevier Science Publisher, Vol. 3, 123.