

*Training Workshop*

*On*

*Protocols for Clinical Trials*

*On*

*Ayurvedic Antidiabetic Drugs*

*Organized By*

*The NSF Research Committee on  
Traditional Medicine*

*Date : 26<sup>th</sup> June 2003*

*Time : 9.00a.m. – 12.30 p.m.*

*Venue : NSF Auditorium*



NA 286

# Training Workshop on "Protocols for clinical trials on ayurvedic antidiabetic drugs"

Organized by

## The NSF Research Committee on Traditional Medicine Programme

Venue: NSF Auditorium  
Date : Thursday, 26, June 2003  
Time : 9.00 a.m. to 1.00 p.m.



9.00 a.m.	Registration	
9.30 a.m.	Welcome Address	Chairman/Director, NSF
9.35 a.m.	Introductory Remarks	Dr S Sritharan, Chairman/RC
9.40 a.m.	Overview of research on antidiabetic medicinal plants	Prof. Eric Karunanayake, Faculty of Medicine, Colombo.
10.00 a.m.	Discussion	
10.10 a.m.	Ayurvedic Aspects of diagnosis of Diabetes	Dr Sujatha Ediriweera IIM
10.30 a.m.	Discussion	
10.40 a.m.	T E A	
11.00 a.m.	Pharmacological method of evaluation for antidiabetic activity	Dr B M R Fernandopulle, Faculty of Medicine, Colombo
11.20 a.m.	Discussion	
11.30 a.m.	Development of Protocols on Diabetes for Clinical Trials of Ayurvedic Drugs	Dr M H A Thisera, Gampaha Wickremarachchi Ayurveda Institute, Yakkala.
11.50 a.m.	Discussion	
12.00 noon	Conducting a Clinical Trial with relevance to Western Medicine	Dr Kusum de Abrew, Faculty of Medicine, Colombo.
12.20 p.m.	Discussion	
12.30 p.m.	Final Discussion and Summing up	

# Overview of Research on Anti-diabetic medicinal Plants

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Traditional medical systems provide a substantial medical service in developing countries. In Sri Lanka more than 70% of the population resort to Ayurvedic medicine as the first line of treatment (Karunanayake & Tennekoon, 1993). The therapeutic agents used in this system are mainly plant based. However, the majority of these plants have not been subjected to scientific evaluation of their therapeutic claims. A project was therefore launched in 1981 to undertake scientific evaluation of plants used in the treatment of diabetes .

Even initiating this project had to be delayed due to inadequate animal facilities available at that time. As for funding, I had by that time obtained a small grant of Rs. 75,000 from NARESA. Preliminary screening using experimental animals showed that *Salacia reticulata* (Kothalahimbutu), *Aegle marmelos* (Beli), *Momordica charantia* (Karawila) (Karunanayake et al., 1984) all had significant hypoglycaemic activity .The aqueous extract of *M. charantia* was shown to improve the glucose tolerance by newly diagnosed type 2 diabetic patients (Welihinda et al., 1986a). A subsequent study showed that the *M. charantia* extract enhanced glucose uptake by the peripheral tissues ( Welihinda & Karunanayake, 1986b), thus throwing some light on the possible mechanism of oral hypoglycaemic activity.

Incubation of isolated beta cells, that produce insulin, with the freeze dried extract of *M. charantia* resulted in significant secretion of insulin (Welihinda et al., 1982). Further studies showed that the administration of fruit juice to streptozotocin (50mg/Kg body weight) induced diabetic rats for

period of one month does not show any beneficial effect on diabetes (Karunanayake et al., 1990). Streptozotocin at a dosage of 50mg/kg is known to irreversibly destroy all islet beta cells. The efficacy of the preparation to improve glucose tolerance in normal animals and its potency to facilitate glucose storage, the beneficial effects in non-insulin dependent diabetes and potent insulin secretory effect *in vitro*, when compared with the lack of any beneficial effect on streptozotocin induced experimental diabetes (50mg/Kg), strongly suggested that the oral hypoglycaemic effect of the fruit juice is primarily via the stimulation of insulin secretion. This hypothesis was tested and further confirmed by the administration of the fruit juice of *M. charantia* to streptozotocin induced diabetes of graded severity.

Thus the administration of *M.charantia* to streptozotocin diabetes of graded severity (10, 20, 30 and 40mg/Kg) showed that the preparation was effective as an oral hypoglycaemic agent only upto 20mg/Kg of streptozotocin (Jeevathayaparan et al., 1995). This simply means that *M. charantia* is effective as oral hypoglycaemic agent only in the case of type 2 diabetes.

Despite the fact that medicinal plants have been used in the treatment of disease over many years, the possible toxic effects have not been elucidated, As part of our investigation on anti-diabetic plants we also investigated possible toxic effects. In laboratory animal experiments *Momordica charantia* was found to have no liver or renal toxicity (Tennekoon et al., 1994) . Furthermore in later studies using radio tracer techniques we have clearly demonstrated that *M. charantia* fruit juice while inhibiting intestinal absorption of dietary glucose, facilitates glucose storage in the muscle and adipose tissue (Jeevathayaran, 2002).

It should also be mentioned that the work we initiated on the scientific evaluation of anti-diabetic plants stimulated several other groups to undertake similar studies using the experimental procedures we have published in peer reviewed international journals (Fernando et al., 1987; 1989; 1990 ; Fernandopulle et al., 1994a; 1994b; 1996; ).

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# AYURVEDIC ASPECTS OF DIAGNOSIS OF DIABETES

*E.R.H.S.S. Ediriweera, Senior lecturer,  
Dept. of Nidana Chikithsa, Institute of Indigenous Medicine, University of Colombo.*

In Ayurveda, there is a disease described as Prameha that has twenty varieties with a main characteristic features being increased quantity and turbidity of urine. (S.S. Ni. 6/6) Prameha means secretions or oozing of fluid from the body with out stopping.

The twenty varieties of Prameha are: Udakameha, Ikshumeha, Sandrameha, Surameha, Pishtameha, Sukrameha, Sikathameha, Shithameha, Shanairmeha, Lalameha, Ksharameha, Nilameha, Haridrameha, Manjishtameha, Rakthameha, Vasameha, Majjameha, Madhumeha and Hasthimeha.

They originate in the following manner. Ten of these Pramehas originate due to vitiation of Kapha, six due to vitiation of Pitta and four due to vitiation of Vata. There are two schools of thought on origination of Madhumeha. In Charaka Samhitha one of the four Vataja Pramehas is described as Madhumeha (C.S. Ni 4 / 44). In Susrutha Samhitha, a type of Prameha called Kshaudrameha with symptoms similar to Madhumeha is described under Vatajameha (S.S.Ni.6/ 12). But Susrutha Samhitha also states all varieties of Prameha, if not treated in time, will ultimately become Madhumeha. (S.S.Ni.6/ 27) Diabetes mellitus can be correlated with Madhumeha.

In order to arrive at a diagnosis, according to Ayurveda, a physician should carry out **Roga pariksha** (Understanding of the ailment) and **Rogi pariksha** (Examination of the patient). Of these two, Roga pariksha should be done first, followed by Rogi pariksha.

## ROGI PARIKSHA

Rogi pariksh (examination of the patient) could be done by using different methods. They are Thrivida Pariksha, Panchavida Pariksha, Shadvida Pariksha, Ashtavida Pariksha and Dashavida Pariksha.

### *1) Thrivida Pariksha* (Threefold method of examination)

Darshana Pariksha - visual inspection

Sparshana Pariksha - examination of patient by touch.

Prashna Pariksha - Interrogation

The questions should cover locality, family, race and cast, articles compatible to constitution and non compatibles, onset and history of present illness, chief complaint, general health, duration of illness normal passage of flatus, urine and stool etc. (S.S. Sut. 10/5)

**2) Panchavida Pariksha** (Fivefold methods of examination) (S.S. Sut. 10 / 5)(C.S.Vi.4/7)

This method of examination is done using the physician's five sense organs.

Darshana Pariksha - as above

Sparshana Pariksha - as above

Gandha Pariksha - examine the odors emitted from various parts of the patient's body and excretions.

Shravana Pariksha - listen to the sounds originate in the body e.g. voice, internal body sounds, sounds of joints.

Rasa Pariksha - tests for taste of the body, urine etc.

**3) Shadvida Pariksha** (Six fold method of examination (S.S. Sut. 10 / 5)

This includes Prashna Pariksha in addition to Panchavida Pariksha.

With Prashna Pariksha, increased frequency of urination, increased quantity of urine, gathering of ants to the place of urination could be confirmed

**4) Ashtavida Pariksha** (Eight fold method of examination)  
(Y.R. purvardha 1/ Ashtasthana Pariksha -1)

Nadi Pariksha - Examine patient's pulse

Muthra Pariksha -Examination of urine

Mala Pariksha - Examination of feaces.

Jihva Pariksha - Examination of patient's tongue.

Shabda Pariksha - As described under Panchavida Pariksha (Shravana Pariksha)

Sparsha Pariksha - As described above

Druk Pariksha - Examination of the patient's eyes

Akruthi Pariksha - Examination of the patient's body in order to ascertain whether within the norms given in Ayurveda regarding a healthy body.

5) *Dashavida Pariksha* (Ten fold method of examination) (C.S. Vi 8 / 14)

Prakruthi Pariksha - Examination of physical and mental constitution.  
(C.S.Vi 8/96-98)

Vikruthi Pariksha - Examination for morbidity (C.S. Vi 8 / 101)

Sara Pariksha - Constitutional dhathus (essences) (C.S. Vi 8 / 102 - 110)

Samhanana Pariksha - Examination to decide whether the physique is properly proportioned. (C.S. Vi 8 / 116)

Pramana Pariksha - Anthropometry. (C.S. Vi 8 / 117)

Sathmya Pariksha - Suitability or compatibility to various food and Rasas.  
(C.S. Vi 8/118)

Sattva Pariksha - Psyche or Mental status (C.S. Vi 8 / 119)

Ahara shakthi Pariksha - Ability of intake of food and Power of digestion  
(C.S. Vi 8/120)

Vyayama shakthi Pariksha - Physical stamina (C.S. Vi 8 / 121)

Vayas Pariksha - Age (C.S. Vi 8 / 122)

## INDICATIVE FACTORS

Having carried out a complete examination of the patient using above methods, certain symptoms indicative of diabetes would become noticeable to the physician. These methods and relevant indications are described in detail hereunder.

1) *Muthra Pariksha* (Examination of urine)

### *Collection of Urine*

For the purpose of testing, both physician and the patient should wake up during the last four ghatika (96 minutes) of the night. Then the patient should pass some urine first and when halfway through, urine for testing should be collected in a crystal vessel and examined after sun rise. (Y.R. purvardha 1/ Muthra Pariksha -2, 3)

Urine should be examined by Darshana Pariksha, Sparshana Pariksha, Gandha Pariksha, Rasa Pariksha and Prashna Pariksha. Since all twenty Pramehas, if left untreated, could

lead to Madhumeha, the physician should pay attention for possibility of existence of all varieties of Prameha.

*With Darshana Pariksha;*

The Rashi (Volume), Varna (Colour) avila (Turbidity) should be examined. Quantity of urine will increase, colour may become similar to honey (Golden yellow) and turbid.

*With Gandha Pariksha;*

Odour may be similar to honey.

*With Rasa Pariksha;*

Urine may have a sweet taste.

Though Susrutha Samhitha advocates tasting of urine by the physician (S.S. Sut.10/5), Charaka Samhitha recommends to observe, insects such as ants gathering where the patient has urinated, in order to confirm sweetness (C.S. Vi 4/7).

*With Prashna Pariksha;*

Increased frequency of urination,

Increased quantity of urine,

Gathering of ants to the place of urination could be confirmed.

*With Sparsha Pariksha;*

By touch acidity, alkalinity, stickiness, rough, level of warmness which could be indicative of various types of Prameha can be felt and identified. Identification of them could help the physician in deciding the possibility of onset of Madhumeha.

By examining the status of urine, the vitiated Doshas in the patient could also be decided. In vitiated Vata, urine will be pale in colour (Pandu Varna), in vitiated Kapha frothy and in vitiated Pitta red in colour. The understanding of vitiated Dosha will also be a factor that would assist the diagnosis of Madhumeha. (Y.R. purvardha 1 / Muthra Pariksha-4).

**2) Sweetness of the body**

The whole body become sweet (*Madhuryathano rathak*) in Madhumeha. One possible indication of this would of flies and ants to the body. Patients also may feel sweetness in mouth.

**3) Ahara shakthi Pariksha**

Ability intake of food would increase and desire for food of all taste could persist.

## **ROGA PARIKSHA**

Should be carried out through Pancha Nidana that is Nidana (Causes, Aetiology), Purvarupa (Prodromal symptoms), Rupa (Clinical features), Upashaya (Test carried out by the physician to arrive at a correct diagnosis in doubtful or difficult conditions) and Samprapthi (Pathogenesis). (A.H. Ni. 1/2)

### **Nidana (Aetiology)**

Main causes for diabetes are:

- i) Sahaja Nidana (Hereditary causes). (S.S. Ci. 11/3)
- ii) Apathyaja Nidana is insalubrious activities such as:

Excessive sleep,  
Use of soft cushions etc. for a long period,  
Excessive consumption of curd, milk, jaggery, sugar, food made out of fresh grains and flesh of domestic and aquatic animals,  
Use of fresh rain water  
Stress generated through unsatisfied sexual urges.  
Factors that increase Kapha (C.S.Ni 4/5, Han. N. prameha nidana 428)

### **Purvarupa (Prodromal symptoms)**

Accumulation of dirt on the teeth, palate, tongue and throat,  
Thirst,  
Dryness of mouth palate and throat,  
Feeling of numbness and burning sensation in the palms and soles,  
Lassitude,  
Matting of hair,  
Stickiness of the skin all over the body,  
Sweet taste in the mouth and gathering of bees and ants on the body and where voided urine has fallen. (C. S. Ni. 4/47, S.S.Ni. 6/5)

### **Rupa (Clinical features)**

Urine become Madhura (similar to honey), Kashaya (astringent), Ruksha (rough) and pale in colour,  
Depletion of tissues,  
Whole body becomes sweet. (C.S. Ni. 4 / 44)

### **Upashaya (Tests that should be carried out to arrive at a correct diagnosis in doubtful or difficult conditions)**

Administering of certain drugs, food or activities and observe whether condition of the disease improves or worsens.

### **Samprapthi (Pathogenesis)**

Vitiated three Doshas, Vata, Pitta and Kapha, with Vata being predominant, will combine with seven Dhathus vitiating them as well and produce Madhu meha.

(In this context Dhathus are substances that govern and support the metabolic and catabolic functions of the body. They are; Rasa dhathu, Raktha dhathu, Mansa dhathu, Medas dhathu, Asthi dhathu, Majja dhathu and Sukra dhathu).

In Roga Pariksha, if it could be confirmed that the aforesaid aetiological factors, prodromal symptoms, clinical features; pathogenesis and upashaya that indicate Madhumeha are present, it would facilitate the diagnosis.

Ayurveda shows that the following complications could occur in Madhumeha. Prameha pidaka (Carbuncles S.S. Ni 6 / 15- 21), anorexia, vomiting, too much of sleep (A.H. Ni. 10 /22), fainting, diarrhoea, fever, cracks in the skin of scrotum, pain in bladder region and penis, (A.H. Ni. 10 /23), increased breathing, headache, desire for eatables of all tastes, tremors and emaciation (A.H. Ni. 10 /24). It is also said that onset of these complications would be at the advanced stages of the disease. Identifying these complications would provide clues to confirmation of existence and the degree of Madhumeha.

### **DIFFERENTIAL DIAGNOSIS**

In diabetes mellitus excessive urination, glycosuria and raised fasting blood sugar are present. According to Ayurveda, there are three Pramehas that would show excessive micturition and presence of sugar in urine. They are Ikshumeha, Madhumeha and Shithameha. Further, in Udakameha, the volume of urine is excessive but there is no sugar present in urine. This could be separately identified using the earlier mentioned methods of examination.

Madhumeha	Ikshumeha	Shithameha	Udakameha
Vitiated Vata Dosha is prominent	Vitiated Kapha Dosha is prominent	Vitiated Kapha Dosha is prominent	Vitiated Kapha Dosha is prominent
Emaciation or obesity	Emaciation	Emaciation	Emaciation
Loss of Ojas (causing loss of vitality and immunity)	No loss of Ojas	No loss of Ojas	Loss of Ojas
Palliative or Incurable	Curable	Curable	Palliative or Incurable
Urine is abnormally warm	Urine is abnormally warm	Urine is cold to touch	Urine is cold to touch
Turbid urine	Turbid urine	No turbidity in urine	Little turbidity in urine
Chronic onset	Acute onset	Acute onset	Chronic onset
Sweetness in the body	No sweetness in the body	No sweetness in the body	No sweetness in the body

I would like to emphasize that most of these aetiological factors, prodromal symptoms, clinical features, investigations and complications were identified and described over 2000 years ago. But when considering with an open mind, all the salient points are very much in line with modern findings and are appropriate even today.

### **Abbreviations**

A.H. - Ashtanga Hradaya

Ci. - Cikithsaathana

C.S. - Caraka Samhitha

Ni - Nidanasthana

Hans. N. – Hansaraja Nidana

Sut. - Suthrasthana

M.N. - Madhava Nidana

Vi. - Vimanasthana

S.S. - Susrutha Samhitha

Y.R. - Yoga Rathnakara

9<sup>th</sup> June 2003.

### Pre-clinical testing of herbal medicines for antidiabetic activity

Dr Rohini Fernandopulle  
Senior Lecturer in Pharmacology  
Faculty of Medicine, Colombo

### Traditional preclinical testing approach consists of ten steps

- Identification of the plant
- Collection of plant
- Transport to the research laboratory
- Storage
- Preparation of extracts
- Administration of extracts to the animal model

### Traditional approach consists of ten steps contd

- Identification of the active substance (s)
- Further fractionisation of the active extract
- Identification of the active principle, chemical structure
- Synthesis of the active principle

### Chandigarh group – Chaudhury et al 1980'

- Toxicity testing in two species of animals for acute and subacute toxicity
- Administration of the total extract or combination of plants used in exactly the same way as it is prepared and used by the population

How do you determine absolute dose for a species?

Table 1

	20g Mouse	200g Rat	400g Guinea pig	1.5kg Rabbit	2.0kg Cat	4.0kg Monkey	12.5kg Dog	70kg Man
20g Mouse	1.0	0.1	0.25	0.4	0.25	0.1	0.02	0.001
200g Rat	0.14	1.0	1.75	3.4	4.2	9.2	17.8	56.3
400g Guinea pig	0.08	0.5	1.1	2.25	2.4	5.2	10	31.3
1.5kg Rabbit	0.04	0.25	0.44	1.1	1.08	2.4	4.8	14.2
2.0kg Cat	0.03	0.25	0.41	0.92	1.0	2.2	4	13.0
4.0kg Monkey	0.016	0.11	0.3	0.62	0.45	1.0	2	6.1
12.5kg Dog	0.008	0.06	0.22	0.42	0.24	0.52	1.0	3.1
70kg Man	0.0026	0.018	0.32	0.62	0.56	1.25	2.5	7.8

Multiply the absolute dose given to the species in a row by the factor given at intersection of relevant row and column

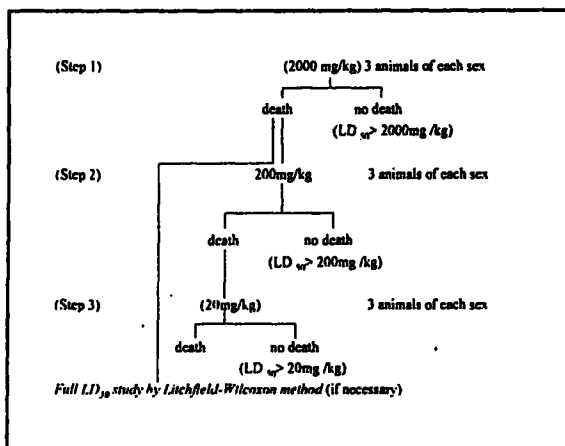
**Example**

If the dose producing an effect in a 12 kg dog is 10mg/kg the absolute dose is 120mg

Extrapolated to man the dose in man = 120mg X 3.1 = 372mg

**Acute toxicity test**

- Yamanaka S et al, A simple method for screening assessment of acute toxicity of chemicals
- Arch Toxicol, 1990;64:262 - 268



**Subacute toxicological tests for plant substances used by people**

- Depends on country and Ethics committees
- Sweden –
  - 30 rats given the decoction for three weeks: 3 doses
  - 4 female monkeys given the decoction daily for 30 days
  - 4 adult dogs given the decoction for 12 weeks
- India – Chandigarh group
  - Six week toxicological profile on two species

**Guidelines on acute and repeated dose toxicity**

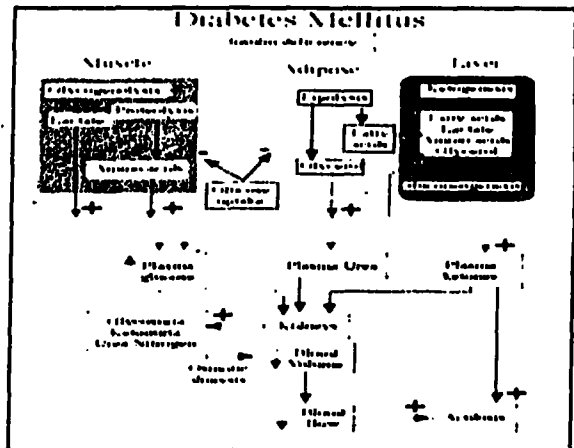
- EMEA guidance on acute and repeated dose toxicity
- <http://www.eudra.org/emca.html>

**History of Biguanides**

- Galenga officinalis, goat's rue  
 Was used to treat diabetes in Europe in medieval times
- Early part of 20<sup>th</sup> century – isolated the active principle, guanadine  
 But was too toxic
- 1920 Biguanides were investigated but overshadowed by discovery of insulin

## Allopathic drugs

- Insulin
- Oral hypoglycaemics:
  1. sulfonylureas
  2. biguanides
  3. competitive inhibitors of intestinal brush-border alpha-glucosidases
  4. thiazolidinediones



## Blood glucose decreasing activity

- Fasting state
- Glucose loaded state
- Diabetic state – alloxan, streptozocin
- Single dose studies
- Multiple dose studies over a period of time
- Compare with western drugs

## Mechanisms of action

- Increase insulin secretion by the pancreatic islets or reduce hepatic clearance of insulin
- Increase the peripheral utilisation of insulin – increased entry into skeletal, cardiac and smooth muscle and adipose tissue
- Inhibit hepatic gluconeogenesis and glycogenolysis
- Decrease glucagon levels

## Mechanism of action

- Plasma insulin levels
- Isolated tissue preparations
- Effects on Glucose transporter GLUT 4
- Effects on glucose metabolising enzymes –
  - Glycerol – 3- phosphate acyltransferase
  - Glycogen synthase

## Monitor control over time

- Measure HbA<sub>1c</sub> levels
- Lipid profile

## Conclusion

- Animal studies
- Toxicity
- Phase II clinical trials
- Phase III clinical trials
- Define possible mechanism of action by performing in-vivo and in- vitro bioassays

## **Development of Protocols on Diabetes for Clinical trials of Ayurvedic Drug**

**Dr. M.H.A. Tissera**  
Gampaha Wickremarachchi Ayurveda College, Yakkala

### **Aims of Clinical trial on a new Drug**

**Find a more effective drug**

**Find a more safe drug**

**Find a more cheap drug**

### **Objectives of Clinical trial on Ayurvedic drug**

**Study of the efficacy of an Ay. Drug**

**Find the mode of action of an Ay. Drug**

**Study the effectiveness of a different type of a  
preparation**

### **Phases of Clinical Evaluation Drug**

**Phase 1:- Preclinical testing by clinical pharmacologist**

**Phase 2:- Clinical testing by clinical pharmacologist**

**Phase iii;- Clinical trial by Clinical investigator**

**Phase iv : Post marketing surveillance by practicing clinicians.**

### **Trial Design**

**Select a trial design.**

**Randomization**

**Control-placebo/Standard drug**

**Open /double blind/single blind**

**Parallel/crossover.**

### **Selection on the Drug**

**Should be a prescribed formula in authentic book.**

**Formulated drug according to Ayurveda Dravya guna Vignana**

**Private formula -**

**Should have good records of its effectiveness.**

Should have subjected to toxicity studies and calculated the effective dose.

Should have proved the efficacy by experimental and primary researches

### **Researcher**

Should have a through knowledge on Diabetes

Should have knowledge on clinical trial

Should have an authority to treat the patients

### **Project title**

Specific, unambiguous

Main aim be understood

### **Introduction**

Problem - Background information

Literature review

Review of previous works

Purpose - How we plan to solve the problem

Benefit - To diabetic patients

To the Ayurvedic system

To economy of Sri Lanka

### **Project Description**

Preparation of the Drug

Selection of patients

Method of Drug administration

Collection of data

Method of evaluation

### **Preparation of the drug**

1. Raw

2. Prepared

Collection

Identification

Method of preparation

### **Selection of Patients**

**Where the trial will take place**

**Blood sugar level**

**Age, Sex**

**Exclusion criteria**

**Ethical consideration**

### **Ethical Consideration**

**Method, how the consent of the patient will be obtained**

**Approval from a Ethical Committee.**

### **Method of drug administration**

**Dose; Should be calculated according to Ayurvedic formula**

**Should be established according to the results of phase 1 experiments**

**Frequency: Should be according to the Ayurvedic regime**

### **Collection of data**

**Daily urine Sugar**

**Blood sugar in every two weeks**

**Symptoms of Diabetic**

**Symptoms of Madhumeha**

**Any other complains**

### **Method of evaluation**

**To Avoid Errors of Type 1 (false positive) and Type 11 (false negative)  
use appropriate method of statistics**

- 1. Student's t Test (paired or unpaired)**
- 2. Wilcoxon's signed rank test (on paired data)**

How to conduct a clinical trial in diabetes mellitus using oral hypoglycaemic drugs

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### A clinical trial of medicinal products

A systematic study in human subjects (patients or healthy volunteers)

To discover or verify effects and adverse reactions

Study their pharmacokinetics

Ascertain the efficacy and safety

### Clinical development of a new product

Phase I : on healthy volunteers

Phase II : therapeutic pilot studies

Phase III : trials in large patient groups and in varied groups to determine long term efficacy and safety

Phase IV : post marketing surveillance

What is considered "Gold Standard" in research are randomised, placebo controlled double blind clinical trials

### Main components of a research protocol

- Research questions (objectives)
- Significance of the objectives
- Study design
- Selection criteria
- Sampling methods
- Predictor variables
- Outcome variables

### Main components of a research protocol (continued)

- Criteria for premature stopping of trial
- Statistical issues
  - sample size
  - estimation methods
  - analytical methods

### Characteristics of a good research question

- Feasible: adequate number of subjects and technical expertise, affordable in time and money, manageable in scope
- Interesting to the investigator
- Novel
- Ethical
- Relevant to scientific knowledge, clinical and health policy

### Two sample research questions

- 1 How effective is drug A in controlling blood glucose in newly diagnosed type 2 diabetics?
- 2 Is drug A (new drug) more effective than drug B (existing drug) in controlling blood glucose?

### Designing inclusion criteria

Specify the characteristics that define populations that are relevant to the research question and efficient for the study

### Inclusion criteria

- Target population: Type 2 diabetics
- Accessible population: Patients attending the diabetic clinic of the NHSL

### Define clinical characteristics (example)

- Newly diagnosed diabetics
- Not previously treated with oral hypoglycaemic drugs(OHDs)
- Age 40 to 60 years
- Six to eight weeks on dietary therapy
- Poor control

### WHO criteria for diagnosis of diabetes mellitus

Fasting blood Glucose (FBG)	Venous blood mmols/L	Capillary blood/venous plasma mmols/L
Diabetes mellitus	>6.1(110mg/dl)	>7(126mg/dl)
Impaired FBG	5.8-6.1(100-110mg/dl)	8.1-7 (110-126 mg/dl)
Diabetes unlikely	<5.8 (100 mg/dl)	<6.1 (110mg/dl)

Diabetes mellitus	>10.0(180mg/dl)	>11.1(200mg/dl)
Impaired glucose tolerance	8.7-9.9(120-179mg/dl)	7.8-11(140-199 mg/dl)
Diabetes unlikely	<5.6(100 mg/dl)	<6.7(120mg/dl)

### Targets for control

	Good	Borderline	Poor
FBG mg/dl	80-110	4.4- <140	>140
mmol/l	6.1	<7.8	>7.8
PPBG mg/dl	80-144	<180	>180
mmol/l	4.4-8	<10	>10
HbA <sub>1c</sub> %	<6.5	<7.5	>7.5

### Define exclusion criteria

- Those likely to be lost for follow-up
- People unable to provide good data
- Ethical barriers –
  - patients with diabetic complications and patients with other illnesses.
  - Patients with very high blood glucose (FBG > 250 mg/dl, PPBS > 300 mg/dl)
  - Patients with FBG < 140 mg/dl and PPBS < 180 mg/dl with two weeks of intensive dietary therapy
  - Patients previously treated with OHDs
- Subjects who refuse to participate

### Study design

- Prospective
- Parallel group
- Randomised
- Double blind
- Controlled
- Weekly dose increment until target blood glucose values are achieved
- Stratify according to blood glucose level

### Time frame and ethical approval

- Starting date 1<sup>st</sup> August 2003
- Sample size 100 patients
- Two weeks of intensive dietary therapy
- Duration: three months
- Informed consent, management of adverse events/ complications

### Exclusion criteria

- Ethical barriers: use of placebo drugs
- Patients with complications
  - Retinopathy
  - Nephropathy
  - Neuropathy
  - Cardiovascular disease

### Variables (what measurements will be made)

- Predictor variables
- Outcome variables
- Weekly blood glucose, FBG & PPBG
- Blood glucose series once in 2weeks
- HbA<sub>1c</sub> in three months