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URGENT NEED FOR DEVELOPING CLINICAL PHARMACOLOGICAL EXPERTISE IN PAKISTAN

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INTRODUCTION

I wish to send you now my views on the need for making available in Pakistan expertise and facilities in clinical pharmacological services at least fifty years after the creation of Pakistan. This is so because of the fact that Pakistan is proud to have developed a dynamic pharmaceutical industry. The Pakistan drug market is in the tune of 20 million rupees. The growth of the pharmaceutical manufacturers has gone upto 275 out of which 30 are multi-nationals. The later earn 70% of the money while the national manufacturers earn only 30%.

The Pakistan drug act of 1976 is in itself 20 years old, this requires carrying out of clinical trials in Pakistan prior to the registration of drugs by the ministry of health. Although the regulation does not make it compulsory but desirable to undertake the clinical trails in Pakistan. This very fact is based on reality as virtually no expertise exists in clinical pharmacology in the entire country, i.e. in academia, the pharmaceutical industry, and in the government institutions who control drugs.

Clinical Pharmacology:

WHO has published a report on principals of clinical pharmacology which means improvement in clinical trials. It is a medical discipline and is meant for improving efficacy and safety of medicines. thalidomide tragedy of 1960 was a severe adverse reaction and it led many governments in setting up central drug control system at national level for registering new drugs.

I would now like to describe briefly the various functions which a clinical pharmacological can undertake.

1. To improve patients care:

The multiplicity of drugs posses serious problems for both the physicians and patients. The quality of patient care could be greatly improved by taking full advantage of existing knowledge about the efficacy and safety of drugs, its indications, contra-indications, dosage schedule and interaction with other drugs. The clinical

pharmacologists can greatly assist physicians in achieving this goal of improving patient care.

2. Research:

After registration of a drug at the national level and its wide availability for use by patients requires a constant effort to monitor its efficacy and safety.

Pharmacokinetic is the study of the absorption, distribution, metabolism and excretion of drugs. Since these processes determine the concentration of the drugs at the site of action, much additional information can be obtained by combining pharmacokinatic with pharmacodynamic measurements.

Pharmacokinetic studies contribute to the safer conduct and more efficient design of human studies. The rates of metabolism and elimination vary widely in different species. These are often more rapid in commonly used experimental animals e.g. rat and dog than in man. Pharmacokinetic studies must be performed in man, therefore in order to obtain information that is relevant to the clinical practice in individual societies. Genetic and environmental factors are responsible for substantial differences in the effects of certain drugs.

Pharmacodynamic is the study of biological and therapeutic effects of drugs. It can also elucidate the mechanism of action of a drug.

Individual variation to drug responses: There are marked individual differences in drug responses even in the same society. Thus results can be obtained on population but cannot always be extrapolated to another area having a different genetic constitution or living under different environmental conditions.

3. Drug evaluation in man and its various phases:

A WHO book has been published entitled "Clinical Evaluation of Psychotropic drugs for Psychiatric disorders" by Graff, Han *et al.* This book reviews this subject and the following are the various phases.

i) Clinical Pharmacological studies (This is referred as phase I study)

The purpose is together evidence of desirable and undesirable pharmacological effects obtained in human receiving single dose of a drug and at times limited multiple dose study. Since the primary objective of this phase of study is to assess the relative safety of a drug, these studies are conducted in a limited number of normal subjects e.g. 20-40 in total.

ii) Early therapeutic studies usually referred to as Phase II studies:

These are designed to obtain reasonable indications of therapeutic potentials,

effective dose, and probable common side effects. The initial studies usually involves fewer than 100 patients. Following the initial investigation additional early studies are also conducted using comparison with a placebo and/or standard medicines. These studies may involve several hundred patients and are usually pivotal to determine if a drug warrants further development.

iii) Main therapeutic studies usually referred to as Phase III studies:

They are undertaken after assurance of relative safety and efficacy of the drug and the likely dose. The task of this study is to gather more evidence of efficacy and safety in large patient groups under varied settings. It is at this stage following the completion of early and main clinical studies including special pharmacological and bio-pharmaceutical study that the accumulated data are submitted to regularity agencies for initiation of the approval process of the health ministry.

iv) Expanded therapeutic studies and drug surveillance usually referred to as Phase IV or post marketing studies:

This is subsequent to approval of a new drug when a series of studies are designed to examine the efficacy of the drug, its safety, drug utilization studies and the cost benefit risk ratio on drugs which are in routine use on a long term basis in the population. Special techniques are available to collect and evaluate reports on adverse drug reactions including a positive addictive potential on a national or international scale.

4. Teaching Medical students and hospital staff and practicing physicians

Basic Pharmacology is usually taught as a pre clinical discipline. Its scientific and educational value are unquestioned but the therapeutic use of drugs in patients cannot be adequately taught or understood by a student who has no knowledge of disease and its modification by drugs. It is extremely important that medical students be thoroughly instructed about the potent pharmacological tools in their trade. Unfortunately instructions in the therapeutic pharmacology during the clinical yeas is totally inadequate in many medical schools. Even after graduation some doctors read little about the subject and rely too much for their information on the promotional efforts of the pharmaceutical industry. Thus there is a strong need for continuing education in this subject and others throughout their career.

5. Services

Provision of information concerning drugs is an important subject. Doctors need a regular source of information about drugs both new and old as well illicit drugs which are available to the population they serve. Many currently used drugs are not available during the training of doctors. Thus publications are needed that provide necessary information in short and easily digested articles. This is an important service which must be provided.

Measurement of drug levels in body fluids. The clinical pharmacologist must have an access to an analytical laboratory. He has an essential role to play in the practical application of Pharmacokinetic data.

Advice on design of clinical studies: Although some clinical trials are carried out by clinical pharmacologists but many are also conducted by clinical specialists. The clinical pharmacologists are a source of advice to their colleagues who are going to conduct clinical trials.

Monitoring of drug usage: Survey of prescribing patterns and study of the incidence of adverse drug reaction is another important service for clinical pharmacologists to offer. ,

Preparation of reference books and manuals on prescribing e.g. pharmacopias and formulary: the clinical pharmacologist help to decide as to which preparation should be included and their dosage schedule along with their therapeutic recommendations.

Advice to the government drug control organization: The services of clinical pharmacologists are necessary for the following tasks:

- Whether animal data on a drug are adequate to justify administration to man.
- Decide whether therapeutic trial justify release for general use.
- To work on drug monitoring including adverse drug reaction and acute intoxication.
- Advice on the restriction on the use of drugs or their withdrawal from the market.

6. Advice to the pharmaceutical industry:

It is essential for the pharmaceutical industry to have the services of the clinical pharmacologist. The industry is responsible for the development of new drugs, application for registration of drugs and advise on their use, misuse and abuse by the population. Thus the services of full time or part time consultants is essential.

Training facilities for clinical Pharmacologists:

I have witnessed during the last 25 years tremendous national efforts in creating training programs not only in developed countries but also in developing countries e.g. India, Malaysia and even Nepal. The high cost of medicines have led to restricting the number of drugs available for use at the national level. Thus it has become essential for countries to have expertise in clinical pharmacology to support clinicians in providing them with safe, effective, of good quality and cost effective drugs. General physicians and specialists in the clinical subjects may spend one or two years working in clinical pharmacology units to obtain a degree or necessary experience. Such

training will equip him to participate in clinical trials, teaching to graduate doctors, drug monitoring for adverse reaction and to set up clinical units for the treatment of poisoning.

A clinical pharmacology unit may be started within a clinical and/or pharmacology departments in a medical school and it is the aim that these units develop into an independent department headed by a professor in due course of time. Facilities required for a clinical pharmacology unit are laboratory facilities, office space, hospital beds and out patient facilities. They should have access to patients and be responsible for their care.

The situation in Pakistan:

During the last 18 months, I have visited Pakistan four times, each time for about a month. The job was to try to promote the rational use of list of essential drugs by physicians. Dr. Arbab Ghaffar who was trained in London in Clinical Pharmacology and returned to Peshawar University two decades ago is presently assigned to PGMI L.R. Hospital in Peshawar. He himself will tell you that he was not an effective clinical pharmacologist because of difficulty of interaction with his clinical colleagues. He is going to retire shortly. A second Pakistani, Dr. Rehan Haffez obtained a Ph.D. in Clinical Pharmacology in Aberdeen University specializing in anti malarial medications. He is now assigned to the drug control and traditional medicine section of the NIH at Islamabad.

I have proposed to the federal health secretary that there is an urgent need for the ministry of health that they have to rely more and more on the staff assigned to the National Institute of Health in preparing reports for drug registration, post marketing surveillance of drugs o the market and dissemination of information to the health care professionals in Pakistan.

The Narcotics control Ministry have to play an active role in these activities rather than giving a lip service. I am also convinced that licit psychoactive drugs create great morbidity and mortality in Pakistan and thus the narcotics control ministry must assume its legal and moral responsibility in ameliorating this situation.

I congratulated the president of PCPS on initiating an FCPS in clinical pharmacology and therapeutics in 1994. What they urgently need is qualified staff led by a clinical pharmacologist, laboratory facilities and training programs in collaboration with an institution in Karachi who have the capabilities to assist them. A program usually develops around a *Guru* who is an expert in the specific field.

I am convinced that the medical institutions and the government of Pakistan as well as the provincial government can rely on the resources in WHO and the

pharmaceutical industry for finding funds and institutes of excellence abroad where training can be imparted. An initiative has to be made from the medical colleges itself, their deans and academic council other wise the situation will remain pathetic as it is for along time to come.

I made a recommendation in July 1995 to WHO, EMRO and the federal ministry of health and the four provincial health departments to include training of clinical pharmacologist in their next budget which they yearly propose to WHO. At the same time I also advise them to create posts of Associate or Assistant Professor at the medical colleges. I have no feed back about these recommendations of mine so far. This must be pursued.

It is high time that the ministry of health make it compulsory that limited local studies be made essential before registering a product from 1997. This will not only encourage but stimulate the pharmaceutical industry to invest in the training of clinical pharmacologists in Pakistan.

I am confident that discussion on this paper will result into realistic recommendations and a mechanism for the follow up.

REFERENCES

1. WHO TRS 446, Clinical Pharmacology, Scope, Organization and Training (1970).
2. WHO Expert series on biological psychiatry, Volume 2 (1993). Clinical Evaluation of Phsycotropic drugs for psychiatric disorders by Graff, Khan *et al.*
3. World Health Forum, What action for rational drug use by Inayat Khan 1996 (in the press).
4. College of Physicians and Surgeons of Pakistan, FCPS Part II, Clinical Pharmacology and Therapeutics Nov. 1994/1995.
5. Promoting rationalize of Essential Drugs in Pakistan (1996) by Khan I, FRY Fazli and Rehan H, Sixth International Conference on Clinical Pharmacology and Therapeutics Buenos Aires, Argentine.
6. Monitoring of adverse reactions, the role of WHO by M. Ten Ham, WHO headquarters. Epla pharma law report No.13, Nov. 1994.
7. Report of a visit by Inayat Khan as a consultant to the department of health, N.W.F.P. Pakistan between the 1st and 23rd of Sept. 1996 to visit the district headquarters hospitals and give presentations to promote the rational use of drugs and prevent drug abuse.