# The Practice of Phase I Study in Japan*

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# 임상 제Ⅰ상 시험의 실제

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**Development of New Drug**

In the process of development of new drug, we must consider firstly GMP: Good Manufacturing Practice which means the rule for manufacturing and quality check of drug preparation. Secondly GLP: Good Laboratory Practice which means the rule for safety test of drug in the laboratory. Finally, GCP: Good Clinical Practice which means the rule for clinical trial based on ethical and scientific consideration. The Science Council of Japan issued the GCP December 1985 (Table I). This is not a complete one but still proposal. I will tell you more details about GCP later. Today, I would like to speak mainly about phase I study of clinical trial.

**Usual Steps in the Development of a New Drug**

Table II shows the usual steps in the development of new drug. First step was the synthesis of new chemical or production of new material from a natural source. Identification of the new chemical or characterization of the new material should be made. Furthermore, we must establish the degree of purity and perform the preliminary stability studies on the compound. This step is regulated by GMP. The substance is then subjected to a wide range of pharmacological tests in animals to detect any effects that may be of therapeutic use. Many compounds are rejected at this stage but those that survive are further investigated to determine their pharmacodynamic and erally designed to determine the metabolism and toxicity. These steps are regulated by GLP. When adequate data available, early studies are initiated in man and if successful, are followed by controlled therapeutic trials. These steps are regulated by GCP.

**The Phases of Drug Development**

Trials of drugs in man are generally conducted in three phases before approval of the drug for sale. Phase I study consists of the introduction of the new drug to human (Table III). These studies are closely monitored and are conducted in either normal volunteers or a few selected patients with the disease to be treated. These studies are gen-

**Table I**—*The Development of A New Drug.*

| | |
|---|---|
| 1979 | : Good manufacturing practice (GMP) |
| 1983 | : Good Laboratory practice (GLP) |
| (1985) | : Good Clinical practice (GCP) |

**Table II**—*Usual Steps in the Development of A New Drug.*

1. Syntheisis of new chemical or production of new material from a natural source
2. Biological screening and acute toxicity
3. Pharmacodynamic studies in animals
4. Pharmacokinetic studies
5. Early Studies in man
6. Controlled therapeutic trials

*과학의 달 기념 심포지움「신약개발과 제Ⅰ상 시험」(1987. 4. 24, 대한상공회의소)에서 발표된 내용임.

**Table III**—*The Phases of Drug Development.*

| | |
|---|---|
| Phase I | : First human administration |
| Phase II | : Therapeutic dosage range |
| | a. Early |
| | b. Late |
| Phase III | : Broad clinical trial, Overall risk-benefit relationship |
| Phase IV | : Investigation of drug safety and efficacy after approval of the drug for sale |

pharmacokinetic properties and to assess their pharmacologic actions of the drug in human to ascertain side effects associated with increasing doses. During phase I, sufficient information about the pharmacokinetics and pharmacologic effects of the drug should be obtained to permit the design of well-controlled scientifically valid phase II studies. Phase II studies involve controlled clinical trials conducted to evaluate the efficacy of the drug for a particular indication in patients with the disease and refine therapeutic dosage range. Phase III studies are expanded controlled clinical trials and intended to give additional data about efficacy and safety needed to evaluate the overall risk-benefit relationship of the drug and to provide and adequate basis for drug labeling.

**Proposed Investigational New Drugs (IND) in Japan**

**Table IV**—*Proposed Investigational New Drugs(IND) in Japan.*

| Drug | 1984 | 1985 |
|---|---|---|
| CNS drug | 6 | 24 |
| Cardiovascular drug | 20 | 20 |
| Biological product | 16 | 14 |
| Hormone | 1 | 12 |
| Gastrointestinal drug | 7 | 10 |
| Antibiotics | 7 | 9 |
| Antineoplastic drug | 14 | 9 |
| Metabolic drug | 5 | 9 |
| Transdermal drug | 4 | 5 |
| Respiratory drug | 5 | 4 |
| Others | 20 | 12 |
| | 105 | 128 |

Table IV shows the proposed investigational new drugs in Japan. In 1985, 128 investigational drugs were proposed for clinical trial to Ministry of Health and Welfare. Drugs acting on central nervous system were 24, followed by cardiovascular drug, biological product, hormone, gastrointestinal drug, antibiotics, antineoplasic drug and so on.

**The Amounts of Product of Drugs in Japan**

Table V shows the amount of product of drugs in Japan. Total amount of product of drugs in 1985 was 4,001,807 million yens. The amount of product of antibiotics was 690,505 million yens in 1985 followed by cardiovascular drug, central nervous system drug, gastrointestinal drug and so on. The order and the amount of product of drugs in 1984 and 1985 were almost similar.

**Newly Approved Drugs in 1986**

Table VI shows the newly approved drug in Japan. The total numbers of drugs were 33 in 1986. Japanese origins were 18 and foreign origins were 15. Seven antibiotics were newly approved followed by antiinflammatory drugs, transdermal drug, antiulcer drug and so on.

## GOOD CLINICAL PRACTICE

In 1985, the Science Council of Ministry of

**Table V**—*The Amounts of Product of Drugs in Japan.*

| Drug | 1984 | 1985 |
|---|---|---|
| Antibiotics | 742,496 | 690,505 |
| Cardiovascular drug | 531,299 | 519,683 |
| CNS drug | 396,492 | 383,855 |
| Gastrointestinal drug | 344,273 | 353,799 |
| Metabolic drug | 330,522 | 314,132 |
| Transdermal drug | 245,530 | 239,679 |
| Vitamin | 245,514 | 238,541 |
| Biological product | 150,996 | 153,355 |
| Respiratory drug | 128,872 | 141,781 |
| Antineoplastic drug | 143,627 | 138,601 |
| Others | 767,364 | 827,872 |
| | 4,026,985 | 4,001,807 |

million yen

Health and Welfare in Japan proposed Good Clinical Practice (GCP) regulation. These items in Table VII are regulated by GCP. This regulation means the rule for clinical trial based on ethical and scientific consideration. Phase I, II, and III studies of clinical trial are included in this regulation. Facilities to deal with all emergencies must be available. Clinical trial protocol must be approved by Institutional Review Board. I will tell you about IRB more details later. The clinician has a duty to supervise closely to record and to measure the functions that may be affected by the new drug. Investigator of Phase I study should be clinical pharmacologist who have been trained in both pharmacology and clinical medicine and may have special interest in the methodology of experimental design. Investigator should primarily consider the safety of volunteer and must be obtain informed consent from volunteer before initiation of trial. I will tell you about informed consent, protocol and documentation later.

**Table VI**—*Newly Approved Drugs in 1986.*

| Drug | Japanese-origin | Foreign-origin | Total |
|---|---|---|---|
| Antibiotics | 4 | 3 | 7 |
| Antiinflammatory drug | 3 | 1 | 4 |
| Transdermal drug | 1 | 3 | 4 |
| Antiulcer drug | 3 | 0 | 3 |
| **Respiratory drug** | 0 | 3 | 3 |
| CNS drug | 2 | 0 | 2 |
| Others | 5 | 5 | 10 |
| | 18 | 15 | 33 |

**Table VII**—*Good Clinical Practice(GCP).*

1. Scientific and Ethical Issues
2. Phase I, II, III
3. Facilities
4. Institutional Review Board(IRB)
5. Investigator
6. Safety of Volunteer
7. Informed Consent
8. Protocol
9. Documentation

**Table VIII**—*Phase I Study.*

| | |
|---|---|
| who? | Normal volunteers-small number |
| why? | Determine biological effects |
| | Pharmacokinetics (metabolism) |
| | Safe dosage range in man |
| By whom? | Clinical pharmacologists |

**Phase I Study**

Phase I is the first trial of a new drug in human (Table VIII). The drug is given for a short time to a small number of healthy volunteers. In the case of antineoplastic drug, the drug is given to patients suffering from the disease for which the drug is intended. The aim is to make a preliminary evaluation of biological effects, pharmacokinetics and safe dosage range in man. Phase I study should be conducted by clinical pharmacologist.

**Preclinical Studies as a Prerequisite for Phase I Study**

Studies of a drug in man must be justified by the demonstration of potentially useful effect in animals. Initial studies in man must necessarily be based on tests in animals. Preclinical studies as a prerequisite for phase I study should be done as follows:

1. Acute and subacute toxicity studies in at least two animal species.
2. Teratogenicity (Segment II)
3. $ED_{50}$ for the particular pharmacologic property
4. Pharmacokinetic and toxicokinetic studies in at least two animal species.
5. Mutagenicity

The clinical investigator must satisfy himself that these preclinical studies are adequate.

## PROTOCOL OF PHASE I STUDY

Important items in protocol of phase I study are given as below:

1. Purpose of study
2. Details of procedure
3. Initial dose determination
4. Selection of volunteers
5. Informed consent
6. Safety consideration

7. Placebo
8. Institutional Review Board

I will tell you more details about each item.

**Purpose of Study**

Purposes of phase I study are safety and tolerance, pharmacokinetics and pharmacodynamics of investigational drug. Healthy volunteers have no personal benefit from this study, then clinical investigator must consider primarily health care of volunteers. In order to minimize risks in man, it is essential to have methods of detecting pharmacodynamic effects, unexpected as well as expected, as soon as they appear. The most sensitive available techniques should always be employed and these will sometimes demand complex equipment and skills. Studies of absorption, distribution, biotransformation (metabolism) and excretion contribute to the safer conduct and more efficient design of human drug studies, allow accurate dosage schedules to be reached at an earlier stage, enhance prediction of the effect of disease on the action of the drug. Early pharmacokinetic studies may be particularly useful for demonstrating that the drug is accumulating even before pharmacodynamic effects become apparent.

**Initial Human Dose Determination**

Extrapolation of animal study to man is very difficult. In general, prediction from animals of what effect a drug will have in man, is more reliable than prediction of the dose at which this effect will appear; in other words, species differences are more often pharmacokinetic than pharmacodynamic. But we must administer the initial dose to human some day.

Table IX shows the initial human dose determination. Least dose among above criteria is usually administered to human as initial dose.

**Table IX**—*Initial Human Dose Determination.*

1. Less than 1/600 of the lowest $LD_{50}$ in any of the species tested
2. Less than 1/60 of $ED_{50}$ for the particular pharmacologic property investigated
3. Less than 1/60 of the highest tolerated dose in the most-sensitive species
4. Less than minimal effective dose in the most sensitive species
5. Less than 1/10-1/20 of expected clinical dose
6. Less than minimal effective dose of a similar drug
7. Less than 1/2-1/3 of foreign usual dose

**Procedure of Phase I Study**

Table X shows the procedure of phase I study. We examine dose relation study with single administrations. The dose is gradually increased until some effects are noted. When the drug is first administered to man, arrangement should be made to record the subject's feelings and the ordinary routine of medical observation (temperature, pulse, blood pressure and urine) must be maintained. Regular examination of the peripheral blood and of hepatic and renal function should be done as a safety precaution even though animal tests have given no reason to expect those to be altered, for laboratory tests generally provide an earlier indication of malfunction than clinical observation. Sometimes it may be desirable to delay or interrupt the clinical programme whilst further animal experiments are done.

Sulphasalazine (SASP) is a drug for treatment of ulcerative colitis, recently for treatment of rheumatoid arthritis. Scheme 1 is a pharmacokinetics of sulphasalazine. SASP may be related to main effect and SP may be related to side effect, or adverse effect.

Fig. 1 shows plasma SP and acetylated metabolites. Acetylated metabolite level is higher than SP level. This may be related to that majority of

**Table X**—*Procedure of Phase I Study.*

1. Single administration
   - Dose relation study
   - Food effect
2. Multiple administration
   - Dosage regimen
   - Steady state
   - Accumulation ratio
   - Duration

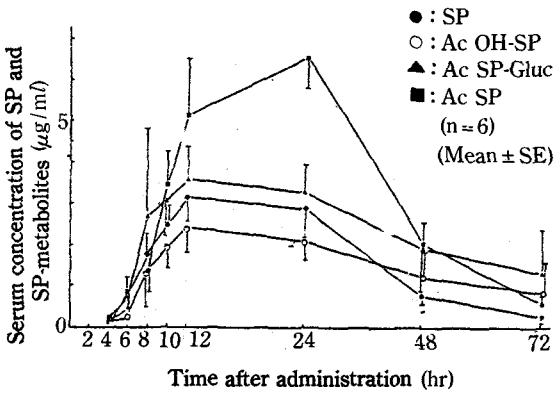



**Figure 1**—Serum concentration of Sp and Sp-metabolites (1,000 mg single dose).

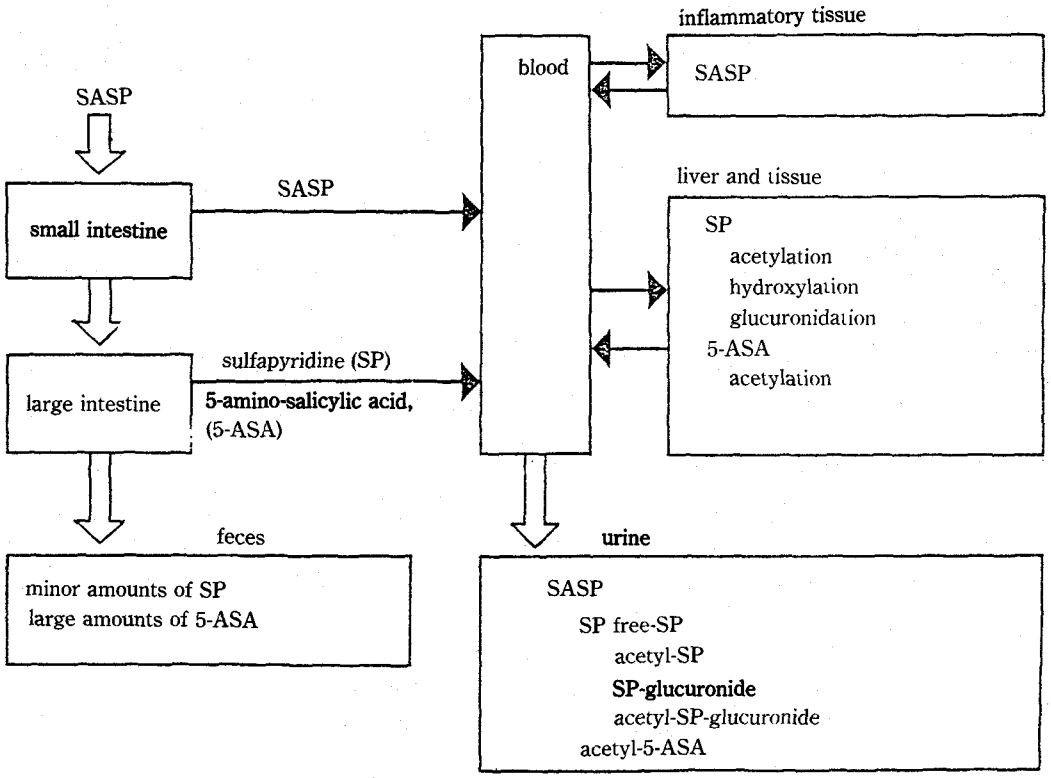
Japanese people are fast acetylators. In fast acetylator, acetylated metabolite level is higher than SP level. While, In slow acetylator, SP level is higher than it's acetylated metabolite. Caucasian has high level of SP than acetylated metabolite beause Caucasian has more slow acetylator than that in Japanese.

Food effect must be examined for proper dosage regimen. Food delays the absorption of some drugs and decreases it's bioavailability but sometimes food increases some drug bioavailability. Fig. 2 is a latter example. CS-807 is a oral cephem antibiotics. This is metabolized by esterase in intestine and produce active metabolite R-3763. The concentration of R-3763 after meal is higher than that before meal.

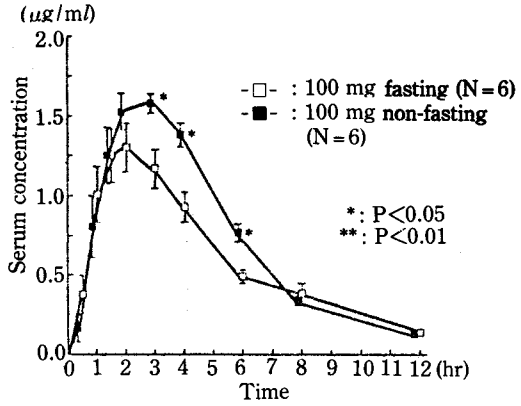
In urinary recovery of R-3763, higher bioavailability was observed after meal (Fig. 3).

Itraconazole is an oral antifungal drug. Similar results were obtained. That is, the concentration of itraconazole after meal is higher than that before meal (Fig. 4).

After a safety of single drug administrations was ascertained, we must investigate the safety of multiple administrations. In this study, we examine dosage regimen, accumulation ratio and steady state level of drug. The duration of multiple administration is a period of time which are re-




**Scheme 1**—The pharmacokinetics of SASP in man. (quoted from Schröder, *et al.*)




| | $C_{max}$ (μg/ml) | $T_{max}$ (hr) | $AUC_{0-12}$ (μg·h/ml) | $T_{1/2}$ (hr) | Urinary recovery (%) |
|---|---|---|---|---|---|
| Fasting | 1.31± 0.15 | 2.2± 0.2 | 7.20± 0.87 | 2.5± 0.2 | 33.6± 3.8 |
| Non-fasting | 1.66± 0.07* | 2.5± 0.2 | 8.63± 0.29 | 1.8± 0.1 | 50.7± 1.9** |

(N=6: Mean±S.E.)

**Figure 2**—Blood level of R-3763 (Influence of Food).

quired to obtain the steady state level. I think the duration is usually one or two weeks for healthy volunteers.

Fig. 5 shows itraconazole levels in multiple ple administration 1 cap/day for 8 days. Biological half life of itraconazole is app. 25 hrs. Trough levels are gradually increased with repeated doses. This means some accumulation occurs.

Fig. 6 shows a case whose liver function was impaired after repeated administration of CS-907. He already had a high γ-GTP value before

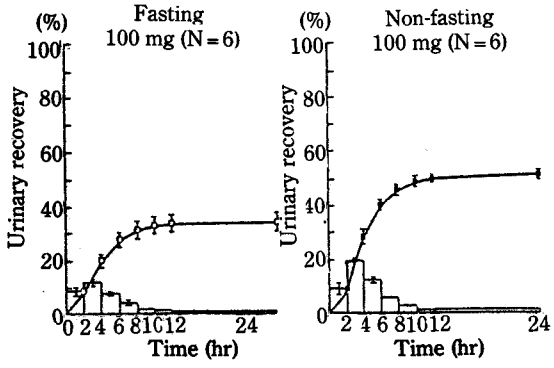
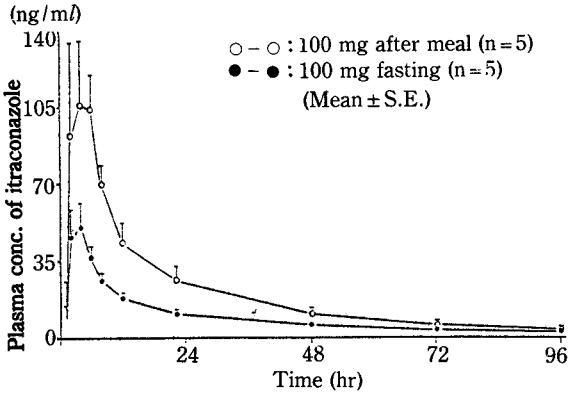



**Figure 3**—Urinary recovery of R-3763.

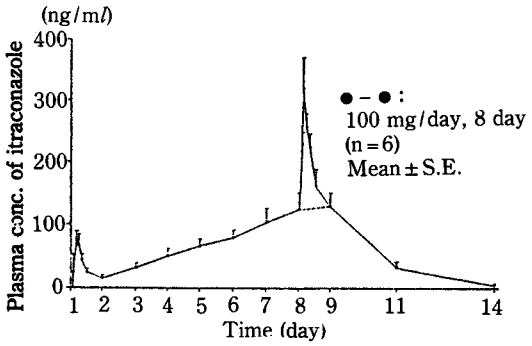



| Dose (mg) | $C_{max}$ (ng/ml) | $T_{max}$ (hr) | AUC 0- (ng·h/ml) | $T_{1/2}$ (hr) |
|---|---|---|---|---|
| 100 mg after meal | 132.2± 80.7 | 4.8± 1.8 | 2221± 1140 | 25.8± 8.6* |
| 100 mg fasting | 53.2± 24.5 | 3.6± 0.9 | 1326± 573 | 33.9± 8.5* |

(Mean±S.D.)

**Figure 4**—Single dose administration (effect of meal).

administration of CS-807. In this case, γ-GTP and GPT or other parameters were increased even after cessation of the drug. At two and half month after cessation of the drug, these parameters re-




| Day | $C_{max}$ (ng/ml) | $T_{max}$ (hr) | $AUC_{0-24}$ (ng·h/ml) | $T_{1/2}$ (hr) |
|---|---|---|---|---|
| 1st day | 81.1± 38.6 | 4.3± 1.5 | 749± 369 | 11.8±7.7* (25.8±8.6**) |
| 8th day | 333.1± 86.2 | 4.3± 0.8 | 4318± 1290 | 30.8±16.6 |

(Mean±S.D.)

**Figure 5**—Repeated dose 100 mg/day, 8 day administration.

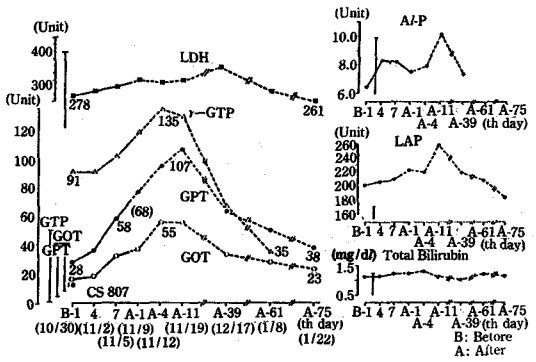



**Figure 6** —No. 4-2 K.H. 28 —CH-807 200 mg×2/day—

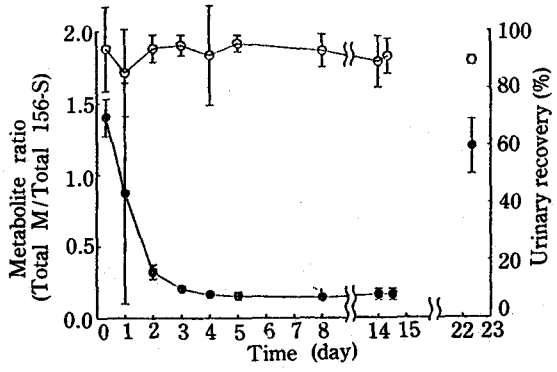



**Figure 8**—Metabolite ratio (-○-) and urinary recovery (-●-) following multiple administrations and single administration after washout period at dose of 300 mg of 480156-S.

turned to normal.

156-S is a antiinflammatory drug. Fig. 7 shows the 156-S levels in multiple administrations. The actual plasma level profile after repeated doses did not fit the simulated curves by plasma level profile of first dose. That is, the actual plasma level was higher than that of simulated curve.

Metabolic ratio (total metabolite/total 156-S) was decreased with repeated doses, but this effect was reversible (Fig. 8). This was found to be autoinhibition by this drug.

Fig. 9 shows the interaction of 156-S and tolbutamide. 156-S inhibited the metabolism of tolbutamide and remarkably increased the plasma level of tolbutamide.

$T_{1/2}$ of tolbutamide was increased from 7 to 43 hrs with 156-S (Table XI).

**Selection of Volunteers**

Table XII shows the selection of volunteers. Depending on the objectives of the study, the subjects chosen may be persons in normal health or patients due regard being paid to ethical criteria. It is preferable to choose a subject who could possibly derive personal benefit from the drug rather than one who could not. In general, new drugs will

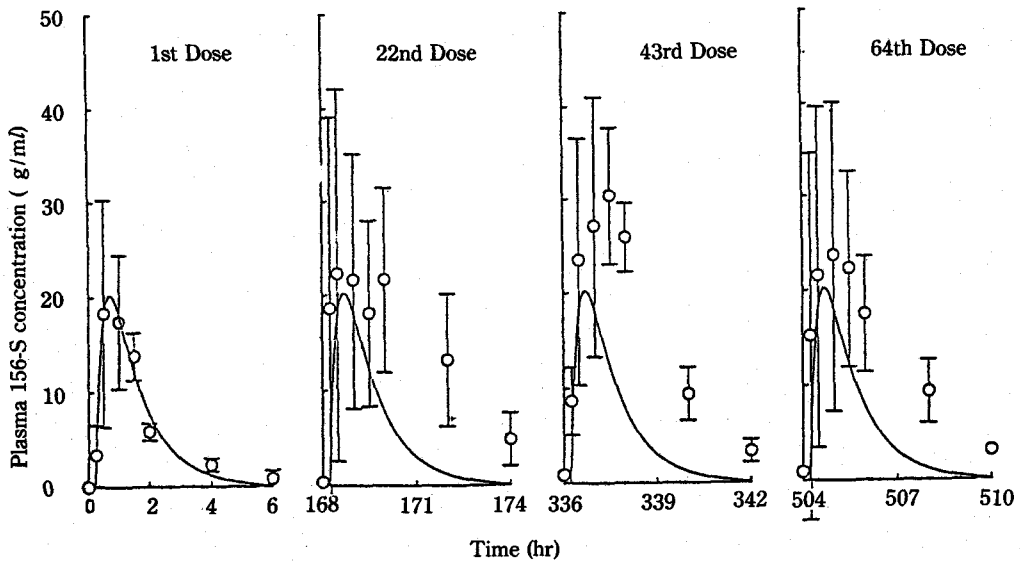



**Figure 7**—Plasma concentrations of 156-S following multiple administrations of 300 mg and the simulation curves calculated using the parameters obtained by pharmacokinetic analysis of the data at the 1st dose. (n=6)

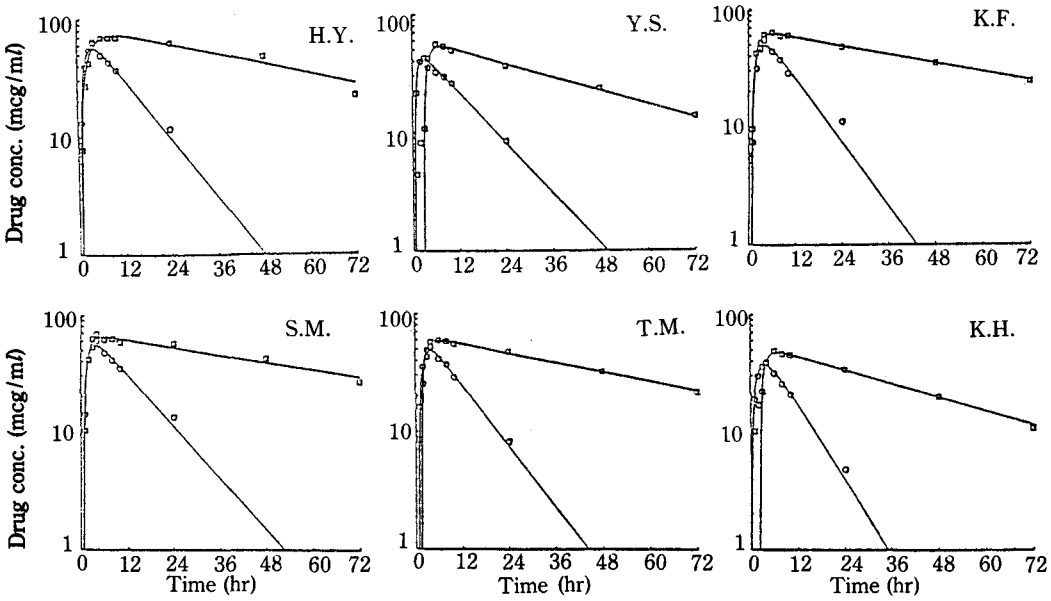



**Figure 9**—The interaction of 156-S and tolbutamide (Tolbutamide 500 mg *p.o.* with and without 156-S).

**Table XI**—*Pharmacokinetic Parameters of Tolbulamide in Volunteer Following Oral Administration of 500mg with and without Coadministration of 480156-S.*

| 480156-S | Subject | $K_a$ $hr^{-1}$ | $K_{el}$ $hr^{-1}$ | V/F *l* | Lag-t hr | $t_{1/2}$ hr | AUC $\mu g \cdot hr/ml$ |
|---|---|---|---|---|---|---|---|
| | H.Y. | 0.718 | 0.095 | 6.46 | 0.77 | 7.33 | 815 |
| | Y.S. | 1.365 | 0.081 | 9.84 | 0.59 | 8.52 | 625 |
| | K.F. | 0.684 | 0.104 | 7.23 | 0.86 | 6.66 | 665 |
| | S.M. | 0.863 | 0.084 | 7.06 | 0.76 | 8.23 | 841 |
| Without | T.M. | 1.053 | 0.099 | 8.02 | 1.50 | 6.98 | 630 |
| | K.H. | 0.594 | 0.122 | 9.04 | 0.29 | 5.68 | 453 |
| | Mean | 0.880 | 0.098 | 7.94 | 0.80 | 7.23 | 672 |
| | S.D. | 0.287 | 0.015 | 1.29 | 0.40 | 1.05 | 142 |
| | H.Y. | 0.375 | 0.012 | 5.93 | 0.80 | 43.04 | 5237 |
| | Y.S. | 0.829 | 0.022 | 8.44 | 2.77 | 31.36 | 2679 |
| | K.F. | 0.804 | 0.014 | 7.45 | 0.80 | 48.46 | 4693 |
| | S.M. | 0.951 | 0.012 | 7.26 | 0.85 | 60.26 | 5989 |
| With | T.M. | 0.693 | 0.015 | 7.75 | 0.80 | 46.20 | 4299 |
| | K.H. | 0.867 | 0.022 | 9.55 | 2.37 | 30.94 | 2337 |
| | Mean | 0.753 | 0.017 | 7.73 | 1.40 | 43.38 | 4206 |
| | S.D. | 0.203 | 0.004 | 1.21 | 0.92 | 11.12 | 1436 |

be evaluated initially in adults, for example, researcher, medical doctor, medical student, pharmacy student, dental student and nurse. These persons could easily understand the protocol.

Women who are known to be or who may be pregnant should not be used in the earliest initial studies with drugs because of potential risk to the fetus.

**Institutional Review Board (IRB)**

An institutional review board is composed of no less than five persons who are able to review adequately the activities in the proposal (Table XIII). Each IRB shall include at least one member whose primary concerns are in nonscientific area. Such a review safeguards the welfare of subjects as well as the clinical investigator. It's function includes the scientific validity and technical aspects of the proposed study, since improperly conducted studies are unethical and it also includes safety consideration and informed consent. These are based on ethics of Declaration of Helsinki.

The ethical and legal aspects of any test involving humans in the evaluation of a drug must be accorded continuing attention. Recommendations for the guidance of doctors engaged inclinical research are embodied in the Declaration of Helsinki. This is consisted of introduction, basic principles, clinical research and non-clinical biomedical research.

**Table XII**—*Selection of Volunteers*.

| |
|---|
| 1. Laboratory test |
| 2. Physical test |
| 3. Mental test |
| 4. Others |

**Table XIII**—*Institutional Review Board(IRB)*.

| | | |
|---|---|---|
| Member | : | No less than five persons who are able to review adequately the activities in the proposal |
| Function | : | Evaluation of preclinical studies |
| | | Validity of protocol |
| | | Safety consideration |
| | | Informed consent |
| Ethics | : | Declaration of Helsinki |

## Declaration of Helsinki

### *Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*

*Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and as revised by the 29th World Medical Assembly, Tokyo, Japan, 1975*

*Introduction*

*It is the mission of the medical doctor to safeguard the health of the people.* His or her knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the doctor with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest". The purpose of biomedical research involving human subjects may be to improve diagnostic, therapeutic, and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease. In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies a *fortiori* to biomedical research. *Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.* In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subject to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, *the World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects.* They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. *Doctors are not relieved from criminal, civil, and ethical responsibilities under the laws of their own countries.*

*I. Basic Principles*

1. *Biomedical research involving human subjects must conform to generally accepted scientific principles and*

*should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.*

2. *The design and performance of each experimental procedure* involving human subjects should be clearly *formulated in an experimental protocol* which should be transmitted to a specially appointed *independent committee* for consideration, comment and guidance.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. *The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research,* even though the subject has given his or her consent.
4. *Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.*
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. *Concern for the interests of the subject must always prevail over the interests of science and society.*
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. *Doctors should cease any investigation if the hazards are found to outweight the potential benefits.*
8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be *adequately informed* of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is *at liberty to abstain from participation in the study* and that he or she is *free to withdraw his or her consent to participation at any time.* The doctor should then obtain *the subject's freely-given informed consent, preferably in writing.*
10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who in completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
12. *The research protocol should always contain a statement of the ethical considerations* involved and should indicate that the principles enunciated in the present Declaration are complied with.

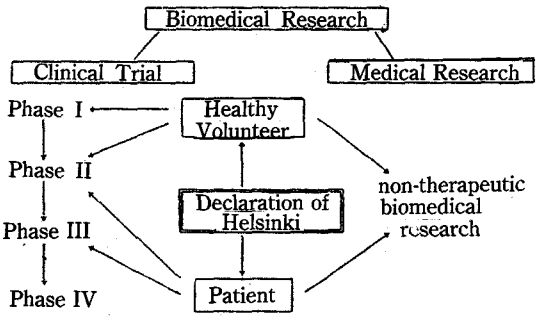
*II. Medical Research Combined with Professional Care* (Clinical Research)

1. *In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure,* if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient-including those of a control group, if any should be assured of the best proven diagnostic and therapeutic method.
4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.
5. *If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee* (1,2).
6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

*III. Non-Therapeutic Biomedical Research Involving Human Subjects* (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is *the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.*
2. *The subjects should be volunteers*--either healthy persons of patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. *In research on man, the interest of science and society should never take precedence over the considerations related to the wellbeing of the subject.*




**Scheme 2**—Clinical trial based on Declaration of Helsinki.

Scheme 2 shows clinical trial based on Declaration of Helsinki, schematically.

**Informed Consent**

We must obtain informed consent from volunteers before initiation of clinical trial. Each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort. They should be informed that they are at liberty to abstain from participation in the study and that they are free to withdraw their consents to participation at any time. The doctor should then obtain the subject's freely given informed consent, preferably in writing.

**Safety Consideration**

Protocol must include safety consideration. The study is carried out under the supervision of a clinically competent medical person who can deal with all emergencies. Risks to subjects must be minimized. If specific organ toxicity is suggested by the preclinical studies, the laboratory and physiological monitoring of sufficient sensitivity and relevance to provide maximum safeguards for the subjects. During the initial studies in man, it is desirable, whenever possible, to ensure that a subject receives only the experimental drug. Investigator should bear in mind the complicating effects of other drugs, whether prescribed or not, as well as those of household remedies, alcohol, caffeine, nicotine, food etc.

*A report titled as Sudden Death of a Volunteer is given in Lancet (1985). Followings are the summary of that report.*

**A volunteer participating in a study of eproxindine, a new antiarrhythmic agent, had a sudden cardiorespiratory arrest and died. Subsequently it became known that he had received a depot injection of flupenthixol on the day before his death; an interaction between these two drugs seems likely. This incident illustrates that it is impossible to guarantee absolute safety in volunteer studies if details of medical history are withheld.**

**Placebo Effect**

The placebo is a control for two types of phenomenon. One, the best known and best understood, is the effect of suggestibility, personality, attitudes, anticipations and other biases on the part of the subject, investigator, or observer. These biases may be in the direction of augmentating the benefit of treatment or of diminishing it, of concealing side effects or of reporting or displaying ill-effects that are unrelated to treatment. In addition, the placebo provides a vital control for spontaneous changes in the course of the desease or the symptoms under study, as well as for events that are independent of the treatments.

**Documentation**

Careful and complete records of all studies should be made. The data accumulated in the phase I studies, should be sufficient to allow a decision on the justification for the phase II or phase III, controlled therapeutic trial.