Pharmacokinetics in Phase I Clinical Trial *

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임상 제 I 상 시험에서의 체내약물동태

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Today, I would like to talk about pharmacokinetics in Phase I clinical trials. Phase I clinical trial is the first test of the new drug in human and therefore, the various pharmacokinetic parameters are important basic data for the following Phase II to Phase IV tests.

As shown in Table I, we can compare the pharmacokinetic data in Phase I with the metabolic data in the preclinical animal studies to clarify the major determinant of the drug disposition. Also we can use as the basic data for the setting of the effective and safety dose schedule in Phase II to IV tests, and for the route of administration, dosage form and bioequivalent test.

HOW TO EVALUATE THE STARTING DOSE IN PHASE I

As the first section, I would like to explain "How to evaluate the starting dose in Phase I".

In Phase I test, the most important problem is "How to evaluate the first trial dose in human" from the preclinical animal data. In this estimation, it is most important to obtain the information for the toxicity and metabolism, considering the well-known species differences.

Usually, Phase I test is divided into two steps. The first step is the single administration study and the second step is the repeated administration study.

The single administration study is the real first trial in human. The most commonly used criteria for the estimation of the first trial dose is that proposed by the Research Committee of the Department of Medicine in Hahneman Medical College. As summarized in Table II, first, in case of the new drug which has the new chemical structure and different pharmacological activity for previous drugs and of which clinical effect is unexpected, the first trial dose is set below one sixtieth of the major pharmacological effect. Second, the first trial dose is set below one sixhundredth of LD_{50} of the most sensitive animals. Third, the first trial dose is set below one sixtieth of the maximum tolerated dose (MTD) in the subacute toxicity study in the most sensitive animal.

Furthermore, there have been used several other criteria. For example, 1) one-tenth to one-twentieth of the clinically expected dose; 2) Below

Table I—*Application of Pharmacokinetic Data in Phase I study*

1. Comparison with the metabolic data in the preclinical animal studies in order to clarify the major determinant of the drug disposition.

2. Use as the data for the setting of the appropriate (effective and safety) dose schedule in Phase II—IV

3. Basic information for the route of administration, development of the dosage from and bioequivalent test

Table II—Dose Setting in The First Clinical Trial I.

I *Single administration study*

1. Proposal by the Research Committee of the Department of Medicine, Hahneman Medical College (1964).

    (1) In case of the new drug which has the new chemical structure and different pharmacological activity from previous drugs and of which clinical effect is unexpected:

    1/60 of ED_{50} of the major pharmacological effect

    (2) 1/600 of LD_{50} of the most sensitive animals

    (3) 1/60 of the maximum tolerated dose (MTD) in the subacute toxicity study in the most sensitive animals

2. *Other proposals*

    (1) 1/10-1/20 of the clinically expected dose

    (2) Below the minimum effective dose of analogs

    (3) The minimum effective dose of the most sensitive animals

    (4) Drugs used in the foreign countries: 1/3-1/2 of the foreign dose

II. *Repeated administration study*

1. Usually, the maximum estimated clinical dose is applied.

2. We can estimate the plasma concentration time course of the test drug using pharmacokinetic parameters obtained in the single administration study.

$$C_{SS} = \frac{F \cdot Dose}{CL_{tot} \cdot \tau} = \frac{F \cdot Dose}{K_{el} \cdot Vd \cdot \tau}$$

F : bioavailability
CL_{tot} : total body clearance
τ : dose interval
k_{el} : elimination rate constant
Vd : distribution volume

3. Dose setting (2nd to n-th)

    (1) $(Dose)_n = (Dose)_1 \times (2)^{n-1}$

    (2) $(Dose)_n = (Dose)_1 \times (1.5)^{n-1}$

    (3) $(Dose)_n = (Dose)_1 \times n$

    n : stage of trial
    $(Dose)_1$: initial dose
    $(Dose)_n$: n-th dose

the minimum effective dose on analogous drugs; 3) Minimum effective dose of the most sensitive animals and 4) in case of the drug used in foreign countries, one-third to one-half of the foreign clinical dose.

In the repeated administration study, usually, the maximum estimated clinical dose is applied. At this step, we can estimate the plasma concentration time course of the test drug using pharmacokinetic parameters obtained in the single administration study. For example, we can use the typical equation for the steady-state plasma concentration to estimate the appropriate dose schedule.

In general, for the dose setting in the 2nd to n-th trials, one of these three dose programs or combination type of these programs is applied (Table II).

Then, I would like to show two practical cases in the first clinical dose setting and also that for anticancer agents. The first case is Anodyne. Sl means the code name of the test drug.

Case 1-Anodyne (Code No. S1)

According to the time schedule for the development of anodyne S1, almost ten years were spent for its development and a lots of preclinical animal studies were requested including repeated tests. Also more than three years were spent for ADME tests in human and for Phase I test really 6 years were spent. This case is really tough development.

Outline of preclinical toxicity tests in animals are summarized in Table III. LD_{50} in the acute toxicity tests in mouse and rat are the most important information for determining the first trial dose in Phase I test in human. In addition to the subacute toxicity test in rat and chronic toxicity test in monkey, effects on the pregnancy was also tested in rat and rabbit. Also ADME tests were done in rat and monkey as summarized in this Table.

After a lots of preclinical tests in various animals, the first clinical trial dose was estimated as shown in Table IV. In the single administration study, the minimum dose was estimated to be 5 mg/60 kg in man for oral administration. This dose corresponds to one-twentieth of the minimum effective dose, 1.7 mg/kg in rat and one-fivehundredth of the maximum tolerated dose (MTD), 40 mg/kg in monkey.

Also, the maximum dose was estimated to be

Table III—*Outline of Preclinical Study in Animals for Anodyne (S1).*

1. *Toxicity test:*

1) Acute toxicity test (p.o., s.c., i.p.)
LD_{50} (p.o.) Mouse 360-1220 mg/kg
            Rat   200-300 mg/kg

2) Subacute toxicity test
Animal: male and female rats (35 days old).
        n = each 15/group
Route : p.o. 35 days
Dose   : 10, 25 and 50 mg/kg/day

3) Chronic toxicity test
Preliminary test
 Animal: Monkey, male and female each n = 1
 Route: p.o. 4 weeks
 Dose: 40, 80, 160 and 320 mg/kg/day for every
      week

Main chronic test
 Animal: Monkey, male and female each n = 6
 Route: p.o. 26 weeks
 Dose: 40, 100 and 250 mg/kg/day

4) Effect on pregnancy
Rat (p.o.)
 Dose: 2.5, 10 and 25 mg/kg/day
Rabbit(p.o.)
 Dose: 20, 40, 80 and 160 mg/kg/day
       Pre-, During- and Post gestation

2. Absorption, Distribution, Metabolism and Excretion
(ADME)
2-1) *Single administration study*
1) Absorption
 Rat: ^{14}C-Sl 5 mg/kg p.o. n = 3
          C_{max}: 140 μg/ml; T_{max}: 15 min;
          $t_{1/2}$: 2.3 hr
 Monkey: ^{14}C-Sl 5, 10, 50 mg/kg p.o. n = 3-4
          C_{max}, T_{max}, $t_{1/2}$

2) Tissue distribution
 ARG: Rat ^{14}C-Sl 1.0 mg/kg
 Tissue concentration: Rat 15, 30 min, 1, 2, 4,
 8, 24 hr 36 tissues and organs
 Distribution to the target tissue (inflamated
 tissue)

3) Excretion
 Urinary and biliary excretion
 Rat 5 mg/kg; Monkey 50 mg/kg --- for 24 hr

4) Metabolism
 Rat, Monkey ---- metabolites in plasma urine,
 bile

5) Others   Rat,
 Monkey --- fetal; enterohepatic circulation
2-2) *Repeated administration study*
 Rat 5 mg/kg twice a day for 14 days + 5 mg/
 kg/day ADME

Table IV—*Phase I Clinical Trials for Anodyne (S1).*

1. Presumptive clinical dose was supposed from LD_{50}
of rat and mice
LD_{50} (p.o).   Rat   200-300 mg/kg
             Mouse   360-1220 mg/kg

1) *Single administration study*
 Minimum dose:
  1/20 of the minimum effective dose (1.7 mg/
   kg) in rat
  1/500 of the maximum tolerated dose (40 mg/
   kg) in monkey 0.085 mg/kg = 5 mg/60kg in
   man (p.o. fasted)
 Maximum dose:
  1/35-1/50 of LD_{50} in rat
  1/50-1/200 of LD_{50} in mouse
   6.7 mg/kg/day = 400 mg/60kg in man/day

2) *Repeated administration study*
 p.o. 1 week; 4 healthy male volunteer
 Maximum dose:
  1200 mg/60kg/day 3 times a day after meal
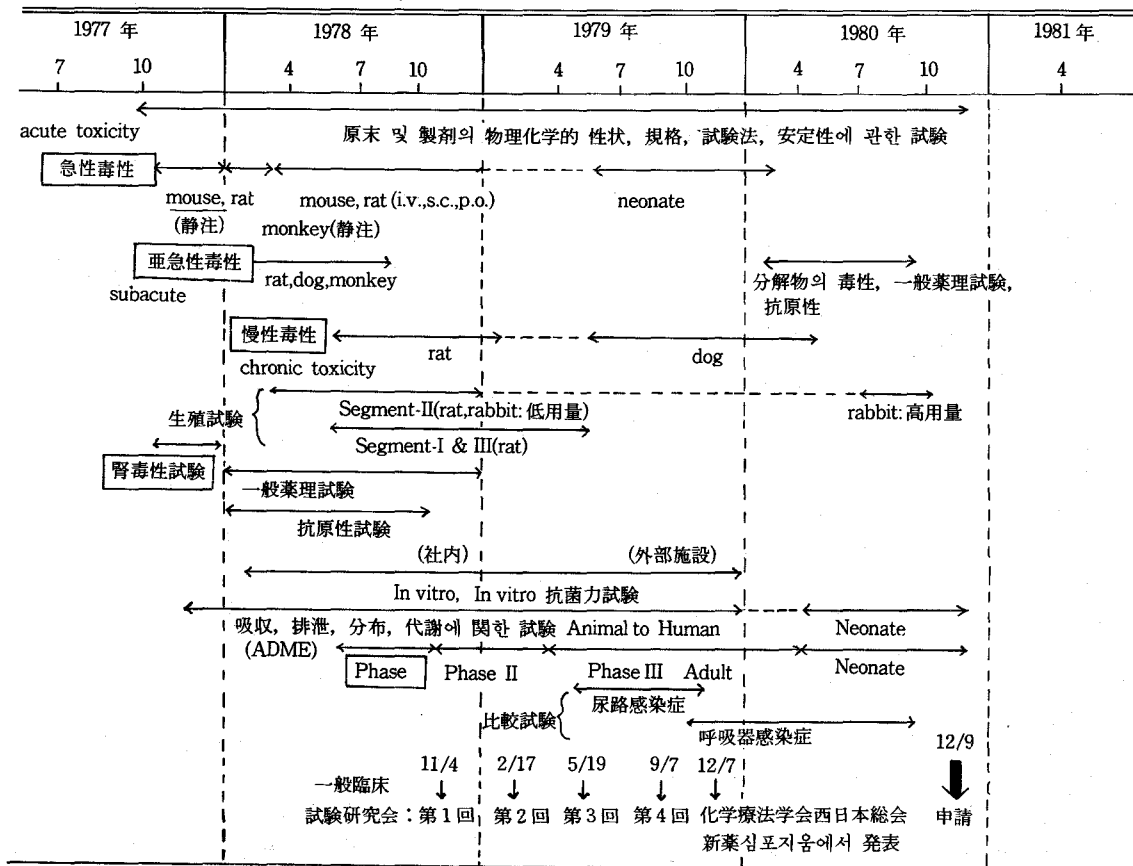   400 mg/60kg a time = 6.7 mg/kg

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400 mg/60 kg in man per day. This dose corresponds to one thirty-fifth to one-fiftith of LD_{50} in rat and one-fiftieth to two-hundredth of LD_{50} in mouse. These dose setting are followed to the general criteria as shown previously in Table II. Well, in the repeated administration study, using four healthy male volunteers, the maximum dose 400 mg/60 kg 3 times a day for one week was orally administered. This dose also corresponds to the maximum dose in the single administration study.

Case 2-Antibiotic (Code No. S2)

The time schedule for the development of antibiotic S2 is summarized in Table V. This case, the total year for the development was relatively short as compared to th former anodyne S1. However, as the remarkable tests, the renal toxicity was examined in the early test period and also in Phase I test, neonate was examined.

Table VI shows the outline of the preclinical toxicity studies. Four animal species were used in the acute toxicity tests in adult animals and four different routes of administration were examined. Also, neonate animal studies were performed in mouse and rat. In case of antibiotics, the clinical

able V—*Time Schedule for The Development of Antibiotics-S2.*

1977 年	1978 年	1979 年	1980 年	1981 年
7　　10	4　　7　　10	4　　7　　10	4　　7　　10	4

acute toxicity

原末 및 製剤의 物理化学的 性状, 規格, 試験法, 安定性에 관한 試験

急性毒性

mouse, rat (静注)　　mouse, rat (i.v.,s.c.,p.o.)　monkey(静注)　neonate

亜急性毒性

subacute　rat,dog,monkey

分解物의 毒性, 一般薬理試験, 抗原性

慢性毒性　rat　dog

chronic toxicity

生殖試験 { Segment-II(rat,rabbit: 低用量)　Segment-I & III(rat)　rabbit: 高用量

腎毒性試験

一般薬理試験

抗原性試験

(社内)　(外部施設)

In vitro, In vitro 抗菌力試験

吸収, 排泄, 分布, 代謝에 관한 試験 Animal to Human　Neonate
(ADME)

Phase　Phase II　Phase III Adult　Neonate

比較試験 { 尿路感染症

呼吸器感染症

12/9

一般臨床　11/4　2/17　5/19　9/7　12/7
試験研究会：第1回　第2回　第3回　第4回　化学療法学会西日本総会　申請
新薬심포지움에서 発表

dose is relatively large and therefore in this toxicity test, to estimate LD_{50}, large doses were applied in mouse and rat. It is clear that LD_{50} of this antibiotic is relatively large and especially, in case of oral administration, it is impossible to obtain LD_{50} in these four animals even at 5 to 10 g/kg dose.

In addition to LD_{50}, the maximum tolerated doses (MTD) were estimated in rat, dog and monkey in both subacute and chronic toxicity tests. Furthermore, effect on the pregnancy, protein binding, urinary excretion were examined as well as tissue distribution.

Considering the toxicity tests in animals, in Phase I test, preliminary test at relatively large doses were done via three administration routes, namely i.v. infusion, i.v and i.m. administration (Table VII).

As shown in this table, in the main single and repeated administration studies, also 0.5 to 1 g doses were applied. In this test drug, it might be not so difficult to estimate the first trial dose, because many similar antibiotics of this series may be used.

Case 3-Anticancer Agents

As the third case, I would like to talk about the estimation of the first trial dose in anticancer agents. In this case, since it is difficult to obtain the practical case report from the company, I would like to introduce the criteria proposed by National Institute of Cancer in the United States.

Fig. 1 shows the current NCI toxicology protocol summary of dose estimation scheme. In general, the acute toxicity study of anticancer agents is examined in mouse, and so basically the toxicity data in mouse in very important in case of anticancer agents. As shown in this figure, LD_{10}

Table VI—*Outline of Preclinical Study in Animals for Antibiotics (S2).*

1. *Toxicity test:*
    1) Acute toxicity test (i.v., i.p., s.c., p.o.)
       1-1) *Adult animals*
            Mouse: ICR, C BL, DS strain male, female 32 days old
            Rat: SD, Wistar, F344 strain male, female 32 days old
            Dog: male, female 1 year old
            Monkey: mole, female 2-3 years old

            LD_{50} (i.v.) Mouse 5500-6200 mg/kg
                          Rat   5600-6100 mg/kg

            p.o. Mouse, Rat   10000 mg/kg---no death
                 Dog, Monkey 5000mg/kg---no death
       1-2) *Neonate animals*
            Mouse: ICR strain male, female 3-21 days old
            Rat: SD strain male, female 3-21 days old

            LD_{50} (mg/kg)   (s.c.)   (i.p.)
                      Mouse 5000-8000   4000-8000
                      Rat   5000-10000 5000-6000

    2) Maximum tolerated dose (MTD)
       2-1) Subacute toxicity test (i.v.)

	MTD (mg/kg/day)
Rat	1260
Dog	400
Monkey	500

       2-2) Chronic toxicity test (i.v.)

		MTD (mg/kg/day)
Rat	35 days	1260
	6 months	300-900
Dog	32 days	400
	6 months	200-400
Monkey	30 days	500

2. Effect on Pregnancy
    Mice, Rat, Rabbit --- Mother and Fetal animals
3. Protein binding
    Human, Monkey, Dog, Rabbit, Rat, Mouse
4. Urinary excretion
    Dog
5. Drug disposition
    Single injection --- Mouse, Rat
    Repeated injection --- Rat

Table VII—*Phase I Clinical Trials for Antibiotics (S2).*

Volunteer: Healthy male adults 22-44 years old (52-72 kg)

1. *Preliminary test*

i.v. infusion:	0.5 g/500 ml/25 hr	(n = 1)
	1 g/500 ml/1.5-3 hr	(n = 5)
i.v.	: 0.5 g/20 ml/4 min	(n = 2)
	1 g/20 ml/1.5-4 min	(n = 4)
i.m.	: 0.5 g/2.5 ml	(n = 1)
	1 g/5.0 ml	(n = 1)

2. *Main test*
    1) Single administration

i.m.	: 0.25, 0.5 g	(n = 4)
i.v.	: 0.5, 1 g	(n = 4)
i.v.infusion	: 1 g/1 hr, 0.5 g/2 hr,	
	1 g/2 hr, 2 g/2 hr	(n = 4)

    2) Repeated administration

i.v.	: 1 g × 2/day	(n = 4)
i.v. infusion:	1 g/1 hr × 2/day	(n = 4)
i.v.	: 1 g × 2/day for 5 days	(n = 5)
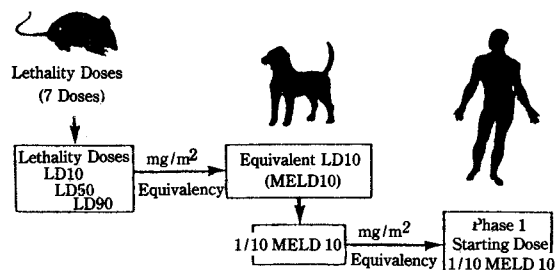
Figure 1—Current NCl toxicology protocol summary of dose estimation scheme.
(Grieshaber & Marsoni, Cancer Treat Rep., **70,** 65, 1986)

Table VIII—*Potential Explanations for Variation in Toxicity between Mouse and Man.*

1. Species differences in drug metabolism/elimination/binding
2. Schedule dependency due to exposure time differences
3. Species differences in target cell sensitivity

(Colins, *et al., Cancer Treat Rep.,* **70,** 73, 1986)

LD_{50} and LD_{90} are determined from the acute toxicity study in mouse. Then scale-up from mouse to dog depends on the body surface area and the equivalent LD_{10} ($MELD_{10}$) for dog is obtained. Finally, the starting dose of Phase I test in human is calculated from one-tenth of $MELD_{10}$ in dog depending on equivalency in the body surface area.

In the extrapolation from mouse to human, we have to sufficiently take into account the species differences between mouse and human. The major points are summarized in Table VIII. First, species differences in drug metabolism, elimination and binding. Second, schedule dependency due to exposure time difference. Third, species

Table IX —*Pharmacologically Guided Escalation of Doses*

Assume: C × T at mouse LD_{10} = C × T at human MTD

1. Determine mouse LD_{10} (current toxicology protocol).

2. Determine mouse C × T at LD_{10} (use preclinical pharmacology task orders).

3. Begin human testing at safe starting does (1/10 of LD_{10}).

4. Measure human C × T at starting dose (pharmacokinetics is part of phase I contracts).

5. Choose escalation strategy based upon how close initial human C × T is to target C × T.

(Colins, *et al., Cancer Treat Rep.,* **70**, 73, 1986)

differences in target cell sensitivity.

Once the starting dose in Phase I clinical trial has been evaluated, subsequent doses are escalated until the maximum tolerated dose (MTD) is reached. Table IX shows the pharmacologically guided escalation method proposed by Collons et al., 1986. In this method, C multiply T, namely AUC is assumed to be equal between at mouse LD_{10} and at human MTD. First, mouse LD_{10} is determined. Second, determine the mouse AUC at LD_{10}. Third, human testing is started at starting dose of one tenth of mouse LD_{10}. Fourth, human AUC at starting is measured. And then, choose the escalation strategy based upon how close the initial human AUC to target AUC. The time of escalation step is one of the important problem in the development of new anticancer agent, and therefore, the minimum and reasonable escalation step is requested. Usually as the entry dose, one-tenth or one thirtieth or one-sixtieth of mouse LD_{10} is used, and this entry dose is most important for the escalation step.

Recently, another interesting approach to estimate the clinically achievable peak plasma concentration (PPCs) proposed by Scheithauer et al., 1986. They examined mouse LD_{50} and human PPCs for 28 commonly used cytotoxic anticancer agents listed in Table X, and ploted mouse LD_{50} versus human PPCs on a log-log scale.

As shown in Fig. 2, a good linear regression

line was obtained with 90% confidence shown by upper and bottom lines. From this regression line, they obtained a regression equation as shown in this figure. This result suggests us the possibility prediction of the human PPCs for new investigational anticancer agent from mouse LD_{50} by using their proposed statistical regression model.

APPLICATION OF PHARMACOKINETICS IN PHASE I CLINICAL TRIALS

In the first clinical test in human by single adminitration, we usually can obtain these pharmacokinetic parameters (Table XI) such as biological half-life, elimination rate constant, distribution volume, total body clearance, area under concentration-time curve, and in the case of oral administration C_{max} and T_{max}. These data are very valuable as the first fundamental pharmacokinetic data in human and give us important basic information for the following clinical trials. For example, using these parameters, we can predict the steady-state plasma concentration, C_{ss} after repeated administraion as explained previously in Table II.

To obtain these pharmacokinetic parameters, as the first step, we have to try curve fitting of the
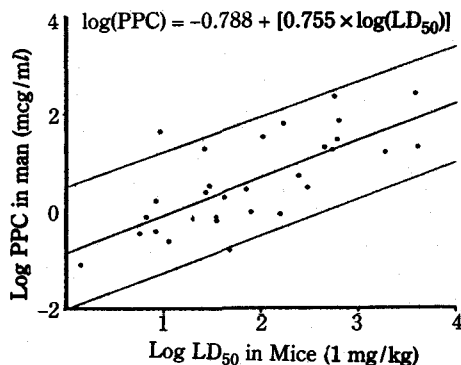
Figure 2—Log-log multiple linear regression model that might prove useful to estimate the magnitude of clinically achievable PPCs in man for investigational compounds with known LD_{50} values in mice. The sample points within the (90%) confidence belts plotted on either side of the regression line represent the known data pairs of 28 anticancer drugs.
(Scheithauer, *et al., Cancer Treat Rep.,* **70**, 1379, 1986)

Table X—*Acute Animal Toxicology Data* and Clinically Achievable PPCs of Various Anticancer Compounds.*

Drug	LD_{50} (mg/kg)	PPC ($\mu g/ml$)	Dose	Route	Ref No.
Dactinomycin	1.4	0.08	0.015 mg/kg	Iv	8
Bisantrene	245.0	5.00	260.00 mg/m²	Iv	9
Bleomycin	303.0	3.00	15.00 U/m²	Iv	8
Busulfan	160.0	0.83	6.00 mg	Oral	10
Carmustine	42.0	1.97	95.00 mg/m²	Iv	8
Chlorambucil	81.0	1.10	0.60 mg/kg	Oral	8
Cisplatin	26.8	2.49	100.00 mg/m²	Iv	8
Cyclophosphamide	609.0	29.40	10.00 mg/kg	Iv	8
Cytarabine	3700.0	250.00	10.00 mg/kg	Iv	8
Daunorubicin	8.6	0.41	100.00 mg/m²	Iv	8
Doxorubicin	35.0	0.60	60.00 mg/m²	Iv	8
Dacarbazine	1900.0	15.28	250.00 mg/m²	Iv	8
Etoposide	105.0	34.18	290.00 mg/m²	Iv	8
5-Fluorouracil	171.0	60.00	15.00 mg/kg	Iv	8
Floxuridine	650.0	73.80	5.7×10^{-3} M/hr	Intra-arterial	11
Hexamethylmelamine	452.0	20.60	200.00 mg/m²	Oral	8
Hydroxyurea	9.1	48.29	1000.00 mg/m²	Oral	8
Ifosfamide	565.0	221.96	130.00 mg/kg	Iv	8
Melphalan	29.6	3.38	0.60 mg/kg	Iv	8
6-Mercaptopurine	523.0	18.00	500.0 mg/m²	Iv	8
Menogaril	47.0	0.16	126.00 mg/m²	Iv	12
Methotrexate	69.0	2.75	30.00 mg/m²	Iv	8
Mitomycin	8.5	1.50	20.00 mg	Iv	8
Mitoxantrone	11.3	0.25	6.00 mg/m²	Iv	13
PALA	4000.0	20.00	200.00 mg/m²	Iv	8
Thiotepa	27.0	19.90	20.00 mg	Iv	14
Vinblastine	6.8	0.78	0.20 mg/kg	Iv	8
Vincristine	5.8	0.37	0.025 mg/kg	Iv	8

* Ip LD_{50} values in nontumored Swiss BDF_1 mice.

(Scheithauer, *et al., Cancer Treat Rep.,* **70,** 1379, 1986)

observed plasma concentration-time curve (Table XII). For this curve-fitting, usually non-linear least squares regression analysis by using a digital computer is applied. As for the program, CSTRIP program written in Fortran or ESTRIP program written in Basic is well-known and often used world-widely. In this fitting, the estimation of the initial parameters and the weight for the observed data are very important. After curve fitting, in

Table XI—*Pharmacokinetic Parameters in Phase I Study.*

$$\boxed{t_{1/2}, k_{el},\ Vd,\ CL_{tot},\ AUC,\ C_{max},\ T_{max}}$$

1. The first fundamental data in human.
2. The important basic information for the following Phase II—IV studies.
3. Using these parameters, we can predict the plasma concentration-time course.

Table XII—*Pharmacokinetic Analysis of Phase I Study.*

1. Curve fitting of the plasma concentration-time curve: Non-linear least squares regression using a digital computer
   Program   CSTRIP   (FORTRAN)
              ESTRIP   (BASIC)
   Initial parameters, Weight
2. Model analysis:
   1) One-, Two- or Three compartment model
   2) Calculation of pharmacokinetic parameters
   Program   AUTOAN (NONLIN 69)   (FORTRAN)
              APAS (MULTI)   (BASIC)
3. Statistical Analysis:
   Criteria for the best fitting
   Akaike's Information Criterion (AIC)
            $AIC = N \cdot \ln(SS) + 2R$
     N : number of data; R: number of parameter
     SS: weighted sum of squares
4. Model-independent analysis:
   1) Clearance concept — Physiological pharmacokinetics
   2) Moment analysis
5. Population pharmacokinetics
   NONMEM
   Bayesian individualization of pharmacokinetics

(Sheiner & Beal, *J.P.B.*, 1980; *J.P.S.*, 1982)

general, compartment model analysis is performed to obtain various pharmacokinetic parameters for the drug disposition, especially the tissue distribution. For this analysis, AUTAN program or APAS program is used. To judge the best fitting in these analysis, we often used Akaike's Information Criterion (AIC), where the smaller value of AIC means the better fitting.

For example, the same data was analyzed by one to four exponential curve-fitting. As can be seen in Fig. 3, the smallest value of AIC was obtained in the 3-exponential. So, this case, we can judge the observed data was best fitted to 3-exponential curve.
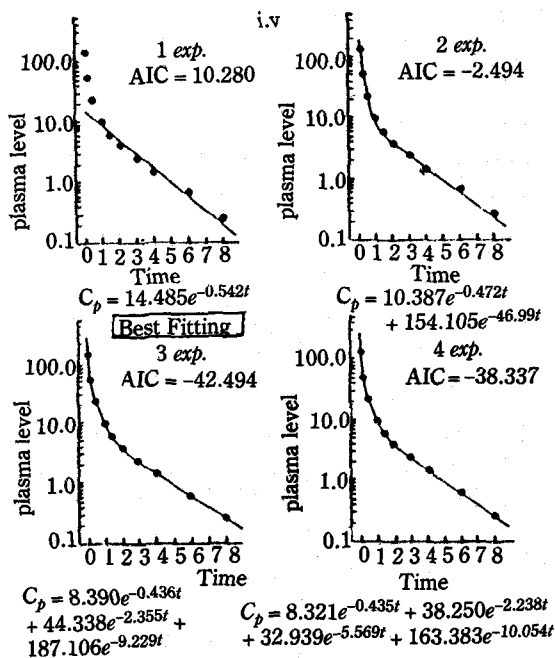
Table XIII summarized most commonly used compartment model analysis, namely one- and two-compartment models in both intravenous and oral administrations. Even if the same drug, the results of the compartment analysis are often different among individuals mainly due to the sampling points and time differences. Therefore, it is important to use appropriate sampling schedule to

obtain the good and significant results in pharmacokinetic analysis. As shown in this table, minimumly six points for intravenous administration and nine points for oral administration are requested to obtain the significant pharmacokinetic analysis in Phase I test.

Recent advance in pharmacokinetics, model independent analysis of Phase I data can be done by physiological pharmacokinetics depending on the clearance concept or by the moment analysis. Also, advance in the population pharmacokinetics makes it possible to analyze small number of data points in individual subject(Table XII).

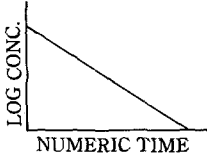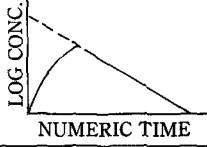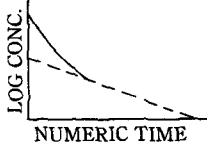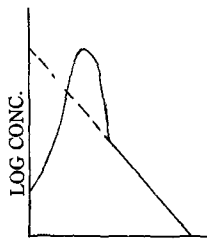## PHYSIOLOGICAL BASIS FOR PHARMACOKINETIC SCALING FROM ANIMAL TO HUMAN

When we start Phase I test, no data is available for human, and therefore, we have to estimate various pharmacokinetic parameters from those obtained in the preclinical animal studies. Until recent years, we do not have any rational reason to estimate the first trail dose in human study, but in

$C_p = 14.485e^{-0.542t}$

$C_p = 10.387e^{-0.472t} + 154.105e^{-46.99t}$

$C_p = 8.390e^{-0.436t} + 44.338e^{-2.355t} + 187.106e^{-9.229t}$

$C_p = 8.321e^{-0.435t} + 38.250e^{-2.238t} + 32.939e^{-5.569t} + 163.383e^{-10.054t}$

Figure 3—Determination of pharmacokinetic model by AIC.   (Applied Pharmacokinetics, 1985)

Table XIII—*Minimum Effective Blood Sampling Method in Human Study.*

Compartment Model	Route of Administration	Semi-log Plot	Minimum Number of Blood Samples	Optimum Sampling Times
Opten One-	Intra-vascular		3	during the first half hour after administration
			3	during the terminal monoexponential phase
Open One-	Extra-Vascular		3	during absorptive phase
			3	in the region of the expected peak
			3	during the terminal monoexpenential phase
Open Two-	Intra-vascular		3	during the distributive phase (steep fall of blood level curve)
			3	during the terminal monoexponential phase
Open Two-	Extra-vascular		3	during absorptive phase
			3	in the region of expected peak
			3	during the postabsorptive distribution phase (steep fall of blood level curve after the peak)
			3	during the terminal monoexponential phase

(Ritchel, 1976)

1973, Dedrick et al. first, proposed pharmacokinetic basis for animal scale-up by the power equation proposed by Adolph in 1949. As shown in Table XIV, in the power equation, "Y" is the physiologic variable of interest, such as blood flow, renal clearance, and "W" is body weight, and "log a" is the y-intercept and "b" is the slope obtained from the plot of log Y versus log W obtained from the second equation in this table.

Depending on this power equation, they found a good relationship between body weight and renal clearance of arabinofuranosylcytosine.

As shown in Fig. 4, we can obtained a good relationship between the organ blood flow, one of power equation to the renal clearance of various

Table XIV—*Pharmacokinetic Scaling in Mammals.*

The power equation   (Adolph, Science, 1949)

$$Y = aW^b$$

on log-log paper

$\log Y = b \log W + \log a$

where b is the slope and $\log a$ is the y-intercept.

$$Y_1 = a_1 W^{b_1} \qquad (1)$$
$$Y_2 = a_2 W^{b_2} \qquad (2)$$
$$\log W = (\log Y_1 - \log a_1)/b_1$$
$$= (\log Y_2 - \log a_2)/b_2 \qquad (3)$$
$$\log Y_1 = \log a_1 + b_1/b_2 (\log Y_2 - \log a_2) \qquad (4)$$
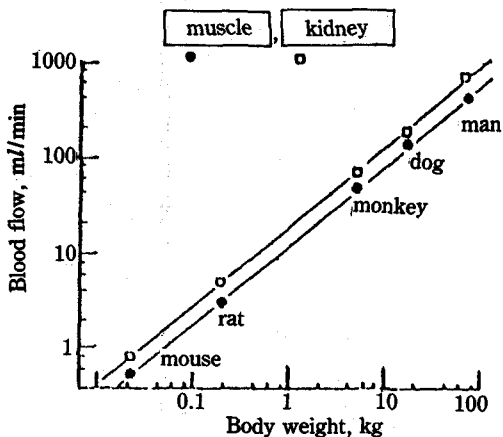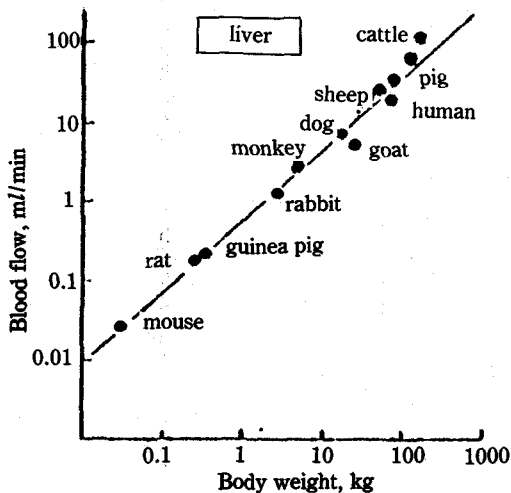$$Y_1 = a_1 (Y_2/a_2)^{b_1/b_2} \qquad (5)$$

Figure 4—Organ blood flow.

Table XV—*Renal Clearance vs. Body Weight.*

CL (ml/min) = A·W(kg)^B	
urea	3.83·$W^{0.72}$
inulin	5.92·$W^{0.77}$
creatinine	8.22·$W^{0.69}$
iodopyracet	16.70·$W^{0.89}$
p-aminohippurate	22.61·$W^{0.80}$
digoxin	3.56·$W^{0.89}$
2-amino-1,3,4-thiadiazole(ATDA)	0.91·$W^{0.73}$
metabolite of ATDA	2.50·$W^{0.68}$
5-methyltetrahydrohomofolate	2.19·$W^{0.65}$
cyclophosphamide	13.45·$W^{0.76}$
Ara-C	3.81·$W^{0.80}$

the physiological parameters, and the body weight of animals.

Also, you can see a good application of the endogenous and exogenous substances including anticancer agents, Ara-C (Table XV).
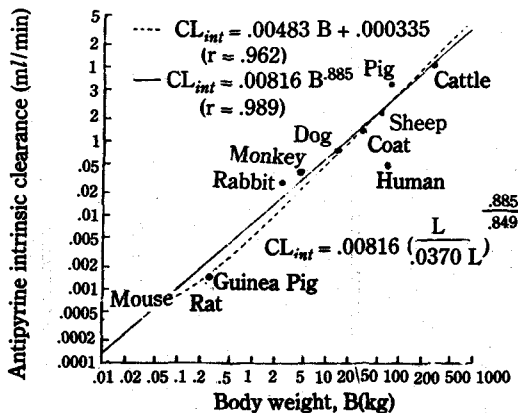
Figure 5—Antipyrine intrinsic clearance in mammals as a function of body weight. Dashed line is the least-squares fit of nonlogarithmically transformed data weighted by the factor $1/y^2$. The solid line is from the equation fitted using the method of least squares on unweighted, logarithmically transformed data.
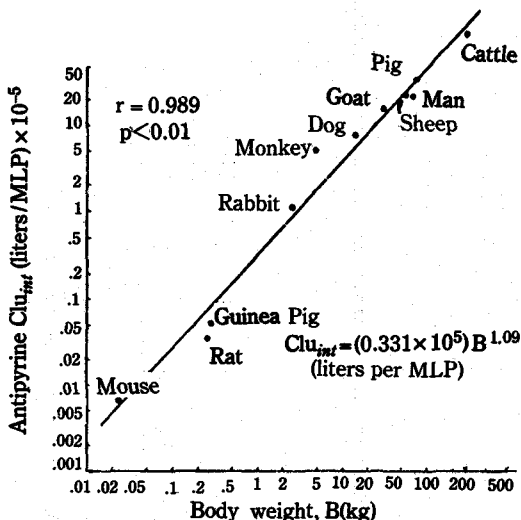
(Mordenti, *J.P.S.,* 75, 1028, 1986)

Figure 6—Allometric relationship between intrinsic clearance of unbound antipyrine per maximum lifespan potential (MLP) and body weight.

In 1980, Boxenbaum successfully adapted the power equation to the metabolic intrinsic clearance of antipyrine, phenytoin and benzodiazepines. As shown in Fig. 5, 9 animal species and human show a good linear relationship between antipyrine intrinsic clearance and their body weight.

More good correlation was obtained among the

same data by correcting the unbound antipyrine intrinsic clearance by the maximum lifespan potential (MLP) of each animal and human (Fig. 6).

As for another pharmacokinetic parameters, for example a good relationship between plasma (or serum) half-life and body weight was reported for various drugs. Fig. 7 shows a typical example for methotrexate.

Fig. 8 also shows a successful application of the power equation to serum half-life of antibiotic, ceftizoxime. In this figure, the triangle represents the mean of the reported half-lifes in human with their range. It is clear that we can predict the human serum half-life from the regression line calculated using several animal data.

As for another pharmacokinetic parameters, from our laboratory successful application of the power equation to various pharmacokinetic parameters, such as distribution volume, metabolic intrinsic clearance, renal clearance for beta-lactam antibiotics and 9 acidic and 9 basic drugs. These findings suggest us the possibility of the prediction of various pharmacokinetic parameters of new drugs from those obtained in the preclinical animals studies.

In the scale-up from preclinical animal study to human, one important point to be considered is that to obtain the same plasma or serum concentration small animal needs more large dose or frequent dose supply. For example, Fig. 9 shows the

Figure 8—Log-log plot of half-life versus body weight for ceftizoxime. The solid circles represent the values reported in the literature for each species. The solid line is the least-squares linear regression line for the animals, excluding humans. The prediction for antibiotic half-life in humans is read off the linear regression line at 70 kg. The triangle represents the reported antibiotic half-life in humans (mode), and the bars represent the range of values from the literature. Numbers in parentheses indicate number of data points.

(Mordenti, *J.P.S.*, 75, 1028, 1986)

case of ceftizoxime. The dose requested for the same serum concentration, a large species difference is observed in the dose requested.

However, as shown in Fig. 10, a good linear relationship was observed between the dose requested and each body weight in mouse, rat, monkey, dog and human.

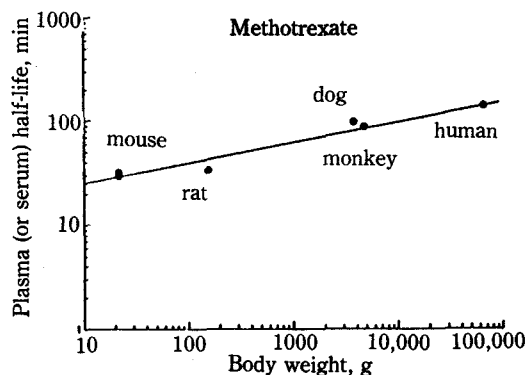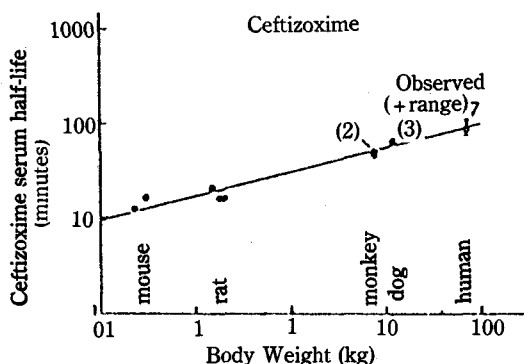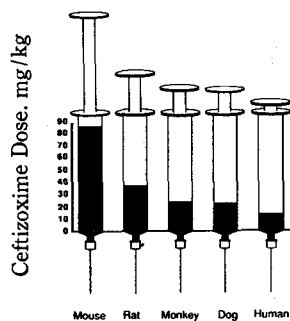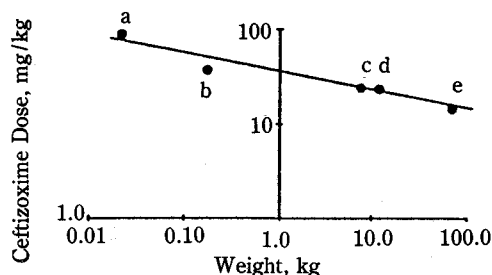Table XVI summarized the equivalent dosage regimens for ceftizoxime in 4 animals and human.

Figure 7—Reported and calculated half-lives of methotrexate in plasma (or serum) of mouse, rat, monkey, dog, and human.

(Mordenti, *J.P.S.*, 75, 1028, 1986)

Figure 9—Dose required to achieve a ceftizoxime peak concentration in serum of 141 μg/ml in each species.

(Mordenti, *J.P.S.*, 75, 852, 1986)

Figure 10—Log-log plot of ceftizoxime dose versus weight. Small mammals require larger doses of ceftizoxime to achieve the same peak concentration as large mammals. The solid line is from equation fitted using the method of least squares on unweighted logarithmically transformed data. Key: (a) mouse: (b) rat: (c) monkey: (d) dog: (e) human.

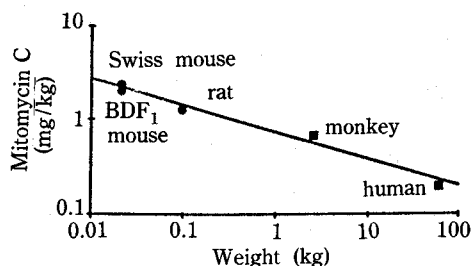(Mordenti, *J.P.S.*, **75**, 852, 1986)

As you can see in the 3rd column from right hand-side, we can obtain the allometric equation for dosage schedule. This suggests that we can estimate human dosage schedule from those obtained in the preclinical animal studies.

Table XVII shows the additional interspecies relationships among various pharmacokinetic parameters for ceftizoxime. Allometric equations were also obtained in all parameters listed.

In case of anticancer agents, to predict the toxicity in human from preclinical animal data is most important problem. Table XVIII suggests us the possibility of prediction of the toxic dose in human from those of animals by allometric equations.

Fig. 11 shows the log-log plot for mitomycin C. Clearly, you can see the linear relationship between the toxic dose and body weight. This sug-

Figure 11—Log-log plot of the minimally toxic dose of mitomycin C versus body weight for mice, rats, monkeys, and humans. Key: (●) LD_{10}; (■) maximum tolerated dose.

(Mordenti, *J.P.S.*, **75**, 1028, 1986)

Table XVI—*Pharmacokinetically Equivalent Dosage Regimens for Ceftizoxime in the Mouse, Rat, Monkey, Dog, and Human.*

Parameters	Mouse	Rat	Monkey	Dog	Human	Allometric Equation	t value[a]	Significance Level
Weight, kg	0.023	0.18	7.5	12	70			
Dose, mg/kg	88.1	37.5	24.3	23.6	14.3	$34.9W^{0.200}$	6.666	0.007
A, μg/ml^b	121.6	91.1	94.8	73	66.8	$91.2W^{0.063}$	3.293	0.046
α, h^{-1c}	7.44	11.0	5.09	4.57	4.18	$6.44W^{0.102}$	2.617	0.079
B, μg/ml^b	19.9	50.3	46.7	68.6	74.7	$43.3W^{0.138}$	3.025	0.057
β, h^{-1c}	2.60	2.08	0.939	0.653	0.520	$1.2W^{0.212}$	10.00	0.002
Peak, μg/ml	141.5	141.4	141.5	141.6	141.6	equivalent		
AUC, μg·h·ml^{-1d}	24.0	32.4	68.4	121.0	159.6	$54.2W^{0.242}$	7.720	0.005
No. Doses/24 h	20	15	7	4	3	$8.89W^{0.243}$	7.794	0.004
Dosage schedule, every-h	1.2	1.6	3.4	6	8	$2.6W^{0.243}$	7.658	0.005
24-h AUC, μg·h·ml^{-1d}	480	486	479	484	479	equivalent		

[a]Null hypothesis: slope (b) = 0; $t_{0.975}$ (3 degrees of freedom) = 3.182; when t = 3.182, accept the null hypothesis; that is, the parameters do not depend on weight. [b]Coefficients of the biexponential equation for the new dose (eq. 2). [c]Exponents of the original biexponential equation (eq. 1). [d]AUC = area under the serum concentration-time curve.

(Mordenti, J.P.S., **75**, 852, 1986)

Table XVII—*Additional Interspecies Relationships for Ceftizoxime[a].*

| Parameters	Species				Allometric Equation	t value[b]	Significance Level
	Mouse	Rat	Monkey	Dog			
Weight, kg	0.023	0.18	7.5	12			
A, μg mL	27.6	48.6	78.0	61.9	$52.2W^{0.137}$	3.449	0.075
α, h^{-1}	7.44	11.0	5.09	4.57	$6.44W^{0.102}$	1.691	0.233
B, μg mL	4.52	26.8	38.4	58.1	$24.8W^{0.339}$	3.042	0.093
β, h^{-1}	2.60	2.08	0.939	0.653	$1.28W^{-0.212}$	6.460	0.023
k_{12}, h^{-1}	0.863	3.47	1.65	1.5	$1.66W^{0.035}$	0.260	0.819
k_{21}, h^{-1}	3.28	5.25	2.31	2.55	$3.11W^{-0.08}$	1.229	0.344
k_{10}, h^{-1}	5.90	4.38	2.07	1.17	$2.65W^{-0.234}$	4.912	0.039
V_1, mL/kg	624	265	172	176	$250W^{-0.194}$	4.204	0.052
V_{ss}, mL/kg	788	440	295	265	$390W^{-0.160}$	6.248	0.025
V_{area}. mL/kg	1411	558	379	299	$518W^{-0.215}$	4.174	0.051
CL, $mL\cdot h^{-1}kg^{-1}$	3670	1160	356	195	$644W^{-0.427}$	8.966	0.012
AUC, μg·h·mL^{-1}	5.45	17.3	56.2	102.5	$30.1W^{0.427}$	8.932	0.012
half-life, h	0.267	0.333	0.738	1.06	$0.54W^{0.211}$	6.446	0.023

[a] All animals received 20-mg/kg iv doses; pharmacokinetic data are from Ref. 9, and allometric relationships are from Ref. 28. [b] Null hypothesis: slope (b)=0; $t_{0.975}$ (2 degrees of freedom)=4.303; when t <4.303, accept the null hypothesis; that is the parameters do not depend on weight.

Table XVIII—*Interspecies Relationship between Toxic Dose (mg/kg) and Body Weight (kg) for 14 Antineoplastic Agents in Six Species[a].*

Agent	Toxic Dose						Allometric Equation	t value[d]	Degrees of Freedom	Significance Level
	Swiss Mouse[b]	BDF$_1$ Mouse[b]	Rat[b]	Monkey[c]	Dog[c]	Human[c]				
Actinomycin D	0.07	0.12	0.09	—	0.03	0.015	$0.04W^{-0.224}$	5.681	3	0.011
BCNU[e]	11	16	6.6	5.3	2.4	2.5	$5.164W^{-0.216}$	5.559	4	0.005
Busulfan	15	15	3.7	6.0	6.0	0.7	$4.560W^{-0.273}$	2.715	4	0.053
Cyclophosphamide[g]	93	110	12	54	12	10	$26.98W^{-0.235}$	1.997	4	0.117
5-Fluorouracil	42	45	25	18	10	15	$20.65W^{-0.159}$	4.102	4	0.015
5—FUdR[h]	160	190	89	59	40	30	$67.76W^{-0.218}$	10.21	4	0.001
Mechlorethamine[i]	1.3	0.9	0.37	0.2	0.48	0.2	$0.409W^{-0.185}$	2.696	4	0.054
Melphalan[j]	6.3	9.7	—	1.5	1.5	0.9	$2.506W^{-0.279}$	8.230	3	0.004
6-Mercaptopurine	86	62	51	56	22	27	$42.66W^{-0.132}$	3.159	4	0.034
Methotrexate[k]	3.3	5.2	0.58	3.0	0.12	0.41	$0.915W^{-0.296}$	1.756	4	0.145
Mitomycin C	2.3	2.2	1.3	0.64	—	0.2	$0.716W^{-0.293}$	18.24	3	0.0005
Nitromin[l]	45	31	7.1	4.8	4.4	2.0	$7.261W^{-0.337}$	5.148	4	0.007
L-Phenylalanine	5.1	5.5	2.3	0.55	0.63	0.2	$1.045W^{-0.398}$	13.55	4	0.0005
THIO—TEPA[m]	5.7	6.5	2.7	1.0	1.1	0.2	$1.377W^{-0.379}$	8.168	4	0.001

[a] Data from Ref. 12. [b] LD_{10}; mice weigh 0.02 kg; rats weigh 0.1 kg. [c] Maximum tolerated dose; monkeys weigh 2.5kg; dogs weigh 7.5 kg; humans weigh 60 kg. [d] Null hypothesis; slope (b) = O; $t_{0.975}$ (3 degrees of freedom) = 3.182; $t_{0.975}$ (4 degrees of freedom) = 2.776; when $t = t_{0.975}$, accept the null hypothesis; that is, the parameters do not depend on weight. [e] Carmustine. [f] Myleran. [g] Cytoxan. [h] Floxuridine. [i] Nitrogen mustard. [j] Alanine mustard. [k] Amethopterin. [l] 2-Chloro-N(2-chloroethyl)-N-methylethanamide-N-oxide. [m] 1.1,1 -Phosphinothioylidynetrisaziridine.
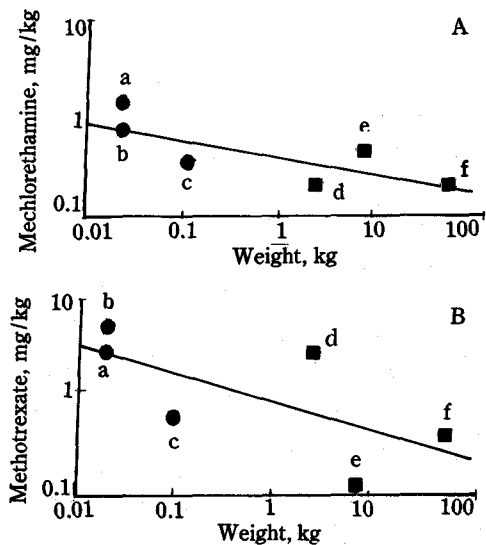
(Mordenti, *J.P.S.*, **75**, 852, 1986)
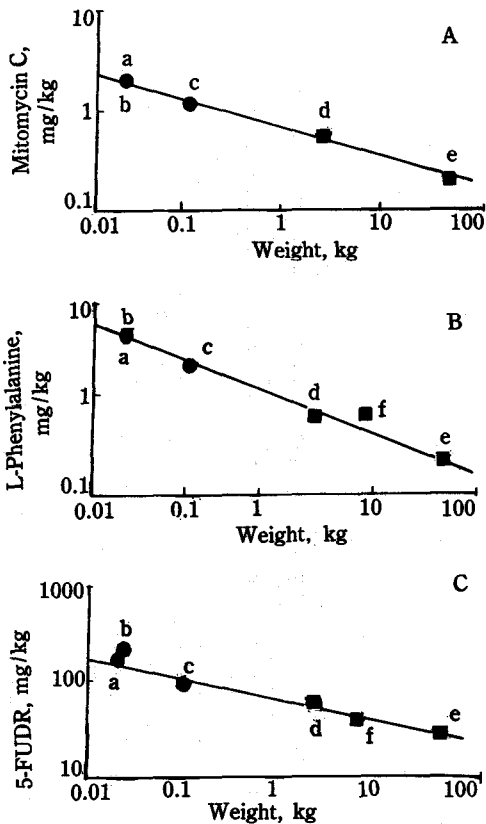
Figure 12—Log-log plot of the toxic dose versus body weight data for (A) mitomycin C, (B) L-phenylalanine, and (C) 5-FUdR (floxuridine). The solid line is from equation fitted using the method of least squares on unweighted logarithmically transformed data. Key; (a) Swiss mouse; (b) BDF, mouse; (c) rat; (d) monkey; (e) human; (f) dog; (●) LD_{10}; (■) maximum tolerated dose.

Figure 13—Log-log plot of the toxic dose versus body weight data for (A) merchlorethamine and (B) methotrexate. The solid line is from the equation fitted using the method of least squares on unweighted logarithmically transformed data. Key; (a) Swiss mouse; (b) BDF, mouse; (c) rat; (d) monkey; (e) dog; (f) human; (●) LD_{10}; (■) maximum tolerated dose.

gests us that even in case of anticancer agents, we can utilize the power equation for animal data to predict the maximum tolarated dose in human.

In Figs. 12 and 13, log-log plots for other anticancer agents are shown including mitomycin C. In case of methothrexate in the bottom of right pannel, the data are not well suited for the analysis by the power equation, and another approach is advisable. For example, Freireich related the toxicity of anticancer agents across animal species as a function of body surface area (mg/m^2). The body surface approach may offer a reasonably good alternate approach when data from only one species are available in such case as often used for the prediction from mouse toxicity data to human.

The allometric approach can be used to predict entire pharmacokinetic profiles for humans from animal data. These predictions are obtained as follows:

1. Determine discrete pharmacokinetic parameters for the drug in young adult animals of four or more species (compartmental or noncompartmental methods can be used).
2. Perform linear regression analysis on the relationship log *pharmacokinetic parameter* versus log *weight* to obtain allometric equations for each parameter (if necessary, longevity, brain weight, or other significant physiologic parameters can be incorporated into the regression).
3. Solve each allometric equation for the average young adult human, that is, substitute 70 kg for weight to predict average pharmacokinetic parameters.
4. Use the predicted pharmacokinetic parameters to write pharmacokinetic equations for drug disposition in humans.
5. Check the prediction by administering the
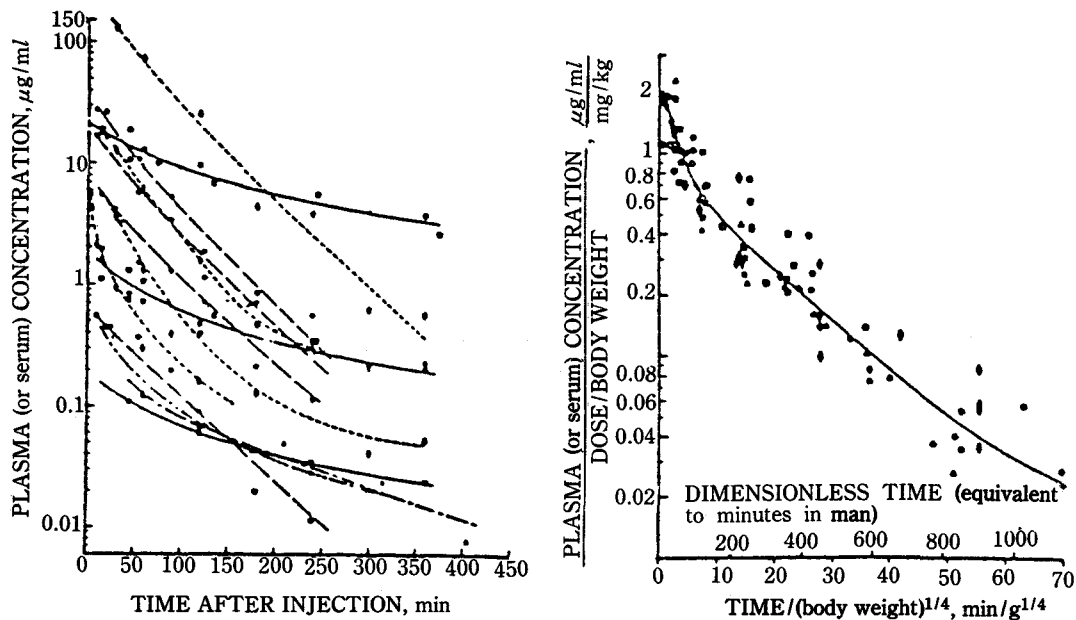
Figure 14—Plasma (or serum) concentrations of methotrexate in the mouse (---), rat (----), monkey (---), dog (---), and human (—) after iv or ip injection (the symbols refer to different dose levels and routes of administration): (a) semilogarthmic plots of methotrexate concentration versus time and (b) semilogarithmic plot obtained after normalization of the axes.

drug to young adult humans or obtain experimental data from the literature.

Another interesting approach for the prediction of human pharmacokinetic profile from those of animals, Dedrick proposed one possibility. The left pannel of Fig. 14 shows a usual semilogarithmic plots of methotrexate in mouse, rat, dog, monkey and human. A remarkable different in plasma time course were observed. However, when the y-axis (concentration) was normalized by dividing the observed plasma concentrations by the dose per unit body weight and when the x-axis (time) was normalized by dividing time after injection by $W^{0.25}$, you can see the pharmacokinetic profiles were beautifully superimposed. The selection for the power value, 0.25 was based on the concept that "equivalent time" between species correlates with weight to the 0.25 power. This result also suggests us the possibility of the prediction of pharmacokinetic profiles in human from those in various animal species.

In conclusion, recent advance in pharmacokinetics, especially in physiological pharmacokinetics makes it possible to predict the drug disposition in human from those in the preclinical animal studies. This also give us the rational basis for the estimation of the first trail dose in Phase I test and the following reasonable dose schedule.