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QUANTITATIVE COMPARISON OF TOXICITY OF ANTICANCER AGENTS IN MOUSE, RAT, HAMSTER, DOG, MONKEY, AND MAN[1, 2]

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SUMMARY

Toxicity data from small animals (mouse, rat, and hamster), large animals (dog and monkey), and humans were gathered, placed on a reasonably similar basis, and compared quantitatively. Each animal species and all species combined were used to predict the toxic doses in man (based on mg/m² of surface area). Two models were assumed for the relationship between the maximum tolerated dose (MTD) in man and the approximate LD10 in each animal system:

$$(\text{dose in man}) = (\text{dose in animal system } i) \quad (1)$$

and

$$(\text{dose in man}) = A_i \times (\text{dose in animal system } i), \ (i = 1, \ldots, 6) \quad (2)$$

where A_i is the fraction of the dose in animals used to predict the dose in humans (assumed different for each animal system, ie, $i = 1, \ldots, 6$). It was found that when animal systems other than the rat were used the very simple model (1) was remarkably good for predicting the MTD in humans, though model (2) leads to slightly better predictions. Based on model (2), the animal systems are ranked in order of predictive ability: rhesus monkey, Swiss mouse, rat, BDF_1 mouse, dog, and hamster. The best estimate of the MTD in man is made by weighting the estimates from the various animal species. Dose on an mg/m² basis is approximately related to dose on an mg/kg basis by the formula

$$(\text{dose in mg/m}^2) = (km)_i \times (\text{dose in mg/kg}), \quad (i = 1, \ldots, 7)$$

where $(km)_i$ is the appropriate factor for converting doses from mg/kg to mg/m² surface area for each species. When the $(km)_i$ factors are known, equally good predictions of MTD in man can be made by either dose unit. On an mg/m² basis, the MTD in man is about the same as that in each animal species. On an mg/kg basis, the MTD in man is about $\frac{1}{12}$ the LD10 in mice, $\frac{1}{9}$ the LD10 in hamsters, $\frac{1}{7}$ the LD10 in rats, $\frac{1}{3}$ the MTD in rhesus monkeys, and $\frac{1}{2}$ the MTD in dogs. In each case the ratio is the (km) factor in the animal system to that in man. Hence relationships among the various animal species and man are somewhat simpler and more direct on an mg/m² basis. These results support the conclusion that the experimental test systems used to evaluate the toxicities of potential anticancer drugs correlate remarkably closely with the results in man.

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[2] Study done under the auspices of the Acute Leukemia Task Force of the National Cancer Institute by the Subhuman Subcommittee.

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The biologic aspect of a drug development program to discover compounds effective against any clinical disease is generally an exercise in comparative pharamacology. In the typical program, compounds are screened in small animals against some easily produced and reproduced pathologic condition. A close relationship must exist between the screening system and the ultimate clinical condition for the program to have the potential for success. Thus examination of this relationship is highly important. In cancer chemotherapy the similarities and differences have often been considered among transplantable tumors, virus-induced tumors, carcinogen-induced tumors, and spontaneous tumors in animals, and between animal tumors and the various cancers and leukemias in man. However the similarities and differences between mice, rats, hamsters, dogs, monkeys, and man have been considered less often in terms of quantitative and qualitative aspects of the toxic effects of drugs. The consistency of the action of therapeutic agents among various mammalian species is a keystone of most drug development programs, yet only rarely has this been studied in a quantitative manner.

Classically comparative pharmacology and physiology have been concerned with differences which permit analytic studies of specific biologic systems, and these studies have yielded valuable information. But it is equally important to consider the much more frequent similarities; we have tried to do this in the present analysis.

Of all the toxicologic end points, lethal toxicity is the easiest to measure with reasonable precision. Therefore we considered the lethal dose of certain cancer chemotherapeutic agents in various laboratory animals. For man the end point was the maximum tolerated dose (MTD). Hopefully two benefits might accrue from this evaluation: (1) If there is reasonable consistency in the reactions of various mammalian species, the toxicologic component of cancer chemotherapy screening will be shown to have a rational basis. (2) If such consistency is found, the problems of introducing highly toxic therapeutic agents into man might be approached more confidently. If major inconsistencies are discovered frequently, this would highlight the deficiencies in present screening systems and raise serious questions about the utility of these schemes for safe introduction of new drugs into man.

No attempt was made to relate therapeutic doses in the various mammalian species. In the future this correlation should be attempted since the therapeutic target in the host is not the same as the toxicity target. However if an agent has therapeutic properties in an experimental system, it is well to know the dose level for patients. Since there is some justification for using MTD's in cancer therapy, these dose levels were studied.

The plan of this retrospective study was to examine considerable toxicologic data obtained in (*a*) small animals, used in primary screening and quantitative secondary drug evaluation; (*b*) larger animals, dogs and monkeys, for the quantitative and qualitative aspects of toxicity at sublethal and lethal levels; and (*c*) man, the target species. The goal was to determine what relationship exists, if any, between certain commonly used toxicologic end points in the various animal species and man for a number of anticancer agents.

Nothing in this report is intended to suggest or imply that short cuts are allowable in preclinical or clinical toxicologic studies. Dose-limiting and serious toxic effects in man are not always apparent from even the most carefully done toxicologic investigations in animals (1). *It is emphasized and should be clearly understood that it is dangerous to attempt to extrapolate directly from animal toxicity data to maximum tolerated doses in man!* New drugs can be introduced safely into clinical trial only through careful toxicologic and pharmacologic study in animals and then very cautious study in man, starting with much lower dosages than those which appear to be tolerated by the animals.

APPROACHES AND ASSUMPTIONS IN THIS STUDY

The published and unpublished data which form the basis for this analysis were obtained by numerous investigators using different protocols and end points. We used consistent and reasonable general assumptions so that the data were comparable. The biologic end points, protocols, assumptions, and corrections necesssary to make the results more comparable are described briefly.

Toxicologic End Points (See Appendix I)

Mouse, rat, or hamster: Lethality—the dose which when administered by a certain route and schedule killed a selected percentage (10%, ie, the LD10) during a specified observation period; 50 to more than 100 animals were used in a typical determination.

Dog or monkey: (*a*) MTD; typically 2–4 animals were used at each dose level, spaced by 2-fold increments. In all instances individual doses which killed 0 and 100% were used. The highest dose killing 0% was considered the MTD. (*b*) Dose-related, hematopoietic effects; localized hemorrhages of the gastrointestinal tract; generalized hemorrhagic lesions (abdominal and thoracic viscera); stimulation of the central nervous system (CNS); others.

Man: (*a*) MTD for a fixed schedule (dose causing mild to moderate sublethal toxic effects in a significant percent of patients); (*b*) MTD for a variable schedule, calculated from the daily dose and median period to toxic effects requiring cessation of drug; the judgment of many clinical investigators was necessarily accepted in making this estimation.

Because of the nature of the available data, the toxicologic end points in the various animal species were related to the MTD in man. Although it was necessary to assume that the dosages resulted in the *same* percentage of toxicity in each species, the results do not depend, in a major way, on this assumption. For the drugs in this study, the dose-toxicity curves were relatively steep so that if the true percentage of toxicity for a given dosage was, say, between 5% and 15%, the actual dosage used would not differ very much from the dosage that should have been used.

It was necessary to use toxicologic data obtained by various routes of drug administration, ie, intraperitoneal (ip) for small animals, oral for small animals and man, and intravenous (iv) for large animals and man. In mice and rats the LD10's obtained by the ip and iv routes are usually comparable.

Another variable for which some reasonable correction must be made is the dosage schedule including the total dose. We assumed that the toxicity of anticancer agents is cumulative. Griswold et al. (3) reported that when the LD10's in BDF$_1$ mice of 70 agents, including the major classes of anticancer agents, were compared for two schedules, qd 1–7 days and qd 1–11 days,[8] the mean ratio (qd 1–7 days/qd 1–11 days) was 1.56. This is very close to that which might be expected from direct cumulative drug toxicity (11 days/7 days = 1.57).

Pinkel (2) and other investigators pointed out that the usual doses of certain drugs in various animal species and man were comparable when the dose was measured on the basis of mg/m^2 of surface area. Consequently most of the results are presented in mg/m^2. However since mg/kg is a commonly used unit of drug dosage, some results are also presented in this unit. Only a simple transformation is required to change mg/kg to mg/m^2; therefore the relationships developed are equivalent whichever unit is used. The quantitative relationships were simpler when expressed in mg/m^2.

A conversion factor (km) was used to transform mg/kg to mg/m^2 by the equation mg/kg $\times$ (km) = mg/m^2; (km) factors for animals, given their weight, are presented in table 1 (Appendix II), and table 2 (Appendix II) presents a way of transforming doses in mg/kg to mg/m^2 for man, given height and body weight. Chart 1 (Appendix II) is a diagram for determining surface area in man, given height and weight.

Calculations based on units of body surface area have no intrinsic merit per se. Very likely some other basis such as surface area of the site of action of the drug, lean body mass, or some fractional power of body weight, possibly related to length or some organ-membrane surface area, would be as appropriate or more appropriate. However the body surface area has been used to relate many physiologic parameters among species and means of transforming the data are readily available. Further, in our clinical studies we routinely use body surface area to adjust drug dose for patients of different size and weight.

RESULTS

The first step in analyzing the data was to correct the daily dosage schedules for man and for animals, when necessary, to a uniform schedule of qd 1–5 days. Thus if an LD10 for mice, or MTD for man, was obtained by a schedule of qd 1–10 days, we calculated that the LD10 (or MTD) for a schedule of qd 1–5 days was twice that value. The next step was to convert doses (LD10's or MTD's) from mg/kg to mg/m^2. This was accomplished by the approximate formula

$$(\text{mg/m}^2) = (km)_i \times (\text{mg/kg}), \quad (i = 1, \ldots, 7)$$

where the $(km)_i$ factor differs according to the species and also according to body weight within each species. In the analysis an average $(km)_i$ factor was used, assuming that individuals in each species were of average height-to-body-weight ratios. The $(km)_i$ factors were derived from standard relationships between weight and surface area as given in Spector (40) and Sendroy and Cecchini (39). Details and other information on relating drug doses in mg/kg to doses in mg/m^2 are given in Appendix II.

[8] qd = drug given once daily for as many days as indicated.

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