ADVANCES IN DRUG RESEARCH

Volume 20

ADVANCES IN

DRUG RESEARCH

Edited by

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Y074566

VOLUME 20

ACADEMIC PRESS

Harcourt Brace Jovanovich, Publishers

LONDON SAN DIEGO NEW YORK BOSTON
SYDNEY TOKYO TORONTO

This book is printed on acid-free paper

ACADEMIC PRESS LIMITED
24–28 Oval Road
LONDON NW1 7DX

United States Edition published by
ACADEMIC PRESS INC.
San Diego, CA 92101

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British Library Cataloguing in Publication Data

Advances in drug research.—
Vol. 20 (1991)
1. Drugs – Serials
615'.1'05

ISBN 0–12–013320–2

Typeset by EJS Chemical Composition, Bath
Printed in Great Britain by Galliard (Printers) Ltd, Great Yarmouth

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PREFACE: "ONE SCORE VOLUMES, AND A DIET"

Two facts will rapidly be evident to faithful readers of *Advances in Drug Research*. First, this volume is the twentieth in the series, an event that cannot be left uncelebrated. And second, it is somewhat leaner than its immediate precursors, particularly volumes 18 and 19.

In recent years, successive volumes in the series have displayed a disposition to become thicker and thicker, most certainly a result of the editor's tender loving care—in the fashion of a *mamma* overfeeding her children. Such an inflationary tendency is well known to librarians, with scientific and other books getting bigger with advancing year of publication. Kerber (1988) has documented this phenomenon for organic chemistry texts, writing on the "Elephantiasis of the Textbook". Fortunately, lucid eyes were on the alert, and Gina Fullerlove and Dr Carey Chapman, two competent and dedicated members of the editorial staff at Academic Press Ltd, could remain silent no longer and expressed their concern in diplomatic and convincing words. It was clear to them, as it is now to me, that somewhat smaller volumes may have advantages over too large ones. As a result, a diet accompanies the coming of age (in terms of number of volumes but not of years) of *Advances in Drug Research*. I use the opportunity of this event to express publicly my deep appreciation to Gina and Carey for their unfailing collaboration and constant help.

Four chapters make up this volume, four chapters of comparable length but vastly different scope. The first two chapters deal with general themes, while the last two are oriented towards some specific drug classes. Thus, the opening chapter by Chappell and Mordenti covers a major problem in drug research, namely the extrapolation of toxicological and pharmacological data from animals to humans. This work opportunely follows the chapter on interspecies scaling published by Boxenbaum and D'Souza in volume 19. Written with mastery and lucidity, it should help many drug researchers in acquiring a clearer grasp of an issue the complexity of which will always escape us.

The second chapter by Fichtl and colleagues deals with tissue binding of drugs. This is again a topic of considerable significance in drug disposition and pharmacokinetics, considering the relative ponderal importance of tissue versus blood macromolecules. Strangely enough, the number of research teams active in this area is rather limited, for reasons that can only be guessed. Perhaps the techniques involved frighten pharmacokineticists or are ignored by them, and it is precisely the originality of this chapter that it discusses not only pharmacokinetic aspects and consequences, but also principles and methods. Of course techniques are not

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given exaggerated coverage because this is not the scope of the series and

> ... since in science as in love a concentration on technique is quite likely to lead to impotence. [Berger, 1966]

The third chapter is especially dear to me for two reasons. First, it was written by my colleague and friend, Hostettmann, and his associates. And second, it will bring pharmacognosy and phytochemistry to the awareness of a number of pharmacologists and medicinal chemists. The therapeutic use of plants has been an art as old as humankind; it has now become a science whose most recent advances are particularly impressive. Pharmacognosy, like astronomy, medicine and a few other arts-become-sciences, belong to our oldest cultural heritage, bringing to mind the pregnant sentence of Medawar (1984):

> Science cannot be divided into what is up to date and what is merely of antiquarian interests, but is to be regarded as the product of a growth of thought.

This spirit is implicit in the chapter by Hostettmann and co-authors, where historical notes often give context and depth to the examples discussed. Most of the latter pertain to chemotherapeutic agents, in particular anti-malarial, antitumour and anti-HIV drugs. It is certainly intriguing that the world of plants should have such a wealth of chemotherapeutic agents to offer when so many diseases affecting humans and animals are caused by parasites in the broadest meaning of the word (i.e. viruses, bacteria, fungi, parasites *sensu stricto* and tumours). It is perhaps more than a coincidence that a parallel can be seen between chemical research and drug research: on the one hand phytochemistry receives fewer resources than chemical synthesis, while in drug research the fight against parasites *sensu stricto* is not pursued as vigorously as that against, for example, cardiovascular and CNS disorders.

The fourth chapter by Timmerman and co-workers is a more traditional one in terms of topic and coverage. Over the years, the field of histaminergic agonists and antagonists has witnessed an unusual series of breakthroughs such as H_2-receptor antagonists, non-sedating H_1-receptor antagonists, and H_3-receptors. A comprehensive, up to date and integrated coverage had become necessary and is offered here by one of the key players in the field. While the chapter is centred on structure–activity relationships, it is also remarkably informative in terms of molecular pharmacology and therapeutic uses.

As always, the preparation of this volume was accompanied by a lively and rewarding exchange of correspondence with contributors. Now that the

volume is published, authors and editor have completed their task and readers can begin their study. May they make the most of it!

BERNARD TESTA

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CONTENTS

Histaminergic Agonists and Antagonists : Recent Developments

R. LEURS, H. VAN DER GOOT AND H. TIMMERMAN

Extrapolation of Toxicological and Pharmacological Data from Animals to Humans

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ADVANCES IN DRUG RESEARCH, VOL. 20
ISBN 012 013320-2

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LIST OF ABBREVIATIONS

AUC	Area under the curve
BME	Body mass equivalence
BMR	Basal metabolic rate
CL	Clearance
DCM	Dichloromethane
ECW	Extracellular water
EDC	Ethylene dichloride
EPA	(US) Environment Protection Agency
GSH	Glutathione
GST	Glutathione-*S*-transferase
ICW	Intracellular water
LOAEL	Lowest observed adverse effect level
MFO	Mixed-function oxidases
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
PB-PK	Physiologically-based, pharmacokinetic (model)
RME	Residual mass exponent
SAE	Surface area equivalence
TBW	Total body water

1 Overview

In this chapter we review the literature concerning the extrapolation of toxicological and pharmacological data from laboratory animals to humans and draw conclusions regarding such extrapolations. Four extrapolation models are discussed.

- *Body mass equivalence* (BME), whereby it is assumed that the equivalent dose in milligrams or milligrams per day is proportional to body mass.
- *Surface area equivalence* (SAE), whereby it is assumed that the equivalent dose is proportional to body surface area.
- *Allometric models*, whereby it is assumed that the relevant measure of toxicity (e.g. the LD_{50} or the lowest observed adverse effect level, LOAEL) is a power function of mass, with empirically determined coefficients and exponents.

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- *Pharmacokinetic models*, whereby pharmacokinetic models are used to simulate the fundamental processes governing the absorption, distribution, metabolism and excretion of chemicals in the body.

This chapter discusses these models in terms of their historical development, empirical bases, pharmacological applications and use in toxicological extrapolation. The discussion is entirely based on information existing in the literature. On the basis of this review we make the following conclusions.

(a) *Regarding the surface area and body mass models*

- The body surface area model is best viewed as a surrogate for complex and incompletely understood mechanisms.
- In view of the difficulty of measurement of body surface area, combined with the inevitable uncertainties in other measurements, there is no reason to use complex equations for surface area calculations. It is quite adequate to assume that

$$\text{surface area} = cM^l,$$

where M is body mass, with the same value of c and l for all species. Typically the value of l encountered in the literature is 2/3; however, in view of the many uncertainties in the data, the exponent l could as easily be 0.7 or 0.75.
- SAE will always predict a smaller dose in milligrams or milligrams per day for humans than BME when extrapolating from smaller animals to humans. Furthermore, while there is a great lack of uniformity in the toxicological literature, the data tend to support SAE over BME.
- The physiological support, both theoretical and empirical, for SAE is equivocal; in spite of many attempts, no convincing proof of the SAE model exists, however the empirical evidence leans more in favour of SAE than BME.
- Where no data other than toxicological data on one or two laboratory animals is present, the most conservative approach (in terms of minimizing false-negatives) and the approach best supported by existing evidence is to use SAE rather than BME to extrapolate to humans.

(b) *Regarding the allometric models*

- The "surface law" (SAE) and the "body weight law" (BME) should be considered subsets of the allometric model where the dependent toxicological parameter Y (e.g., maximum tolerated dose) depends on body mass (M) according to

$$Y = bM^k.$$

Both b and k are determined empirically and are assumed to be the same for all species. In the case of BME, the value of k is 1 and in the case of SAE, it is 2/3. In the early 1930s, another popular model came into existence. This model, often known as the Kleiber–Brody Law, states that basal metabolism rates scale with an exponent of 0.75 rather than 2/3 (which is equivalent to SAE). This model was first developed by the application of linear regression analysis to metabolic data for many species. There have been some interesting theoretical arguments put forward to attempt to provide a general proof for the value of 0.75 for the allometric exponent. While many of these arguments are appealing, they do not offer an unequivocal proof that the exponent is 0.75.

- The existence of such allometric relationships for a wide variety of physiological parameters is well-documented. These relationships are probably a reflection of fundamental physical, chemical and biological constraints on natural selection.
- The vast body of empirical data (including data used to support SAE) supporting allometric relationships of a wide variety of fundamental physiological parameters strongly suggests that it is possible, in many cases, to extrapolate pharmacological and toxicological data from animals to humans.
- The application of allometry to toxicological and pharmacological dose extrapolation frequently results in values of k between 0.6 and 0.8. These values are not very different from 0.67 for the surface area law or 0.75 for the Kleiber–Brody Law, but generally they are significantly different (both in a statistical sense and in their consequences) from the value of 1 for the BME model. In view of the uncertainties, the value 0.7 for the exponent seems a reasonable compromise that is not inconsistent with the surface law (SAE) or the Kleiber–Brody law (the use of 0.7 to extrapolate from a mouse to a human gives a result differing by roughly 30% from that obtained using either 0.75 or 0.67). Indeed, one danger in using two significant figures is that it can give the appearance of greater certainty than actually exists.
- In the context of the allometric model, where mass is a surrogate rather than a cause, it is more appropriate to view k simply as an empirical parameter. Preferably the exponent should be empirically determined. If, however, extrapolation must be made on the basis of inadequate data, we recommend the use of the allometric equation with an exponent of 0.7. The result will be more conservative than the use of BME (exponent = 1) and, in view of the many uncertainties in measurement, essentially indistinguishable from the result obtained using either the surface law (SAE) or the Kleiber–Brody law.

(c) *Regarding the pharmacokinetic models*

- Developments in pharmacokinetics over the last two to three decades lend further support to the idea that toxicological and pharmacological data can often be extrapolated from laboratory animals to humans.
- Pharmacokinetic concepts, such as clearance and distribution volume coupled with the allometric model, provide a more satisfactory mechanistic basis for extrapolation than surface area equivalence or the Kleiber–Brody law for extrapolating pharmaceutical and toxicological data.
- Although the value of k is frequently in the range of 0.6–0.8, as mentioned above, there are chemicals where the exponent is neither unity nor in the range 0.6–0.8; therefore no single exponent can be used in all cases, and the safest approach is to empirically determine the best value for k in the particular case of interest.
- The so-called allometric pharmacokinetic model, where allometric equations are used to scale pharmacokinetic parameters such as volume of distribution, half-life and clearance, is probably adequate for a large number of chemicals. Because of the empirical and "black box" nature of this model, it is not clear exactly when this approach is inadequate and when it needs to be replaced by more complex approaches. Additional research is needed to clarify this issue.
- The physiologically-based, pharmacokinetic (PB-PK) model, which involves detailed mass-balance calculations for organs and tissues believed to be important in a compound's disposition, is viewed by some workers (e.g. Anderson *et al.*, 1987) to have a greater potential than the allometric pharmacokinetic model in providing accurate predictions; however, others disagree with this assessment. These models are very labour-intensive and costly and have only been used for a limited number of chemicals.
- It is possible, for some chemicals, to use short-term, relatively inexpensive experiments to develop the parameters needed for toxicological and pharmacological extrapolations.
- In view of the complexity of the PB-PK models, the allometric pharmacokinetic model is probably adequate and more practical, except where it can be demonstrated that it will not work.
- In view of physiological differences among humans, including effects of age, disease and gender on clearance and other pharmacokinetic parameters, it is prudent to use a safety factor when extrapolating doses across species, even if it is felt that the pharmacokinetic model in a particular case is quite accurate.
- The pharmacokinetic and toxicological data base is inadequate to make valid comparisons of the different extrapolation models discussed here.

We believe that the use of allometry coupled with pharmacokinetic data can not only provide for more accurate extrapolation, but can also significantly reduce the cost involved in determining reference doses and other parameters required for setting environmental standards or determining Phase I doses for therapeutic agents. However, there is a need to improve the knowledge base in this area.

It is clear that the paucity of data does not allow for much confidence in extrapolation from animals to humans. In view of the importance to public health and the possible economic impacts of such extrapolations, it is important to improve our knowledge in this area. In the case of toxic chemicals released into the environment, an incorrect value could have public health impacts (by being too high) or economic impacts (by being too low) that could easily "pay" for the research needed to avoid such mistakes. Since the economic cost of inaccurate extrapolations is borne by government, industry and the general public, it is entirely appropriate that the cost of such research should be supported by government and industry. Clearly, this research has applications not only to the toxicology of environmental contaminants, but also to drug testing and the selection of treatment protocols (e.g. chemotherapy). On the basis of our review we recommend the following.

(1) Research should be carried out to develop the data required to test various extrapolation models for a number of chemicals representing different classes of chemical and toxicological profiles. These studies should include area under the total and unbound blood concentration versus time curve for both single- and multiple-dose experiments.
(2) A protocol should be developed that would involve acute and chronic toxicity studies on perhaps two species, with short-term pharmacokinetic studies on four to five species. The latter studies would be used to develop allometric equations, for clearance, volume of distribution and half-life, that could then be used to extrapolate the results of the toxicity studies. Numerous factors can affect pharmacokinetic variables such as clearance; these include age, genetic variability, sex, illness and chemical exposures. The determination of appropriate safety factors can be addressed by research programmes, but is ultimately a policy decision.

2 Introduction

Laboratory animals have often served as models for the study of humans. This use has been based on the assumption that the extrapolation of

biological data from such animals to humans is valid, at least for some physiological parameters. In recent years, the perceived need to develop regulations for chemicals in the environment, as well as the development of synthetic drugs, has greatly increased the use of animal models for toxicological and pharmacological extrapolation.

Three extrapolation techniques are used by regulatory agencies. One of these is the use of body mass or what we will call body mass equivalence (BME). It assumes that the equivalent dose (i.e. the dose in milligrams or milligrams per day, depending on whether it is a single- or multiple-dose situation) is proportional to body mass. Another way to state this is that the same dose as milligrams per kilogram of body mass or milligrams per kilogram of body mass per day will have the same effect in all species.

Another widely used approach has been the use of body surface area. In this approach, which we will call surface area equivalence (SAE) (more widely known as the surface law or surface area rule), it is assumed that the equivalent dose in mg or mg/day is proportional to the body surface area of the animal. Thus, if the same chemical is given to animals in such a way that the dose per surface area in milligrams per square metre or milligrams per square metre per day is the same for all the animals, then the response to the chemical will be the same.

A third approach is given by assuming that, for chronic experiments, equal proportions of the diet will lead to similar effects. That is, if a chemical is given to an animal as 10 ppm in the diet and has a particular effect, it will have the same effect on all other animals if given as 10 ppm in their diets. This method generally gives results similar to those given by the "surface rule" described below.

The assumption of BME is very natural and was probably the earliest method used. Indeed, it would have been very natural to assume that the equivalent dose of a drug for a 5 kg child is about 1/15th of that for a 70 kg adult; however, as early as 1830 it was recognized that this approach sometimes led to poor estimates. When an adult was given 15 times the dose safe and effective for children, the adult would sometimes suffer toxic effects. Conversely, when a child was given 1/15th of the safe and effective dose for adults, the result often was an inadequate pharmacologic response. Interestingly, at about the same time as this problem was first reported (1830), two French investigators (Sarrus and Rameaux, 1838) proposed that energy metabolism in animals is proportional to their surface area and that the surface area of an animal is proportional to the two-thirds power of its mass (which explains why the method involving equal proportions of the diet gives similar results). It was not until the first decade of this century that a connection between energy metabolism, surface area and toxicity was made.

Since 1910, a number of investigators have considered the general problem of intraspecies and interspecies scaling or extrapolation. Much of this work has focussed on issues other than, but potentially related to, toxicity. That is, investigators have considered the scaling of the size of organs (heart, liver, kidney, etc.), the function of organs (heartbeat, breath rates, enzymatic activity, etc.) and parameters related to drug metabolism (half-life, clearance, distribution volumes, etc.). A considerable literature has developed regarding the relative success of the attempts to scale these and other physiological parameters. While the vast majority of these investigations did not directly relate to extrapolating toxicity data, clearly the various physiological parameters mentioned above have an important bearing on the toxic effects of chemicals. Thus, those techniques that have been successful in extrapolating relevant physiological parameters, such as the rate at which a chemical is cleared from the blood, should have a reasonable chance of working for toxicological extrapolations. Indeed, comparisons involving toxic endpoints have been made using chemotherapeutic agents. Surface area equivalence was reasonably successful in predicting the toxic effects (Freireich *et al.*, 1966) of many such agents. This approach has also been successful in predicting the therapeutic level for a variety of other drugs (Crawford *et al.*, 1950).

Nearly 100 years after Sarrus and Rameaux (1838) proposed that energy metabolism rates (generally meaning basal rates) for animals are proportional to the two-thirds power of the mass, Kleiber (1932) and Brody and Proctor (1932) reported that the use of linear regression analysis of the metabolic data gave the result that energy metabolism was proportional to the three-fourths power of the mass. The use of linear regression analysis on data for organ weights and other physiological parameters led to numerous equations of the type

$$Y = bM^k, \tag{1}$$

where M is the body mass, Y is the physiological parameter of interest (e.g. liver weight), and b and k are constants. These equations were obtained by fitting the equation to both intraspecies and interspecies data. In a sense, this approach contains the surface area approach as a special case ($k = 2/3$). But in another sense, the approach is different in spirit because it uses body mass or a power of body mass as a surrogate and is strictly empirical in nature.

This approach is called allometry or the study of size. Haldane (1928) has noted that "the most obvious differences between different animals are differences of size, but for some reason the zoologists have paid singularly little attention to them". Galileo may have been the first allometrist. He pointed out that the effect of gravity has serious consequences for the

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