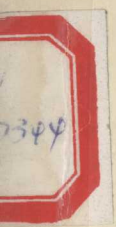
DOSE~RESPONSE RELATIONSHIPS IN CLINICAL PHARMACOLOGY



DOSE-RESPONSE RELATIONSHIPS IN CLINICAL PHARMACOLOGY

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About the Esteve Foundation

The Esteve Foundation was established in 1983 to honor the late Dr. Antonio Esteve in the manner that would best fit his temperament, intellectual curiosity and dedication to science. Antonio Esteve was born in Manresa (Barcelona) in 1902, obtained a Doctorate in Pharmacy and in 1927 became manager of the pharmacy that his great-grandfather had founded in 1787. Having been actively involved in research during his student years, Dr. Antonio Esteve felt an urge for drug investigation that resulted in the establishment, in 1929, of what was to become one of the largest pharmaceutical firms in Spain. Dr. Antonio Esteve was actively involved in its research activities, actually heading this department, until his death in 1979.

The Esteve Foundation operates independently of any pharmaceutical enterprise and its main goal is to stimulate progress in pharmacotherapy through scientific communication and discussion. As a way to promote international cooperation in research, it organizes international multidisciplinary meetings – The Esteve Foundation Symposia – as well as meetings on topics of interest in its geographical area. The Esteve Foundation also sponsors lectures – among them an Antonio Esteve Lectures international series – seminars, courses and study groups on areas related to pharmacotherapy.

Preface

It is commonly acknowledged that, to a pharmacologist, the finding of a clear relationship between an effect and the dose or concentration of the agent that elicits it is a sure indication that he or she is on solid ground. In clinical pharmacology, obtaining this type of relationship is, indeed, a true achievement. On the one hand, it is a definite contribution to the discipline, as it offers valid information on the effects of drugs in man and, on the other, provides a tool for understanding the true magnitude of these effects and for making educated guesses about what is to be expected of doses not directly tested. A century ago, Lord Kelvin suggested that only information that could be quantitated should be considered scientifically sound, but time has shown that this guidance conveyed a risk: that whatever is expressed in numbers would automatically be credible or considered of interest. Clinical pharmacology still suffers from a scarcity of reliable quantitative data about the effects of drugs in man, among an abundance of contributions full of numerical values of doubtful clinical consequence. With this in mind, it was a challenge and a pleasure to explore the possibilities of and limitations in obtaining clear dose-response relationships for pharmacological and toxicological effects in man. From the presentations and discussions in this symposium, it is obvious that much can be accomplished.

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Dose-response relationships in clinical pharmacology.
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PHARMACOMETRY IN MAN: THE STATE OF THE ART

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The neglect of the dose-response curve in clinical research and in clinical practice represents a major scientific deficiency, and stands in striking contrast to the traditional importance of this principle in classical pharmacology. Why should this be the case?

The reasons, I submit, are many. If one considers the use of drugs in treating the sick, the following considerations come to mind:

1. For some medicine (penicillin, e.g.), the therapeutic ratio is so large that the use of doses far larger than are needed to treat most patients exacts no significant toxic price and achieves the therapeutic goal very nicely.
2. The practice of medicine is admittedly simplified if the prescribing physician feels no need to individualize the dosage regimen for each new patient. A drug like levodopa for Parkinsonism, which requires a lot of trial-and-error dosage experimentation for individual patients, makes the physician's life "not a happy one" (pace W.S. Gilbert).
3. When a patient finds a prescribed drug wanting - either because of unpleasant adverse effects or lack of therapeutic response - a psychological pressure develops to try a new drug regimen rather than a new dosage regimen. In my experience "switching" by physicians is much more common than "fine-tuning".
4. The all too available laboratory measurements of drug concentrations in biological fluids will at times lure the unsophisticated physician away from a proper exploration of the dose-response curve because of robotic reliance on recommended (and arbitrary) "therapeutic" or "toxic" levels which can be misleading even when the laboratory has correctly carried out the determination. It is depressing to see a physician fail to increase the dose of a drug, despite the absence of both toxicity and efficacy, because the plasma level of the drug is "in the therapeutic range".

The reasons for neglect of the dose-response curve in clinical research have a different set of origins, which include the following:

1. Regulatory agencies rely primarily, in their decision-making process vis-a-vis registration of a new medicine, on the "group" performance of the drug. In the U.S., e.g., a new drug application must generally include at least two well-controlled trials that demonstrate therapeutic benefit for the treated patients as a group that compares favorably with the benefit achieved with a placebo, a standard drug, or both. "Safety" as well as effectiveness must also be documented, but again the focus is on the group, rather than on individual patients. While this approach is by no means antithetical to dose-response studies, it is possible to provide evidence that a drug, if marketed, is likely to do much more good than harm in the target population if prescribed at a certain dose, or within a narrow dose range, without dose-response data.

2. Until recently, regulatory agencies have not pressed drug sponsors or clinical investigators to delineate optimal or minimally effective doses.

3. Except for single dose studies, where flexibilization of dosage is not possible, protocols usually contain provisions for lowering dosage in the event of toxicity, or increasing dosage if therapeutic response is not seen. Such "escape clauses" attempt to mimic the kind of dosage modifications desirable in clinical practice and to satisfy professional and ethical precepts, and are thus admirably defensible, but tend to obscure dose-response relationships.

4. In addition to the changing dosage invoked for the reasons and by the mechanism just described, there are other changes contributed by the experimental subject's ability to alter ingested dose by non-compliance. Failure to follow prescribing directions in outpatient trials has been repeatedly described. Non-compliance can occur for the same reasons that flexibilization of dosage "escape clauses" are built into protocols, i.e. for perceived or actual toxicity or lack of benefit, but it can also occur because of human error (e.g. forgetfulness) and can therefore not only reflect drug inadequacies but cause them (toxicity due to unintended overdosage or therapeutic failure due to unintended underdosage). Because of these quite different types of non-compliance, the variance contributed by noncompliance must be examined cautiously, with the aid of attempts to explain the reasons for non-compliance. While caution is necessary, the advantages to making use of this

contribution to dose-response relations are significant, and it is a pity that compliance data are so rarely used in this way, despite the fact that information on compliance is often collected as a part of the protocol in a clinical trial ("pill count", patient diaries, drug level measurements in biological fluids, "tracers", etc.).

Neglect of dose-response relationships has exacted a considerable scientific and social cost. Consider the following:

1. Drugs have been marketed at recommended doses that were far from optimal. Captopril and hydrochlorothiazide were initially used at doses perhaps eight times those now considered optimal.
2. Because estimates of recommended doses have been based on "group" averages, which include data on compliant as well as noncompliant patients, such doses may be excessive and needlessly toxic for scrupulously compliant patients who receive the drug after registration (see Fig. 1).

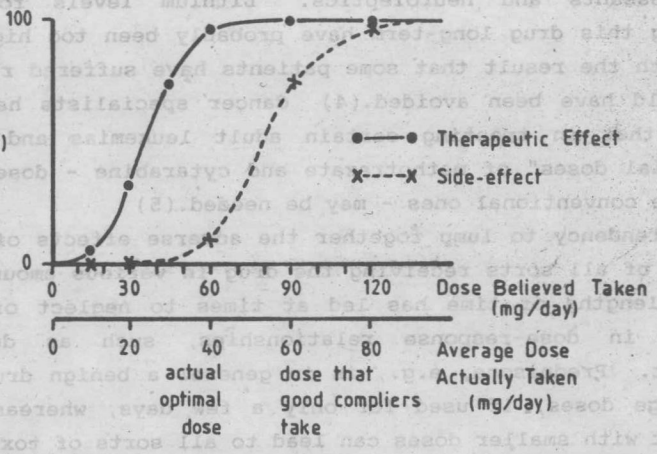

Figure 1

3. Generally ignored has been the potential for studying dose-response relations, even in fixed dose protocols, that lies in the fact that patients in a trial often differ significantly in weight.
4. Important co-variables that alter the shape or "location" of the dose-response curve have often been ignored, giving rise either to avoidable toxicity or to inadequate therapeutic benefit. Benoxaprofen, e.g., might still be on the market today had its

special elimination by certain patient groups been adequately appreciated. Triazolam's undesirable effects on memory are probably related both to dose and to alcohol intake. Flurazepam must be prescribed at lower doses to the elderly to prevent adverse reaction rates of intolerable magnitude. Oral contraceptives are now safer and still effective as the result of lowering their dosage of the estrogen component. Anticoagulant regimens have been employed at doses that were unnecessary for optimal benefit and produced major hemorrhagic complications.(1) Furthermore, certain non-drug conditions can dramatically alter the susceptibility to bleeding from anticoagulants. These include age; liver, kidney, and cardiac dysfunction; severe amenia; and cancer.(2) Fluphenazine decanoate has been used at doses five times higher than is necessary.(3) It seems likely that the optimal dose of aspirin for preventing vascular thrombosis is rather low, so that "less is more", prophylactically speaking, with a paradoxical loss of efficacy at higher doses. A similar situation probably obtains for some antidepressants and neuroleptics. Lithium levels for patients receiving this drug long-term have probably been too high in years past, with the result that some patients have suffered renal damage that could have been avoided.(4) Cancer specialists have come to realize that in treating certain adult leukemias and lymphomas, "industrial doses" of methotrexate and cytarabine - doses 10 to 30 times the conventional ones - may be needed.(5)

5. The tendency to lump together the adverse effects of a drug in patients of all sorts receiving the drug in various amounts and for varying lengths of time has led at times to neglect of important elements in dose-response relationships, such as duration of treatment. Prednisone, e.g., is in general a benign drug, even in very large doses, if used for only a few days, whereas long-term treatment with smaller doses can lead to all sorts of toxic events.

There are a number of challenges facing us as we work to improve on our past performance in regard to dose-response relationships. These include the following:

1. We must remember that for every drug there are multiple dose-response relationships, involving toxicity as well as benefit. Consider, e.g. the curves shown in Figure 2 for just some of the effects of atropine given subcutaneously to man.

2. While it is not possible to study all possible co-variables of interest, it is incumbent on us at least to study, in man, those variables suggested by preclinical studies or by the medicines

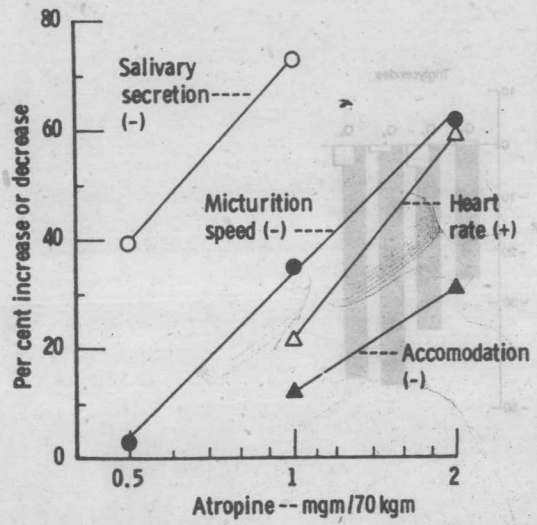

Fig. 2.—Some effects in man of varying doses of atropine sulfate subcutaneously. The + and — signs refer to increase or decrease, respectively. (Redrawn from Herxheimer, A.: *Brit J Pharmacol* 13:184, 1958.)

anticipated to be used concomitantly with the new drug in a high percentage of cases. Age and insufficiency of the major excretory organs will often deserve attention.

3. We should not miss opportunities for insights into dose-response relationships available from the aforementioned realities of individual weight differences and of noncompliance with prescribing directions. In the case of hypercholesterolemia, e.g., the lowering of serum cholesterol and of coronary risk have been nicely shown to be related to compliance (i.e. dose) for both cholestyramine and gemfibrozil. (See Figs. 3 and 4). Now, more sophisticated techniques for assuring compliance (see Fig. 5) give promise of quantitative information of higher quality than has been available in the past. These techniques can at times be usefully supplemented by drug level measurements, but may be far superior to the latter in outpatient studies, where the exigencies of sample timing limit the information to the latest dose ingested rather than describe what has been the pattern of ingestion since the last visit.

4. Clinical trial data need to be analyzed not only on a "group" or "average" basis, but in a form that couples therapeutic response and adverse effects in individual patients. It is this latter type of information that is likely to be especially useful to the

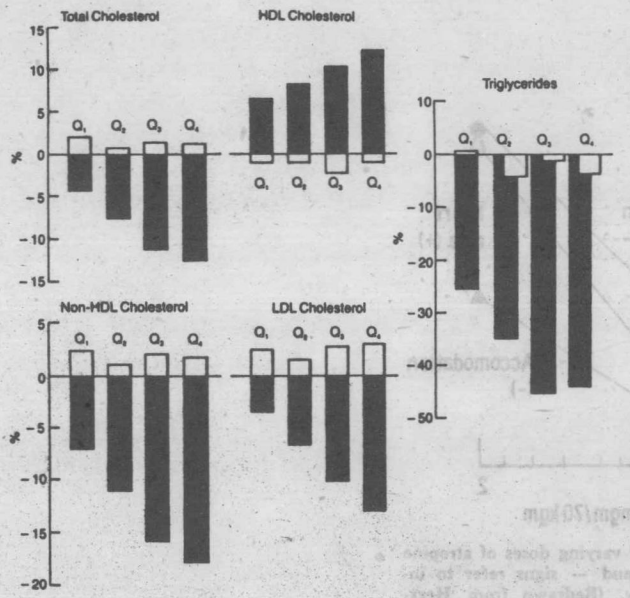

Fig 3.—Serum lipid percentage changes by treatment and quartiles (Q) of capsule count in Helsinki Heart Study. Open bars indicate placebo; black bars, gemfibrozil; HDL, high-density lipoprotein; and LDL, low-density lipoprotein. According to Mantel-Haenszel analysis of differences in incidence of coronary heart disease between treatments among Fredrickson types, $\chi^2 = 5.91$; $df = 1$; $P < .02$. Standardization was by direct method for inequalities in smoking and hypertension in comparison groups using total population as standard.

RELATION OF REDUCTION IN CHOLESTEROL TO REDUCTION IN CORONARY HEART DISEASE RISK

Packet Count	No.	Total Cholesterol Lowering	Reduction in CHD Risk
0-2	439	4.4%	10.9%
2-5	496	11.5%	26.1%
5-6	965	19.0%	39.3%

Figure 4

practitioner in selecting both drugs and doses. If new Drug Z is introduced for treatment of Disease X, I would submit that the physician needs to know, when consulted by Patient A, what would happen if he treated 100 patients with a given dose of Drug Z, i.e., how many of the 100 would respond beautifully, with satisfying therapeutic response and no side effects of consequence, how many would respond reasonably well but at the cost of significant side