European Journal of Clinical Pharmacology

Volume 34, 1988

Springer International

Springer-Verlag GmbH & Co. KG, D-1000 Berlin 33
Printed in Germany by aprinta, Wemding

Eur J Clin Pharmacol (1988) 34: 15–19

European Journal of Clinical Pharmacology

Dose-Finding Studies in Clinical Drug Development

R. Schmidt

Clinical Research Department, SANDOZ Ltd., Basel, Switzerland

Summary. A correct dose-finding study is of the utmost importance during clinical development of a new drug. It must define the no-effect dose and the mean effective and maximal effective doses. Then taking tolerability into account, the optimal therapeutic dose range can be selected.

To define the dosage schedule the duration of action in man must be tested, if possible together with blood concentration measurements. An adequate dose-finding study shows the optimal doses for double-blind trials in Phase II and large scale trials in Phase III, thereby saving time and effort and reducing the number of patients required.

The tendency of clinical experts to try to demonstrate superiority of one drug over another by using doses higher than patients really need must be resisted. The price paid in poor tolerability exceeds any potential benefits.

Key words: dose-finding, drug development; clinical trial, therapeutic dose range, proposed procedure, dose optimisation

The clinical development of a new drug is usually divided into three phases [1, 2]. Phase I is devoted to tolerability testing and pharmacokinetic evaluation. Trials in late Phase I or early Phase II are aimed at elucidating clinical efficacy in the intended patient population and to define the dosage and dosage schedule. Controlled trials are performed subsequently to compare the new drug with the standard medications. In Phase III, large scale trials are performed to confirm the efficacy and safety of the new drug in the target population.

Definition of the dosage and dosage schedule is a key question during clinical development of a new drug, and it is the objective of the so-called dose-finding studies. The goal is to satisfy the requirement that patients be exposed only to the quantity of drug that they really need [3]. It is mandatory that the therapeutic dose-range be established prior to initiation of double-blind studies, in which a fixed dosage and dosage schedule are the rule. In spite of the crucial importance of dose-finding studies, national and international guidelines as well as recommendations for clinical drug development at the best contain a few general suggestions on how to perform such trials. In the following a proposal for the procedure is described in more detail.

Selection of Subjects

Whether healthy human volunteers or patients are selected depends largely on the indication [4].

Healthy Volunteers

The involvement of healthy volunteers in drug studies is officially permitted in most countries and is specifically mentioned in the Guidelines laid down in the 1975 Tokyo Amendment of the 1964 "Declaration of Helsinki" [5]. In France the legal situation neither prohibits the administration of drugs to healthy volunteers nor does it make provision for it [6].

Studying healthy volunteers has the following advantages [7]:

They are
1. in a steady-state condition showing
   - no variation due to disease
   - no different stages of disease
2. easy to recruit
3. easy to select for age, sex, race, etc.

4. tested under identical conditions (climate, food, laboratory values)
5. not taking concomitant medication
6. easily prepared to consent in writing
7. in a condition in which the test can be repeated.

Dose ranging studies can be only performed in normal volunteers when there is a reliable test model with high predictability for the therapeutic effect, e.g. prevention of ergometer-induced tachycardia for betablockers, prolactin-lowering effect for endocrine indications of dopaminergic compounds, histamine flare test for antihistamines, etc.

The disadvantages of treating healthy volunteers are that they cannot receive any potential benefit and, in the case of pharmacodynamic studies, that they do not show the symptoms of the disease. To overcome this shortcoming "symptoms" can be produced by "provocation tests" [8], e.g. ergometer tachycardia. In this way the new substance can be tested with regard to whether and to what extent it reverses the "provoked" effects in healthy volunteers in comparison with placebo and/or a standard drug. Another possibility is to compare the new substance with a standard drug which itself evokes typical changes or effects in normals, e.g. the decrease in REM sleep evoked by classical antidepressants [9]. In such cases the new compound is tested to see if it produces the same changes and to compare these changes qualitatively and quantitatively with the effects of the standard drug. The new substance is thus "identified" in terms of changes produced by a standard drug, and such tests can be classified as "identification tests" [8]. As mentioned above, only those test methods should be used whose predictability for the foreseen disease has been clearly established. In addition, the tests must be safe.

Patients

The performance of dose-ranging studies in patients is

1. mandatory for drug groups for which potentially harmful effects may be anticipated, such as cytostatics, immunosuppressants, narcotics etc., and
2. necessary for drug groups for which there is no valid test model in healthy volunteers, e.g. drugs for senile dementia, parkinsonism etc.

Indication

In patients the indication should be defined qualitatively and quantitatively. Not only the disease for which the drug is foreseen must be carefully defined, but also its gravity and stage. The more innovative a drug, the more prepared are the clinical expert in the company and the investigator in the clinic to select end-stage patients rather than those in an early stage of the disease. This may result in the recommendation of a too high a dosage for the study population in Phases II and III trials. Therefore the involvement of patients with different but well defined stages of the disease is essential in dose-finding studies, and interpretation of the results must take into account the various degrees of the disease state.

Study Design

Whether several doses can be tested in the same individuals (intrapatient comparison) or whether a parallel group design, i.e. one dose per group, should be chosen depends on the nature of the disease, and on the condition of the patients. Only when the disease is in a steady state is a stepwise increase in dose in the same patient allowed. If the disease is expected to show variation over the period of the trial, a parallel group design is preferable.

If objective and measurable parameters of the disease process can be chosen an open design may be sufficient. When subjective symptoms or syndromes must be assessed, treatment must be blinded. In both cases the performance of the study should be controlled ("controlled trial").

Definition of the Optimal Dosage

Dose-finding studies should define

- the no-effect dose range
- the minimum effective dose
- the mean effective dose
- the maximum effective dose
- the optimal dose range

The minimum effective dose is the dose which has only a borderline effect in a small number of subjects, and the maximum effective dose will produce a marked effect in a large proportion of patients. Since it is the goal with most developmental drugs to produce a greater therapeutic activity and a larger proportion of responders than competitor drugs, there is a real risk of choosing a dose that is far above the optimal level for use in further studies. Another possibility contributing to recommendation of too high a therapeutic dose is, as mentioned above, the selection of severely disabled or end stage patients in early clinical trials. It is essential al-

ways to keep in mind the general rule that the higher the dose the higher the incidence of side effects. As dosage and tolerability are inversely correlated, it is of the utmost importance to define the position of the "optimal dose range" between the minimal and maximal effective doses. Within the optimal dose range, the desired therapeutic effect should be associated with good tolerability. For a promising new drug this means that efficacy and/or tolerability will show advantages over competitor drugs, i.e. that the new drug is superior. The definite proof of any claim of superiority will be provided later in the controlled (if possible double-blind) trials in Phases II and III.

During tolerability studies in Phase I, the highest well-tolerated dose will have been defined. In practice this highest, well-tolerated dose should be used as the initial dose in dose-finding studies. If this dose has a weak or only a borderline effect, the further development of the drug for the selected indication becomes questionable. If the highest well-tolerated dose produces a clear effect, lower doses, e.g. 50% and 25% of it, should be tested in order to establish the dose-effect relationship. In addition, the dose range must be defined which gives the zero value, i.e. which has no therapeutic effect. Whenever possible a placebo should be included to demonstrate the placebo response, which varies for different indications and populations.

The correlation between efficacy and tolerability is illustrated in Fig. 1.

Curve Eff shows the increase in efficacy and curve Tol the inverse decline in tolerability with increasing dose (d). In the middle, between the "maximal effective dose" and the "minimal effective dose" on curve Eff lies the "mean effective dose". The distance between the maximal and minimal effective doses is the "therapeutic dose range", which includes all effective doses. Above the maximal effective dose lie the supramaximal doses, which do not further increase efficacy but only worsen tolerability. Below the minimal effective dose lies the no-effective dose or placebo range. That is the range where effects or side-effects occur which should not be attributed to the drug, as they are also observed to the same extent and with the same incidence after placebo. This is the reason why the effect curve starts above the zero point and the tolerability curve below the 100% point.

For some indications the placebo response is remarkably strong, as in hypertension and analgesia. An analgesic produces "effects" at dosages clearly below the minimal effective dose. It is important to be aware of the differing placebo range for different indications and populations [10], and to perform

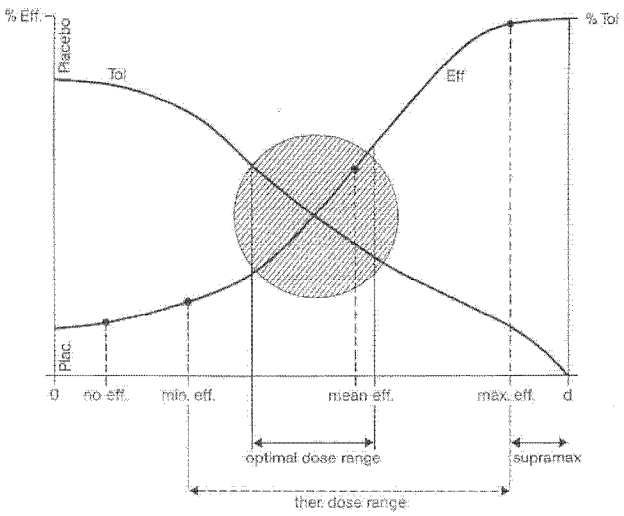

Fig. 1. Interrelation between efficacy (Eff) and tolerability (Tol) in a dose-finding study. d = dose

dose-finding studies strictly as "controlled trials", especially when the placebo range is large.

Each patient will have an individual optimal therapeutic dose. That dose is only valid for that patient and not for a study population. For the latter an optimal dose "range" must be defined, which is effective and well tolerated by the majority of responders. From the two curves in Fig. 1 it is evident that it is exceptional for the optimal dose range to be centered around the mean effective dose. It lies around the point of intersection of the two curves, clearly taking into account not only the efficacy but also the tolerability curve [11]. If the optimal therapeutic dose range is broad, more than one dose should be selected for double-blind trials, or it may even be necessary to treat patients with individual dosages, as is usually the case for psychotropics and antiparkinsonism drugs. In order to keep the number of patients low, as well as for reasons of time and capacity, the numbers of doses in comparative trials should be as small as possible, and should not usually exceed three. Whenever possible a individual dose titration must be avoided.

Duration of Administration

For some compounds (analgesics, diuretics, dopaminergics in endocrinology etc.) a single dose or single day application will permit definition of the optimal dose range as well as the dosage schedule, but for other drugs several days or even weeks of treatment are necessary, e.g. psychotropics and antiphlogistics.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.