

Systematic Evaluation of Dose Proportionality Studies in Clinical Pharmacokinetics

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Abstract: An understanding of dose proportionality is essential in drug development, and the results are of great clinical importance for predicting the effects of dose adjustments. However, little consensus exists with regard to study design and analysis. The aim of this paper was to produce a detailed profile of the information on dose proportionality studies in the last 10 years and to provide a foundation for reflection and debate on future priorities. A total of 147 publications comprising 156 studies were analyzed. The typical dose proportionality study enrolled 20 to 30 subjects and randomly allocated them into 3 to 4 dose levels to investigate pharmacokinetic behaviors within a dose ratio range of 2-6. The most common design was the crossover experiment (52.6%), and evaluating dose-adjusted pharmacokinetic parameters followed by hypothesis testing (43%) was the most frequent statistical approach. However, the alternative crossover design and equivalence criterion based on the power model represented only 4% and 8% of studies, respectively. The power model as a recommendable empirical relationship to assess dose proportionality was applied in 25 (16%) studies. This research suggests that the alternative crossover design and power model statistical method should be attracting more attention in order to obtain more information in studies with limited subjects.

Keywords: Pharmacokinetics, dose proportionality, power model, equivalence criterion, nonlinearity.

INTRODUCTION

As a fundamental component of pharmacokinetic (PK) research in drug development, dose proportionality characterizes the relationship between dose of drug and its pharmacokinetic effect [1, 2]. If the drug possesses this property, increasing the dose should increase the PK parameter (such as AUC, C_{max}) by the same factor [3, 4]. Hence, it is easy to predict the medication effects within a certain dosage range. 'Greater than proportional' may imply a saturable metabolism at higher doses, while 'lower than proportional' may imply a saturable absorption at higher doses. These two situations suggest that the pharmacokinetic behavior of an investigated drug is nonlinear and may undergo loss of predictability in dosage adjustment. Such drugs often require therapeutic concentration monitoring to achieve the targeted therapeutic plasma concentration. Because almost all drugs may show nonlinear pharmacokinetics when the doses are extremely high, dose proportionality assessment provides evidence to support the statement that the pharmacokinetics of an investigated drug are linear over a certain dose range, i.e., that any degree of nonlinearity is negligible. Thus, the assessment of dose proportionality is of great clinical importance for predicting the consequences of rational dose adjustments.

Despite the fact that dose proportionality studies are very important in the drug development process, a lack of consensus exists concerning the optimal study design for assessment of dose proportionality [3, 5]. In the past decade, there have been many articles [6-8] focused on the methodology of dose proportionality studies in an attempt to quantify the relationships between dose and PK parameters. Although some more efficient techniques for design and analysis have been developed, so far no standard approach has been identified, and the method chosen is based on practical considerations rather than any statistical rationale. There is considerable variety in how such studies are conducted, and not all such studies are published when performed in phase I clinical trials [9], making it difficult to get a profile of dose proportionality studies.

The goal of this article is to quantitatively evaluate the detailed designs and assessments of all dose proportionality studies published during the past decade in order to show how dose proportionality studies are being performed and to discuss the differences

in these studies. We hope that our research presents a useful profile of dose proportionality studies and provides a focus for reflection and debate on future priorities

METHODS

Search Strategy

Because the phrase, 'dose proportionality', was not included in MESH terms, initial article selection was conducted in Medline (Pubmed) using the keyword "dose proportionality" in all fields. Additionally, the search was limited to 'English language' and 'humans', as well as to studies published from 1 January 1999 to 12 December 2008. Retrieved articles further limited to those dealing with medications or analyses performed on original clinical data were assessed by one of the authors (YS), who screened the papers based on the abstract or, if necessary, on the full article to identify the relevant studies. Articles were included only if the study was identified as a dose proportionality study and published as a full-text article. Population pharmacokinetics studies, reviews, methodology articles, and articles published as abstracts only, editorials, news, or correspondence sections were excluded.

Data Extraction

Each article was assessed independently by two reviewers (YS and YH). Any disagreement between the two researchers was resolved by discussion. In order to gather data on the characteristics of the articles, a Microsoft Excel database was developed and used as a template for data collection. The database was constructed around the design and assessment of dose proportionality studies within selected articles rather than the article itself because our work focused mainly on the methodology used in published dose proportionality studies rather than on the quality of published papers. Consequently, when an article described more than one dose proportionality study, it had as many entries in the database as the number of studies described in the article. The database contained 56 fields, most of which included a coding framework of predefined options. Free-text fields were also offered in the database, some of which contained article identification and useful information contained in the article, and others enabled reviewers to highlight any coding in need of additional clarification, any ambiguities, and issues for discussion among the research team. Such discrepancies were clarified and defined further.

Recorded data variables related to a range of study characteristics were as follows: article identification (5 items) contained

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PMID, first author's name, article title, year of publication, and the journal in which it was published. Context of the analysis (5 items) collected information about the phase of clinical development, first-in-human, objectives of the study (PK or PK & safe), therapeutic area and routes of administration. Therapeutic classes were defined according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system. Study design (15 items) included design type, wash-out period, number of doses (single-dose, multiple-dose or both), number of study subjects and sample size estimations, randomization, blinding, control, cohort size, distribution of subjects within the cohorts, dose levels, dose increments, target population, percentage male and age range. Dose proportionality information (10 items) was gathered about the pharmacokinetics group size, blood sample volume, sample time, blood sample numbers, results of the dose proportionality assessment, the dose proportionality range, PK parameters, AUC calculation methods, and the dose proportionality analysis approach and criteria.

Statistical Analysis

For each item, descriptive statistics (mean, SD, minimum and maximum values) were used to report the results for continuous variables, whereas frequencies and percentages were used to describe categorical variables. All data analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

Selected Articles

Of the 194 published articles initially identified in Medline, 165 were selected for assessment. The 29 excluded articles were reviews ($n=9$) or population pharmacokinetics studies ($n=5$), did not assess medications ($n=11$), or were not in humans ($n=4$). Eighteen articles were secondarily excluded because the full texts were not available ($n=2$), or after the full text was obtained, they were found not to be dose proportionality studies ($n=16$). A total of 147 articles [10-156] comprising 156 studies were included in the final analysis.

Of the 147 final articles included between 1999 and 2008, the number in any one year varied from 9 to 20 (Fig. 1). More than half of these articles were frequently published in pharmacological journals, with most coming from leading journals in the pharmacology field (Fig. 2). The routes of administration included oral (56%), parenteral (35%), inhalation (9%), sublingual/buccal (7%), nasal (4%) or transdermal (3%). There were two administration routes in four articles [51, 61, 76, 78]; in these cases, each article was analyzed with the two routes (Fig. 3). The distribution of therapeutic classes according to the WHO's Anatomical Therapeutic Chemical (ATC) classification system is presented in Fig. (4). Consistent with Table 1, nervous system, anti-neoplastic and immunomodulating agents were among those for which a dose proportionality study has been most often published in the last decade. At level 2 of the ATC classification system, these studies could be divided into 36 subgroups. The two largest subgroups, drugs for obstructive airway diseases and analgesics, contained 15 and 14 studies, respectively. One study was seen in 12 subgroups.

Study Design

All included studies comprised a total of 7869 subjects ranging from 3 to 1300 subjects per study (Fig. 5A). The median number of subjects for each study was 25 and 55% of studies enrolled 20 to 30 subjects. Likewise, the cohort size in each study also showed great variation and varied from 2 to over 200. As illustrated in Fig. (5B), over 50 percent of these studies' cohort size was 4 to 9. Ninety-nine studies (62.8%) were single-dose, 23(14.1%) were multiple-dose, and 36 studies (23.1%) were single- and multiple-dose. Except for two studies [18, 111] that did not report sex, 26.6%, 4.5%, and 68.8% of the studies were conducted in males, females, or both males and females, respectively. The majorities (66.7%) of these

studies were performed in healthy subjects, with 32.7% in patients, and one (0.64%) study [29] included both patients and health volunteers.

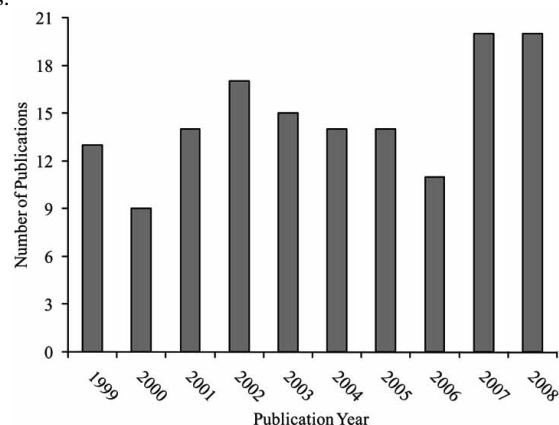


Fig. (1). Number of dose proportionality studies published between 1999 and 2008.

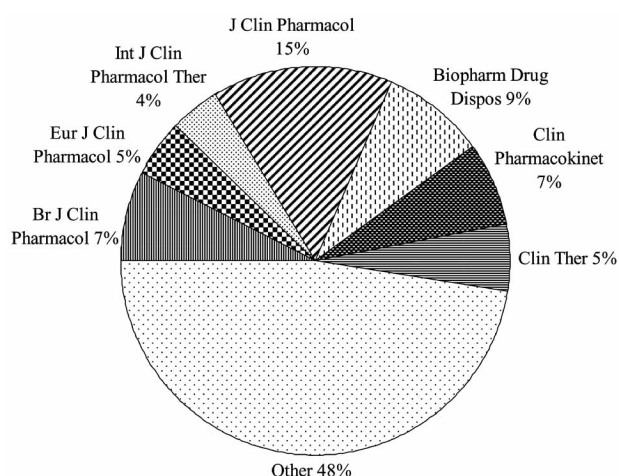


Fig. (2). Journals in which articles on dose proportionality ($n = 147$) were most frequently published; other: journals in which <4% of the papers were found.

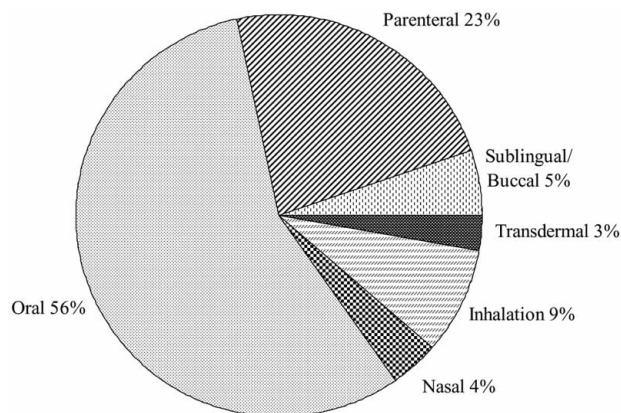


Fig. (3). The routes of administration in published dose proportionality studies ($n = 151$); four articles containing two administration routes were analyzed for each route.

Within 130 studies reporting randomization, a large majority (126 studies; 96.9%) had random allocation of participants. However, most of the included studies (117 studies; 75%) did not have a

control group. Thirty-two (21%) of the remaining 39 studies were placebo controlled. Some degree of blinding was present in 145 studies: 96 (61.5%) of the studies were open, 37 (23.7%) were double-blind, 9 (5.8%) were single-blind, and for 3 (1.9%) of the studies [29, 30, 76], the degree of blinding could not be grouped into the classes above.

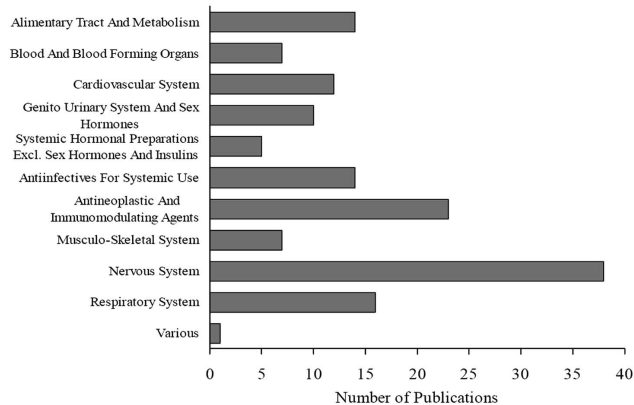


Fig. (4). Therapeutic areas of dose proportionality studies according to the WHO's ATC classification system (n = 147).

In Fig. (6), the results concerning dose range ratio and the number of dose levels were reported. The considerable variation in these two aspects of the study schemes was also shown within these studies. The dose range ratios were from 1.33-fold to 50-fold, and 57% were from 2-fold to 6-fold. The number of dose levels in each study varied from 2 to 11, and about 60% of the studies contained 3 or 4 levels.

Various designs were employed in the dose proportionality studies, so that it is difficult to categorize (Fig. 7). For the purpose of analysis, the studies were roughly divided into six groups as follows: (1) parallel single-dose design, (2) parallel multi-dose design, (3) alternating crossover design, (4) crossover and grouped crossover design, (5) parallel single- and multiple-dose design, and (6) idiosyncratic study design. All parallel designs included time-lagged study. Time-lagged study means that the drug was given in a lagged order, with dose progression to the next higher dose level being made only if the safety and tolerability of the preceding dose level were satisfactory [79]. According to this categorization, 82 (52.6%) of the studies were crossover design, and 6 (3.85%) were alternating crossover design. This finding indicates that a crossover experiment at several predetermined dose levels was the most commonly employed design in dose proportionality studies.

Because dose proportionality studies were commonly performed as part of phase I clinical trials, sample size estimation for most of these studies was dependent on practical considerations rather than power calculations. Only 28 studies stated that sample size calculations were based on statistics estimation.

Sampling and Pharmacokinetic Analysis

Except for four articles that did not report the time of blood sampling [13, 20, 147, 151], in single-dose studies blood samples were from 6 to 25 time points, with the median number 15 in each dose, while in multi-dose studies, the number of time points were from 1 to 29, with the median number 12 in each dose. The 94 studies that mentioned the related information showed significant differences in blood sample volume over a range of 0.5-20 ml (Fig. 8). Furthermore, blood sample volume was 4-8 ml in more than half of these studies.

Almost all dose proportionality studies use non-compartmental analysis to estimate relevant PK parameters. Only two studies [59, 148] used compartmental PK parameters to display dose propor-

tionality results. All included studies used AUC or/and Cmax as exposure PK parameters to evaluate dose proportionality. Urine collection was reported in 23 studies, but only one article [104] indicated that total-drug excretion over 24 h (Ae_{0-24}) was included in the PK parameters for the dose proportionality assessment. In one study [35], the pharmacokinetic parameters were determined using a population pharmacokinetic model; this study was still designated as a PK study rather than a population pharmacokinetics study by two independent reviewers and was also included in our study.

Statistical Evaluation

The methodology used for classifying the statistical approaches for assessing dose proportionality was referred to in the work of Hummel *et al.* [5]. Thus, the statistical analysis approaches used for the assessment of dose proportionality were as follows: (1) linear regression approach, (2) dose-adjusted PK parameter followed by hypothesis testing (parametric or non-parametric), (3) power model, (4) equivalence criterion, (5) others, (6) more than one approach and (7) no statistical testing or confidence intervals. If one study used equivalence criterion for assessment and the confidence interval was calculated by another of these approaches, this study was still recognized as using the equivalence criterion method.

Twenty-nine (19%) studies used more than one approach for dose proportionality assessment. A dose-adjusted PK parameter following hypothesis testing was applied in all of these studies; the other approaches in these studies included the linear regression approach (14), power model (12), and equivalence criterion (3). The dose-adjusted PK parameter followed by hypothesis testing was applied as the only method for evaluation in 38 (24%) of the studies and was therefore the most frequent methodology for dose proportionality assessment. A power model was employed in 25 (16%) of the studies (it was the unique approach in 13, and in 12, the equivalence criterion was based on the power model). Equivalence criterion was used in 31(20%) studies as the unique technique and in 3 studies as one of the evaluation methods. In 12 of these 34 studies, equivalence criterion was based upon a power model, and in the other 22 studies, it was based upon a dose-adjusted PK parameter followed by hypothesis testing. Other statistical methods (Mann-Whitney U test, Student's t test, etc.) were employed in 5 studies. The distribution of statistical analysis methodology for dose proportionality is presented in Fig. (9). Of note, about 15% (23) of the included studies did not report any statistical testing or confidence intervals.

Based on the methodology introduced above, 119 (76%) studies declared that the dose proportionality was met. In 37 studies that deviated from dose proportionality, 12 were greater than proportionality, 20 were less than proportionality, and 4 were inconclusive. One study [43] reported AUC was greater than proportionality while Cmax was less than proportionality. Nineteen of these non-proportional studies stated that dose proportionality over a certain dose range was observed.

DISCUSSION

The focus of new drug development in human is to determine an appropriate dose range in which the drug produces the desired therapeutic effect without undue toxicity, but it is impossible to observe the human response to all doses of investigated drugs. Once dose proportionality has been proven, it is easy to predict the pharmacokinetic response of the investigated drug in humans over a specific dose range, and then the dose can be adjusted accordingly to achieve the desired magnitude of effect.

Note that dose proportionality is different from dose linearity. The existence of dose proportionality implies dose linearity, but not vice versa. Dose proportionality requires dose linearity and means that a dose of zero leads to an AUC of zero. This is also the reason why this paper used the term "dose proportionality" rather than

Table 1. Therapeutic Catalogues According to the WHO Anatomical Therapeutic Chemical (ATC) Classification System

ATC Group	ATC Subgroup	Number of Studies
Alimentary Tract And Metabolism	Drugs For Acid Related Disorders	1
	Drugs For Functional Gastrointestinal Disorders	1
	Antiemetics And Antinauseants	2
	Bile And Liver Therapy	1
	Drugs Used In Diabetes	9
Blood And Blood Forming Organs	Antithrombotic Agents	3
	Antihemorrhagics	3
	Other Hematological Agents	1
Cardiovascular System	Cardiac Therapy	2
	Antihypertensives	1
	Vasoprotectives	1
	Calcium Channel Blockers	1
	Agents Acting On The Renin-Angiotensin System	2
	Lipid Modifying Agents	5
Genito Urinary System And Sex Hormones	Sex Hormones And Modulators Of The Genital System	6
	Urologicals	4
Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins	Pituitary And Hypothalamic Hormones And Analogues	5
Antiinfectives For Systemic Use	Antibacterials For Systemic Use	4
	Antimycotics For Systemic Use	3
	Antivirals For Systemic Use	6
	Immune Sera And Immunoglobulins	1
Antineoplastic And Immunomodulating Agents	Antineoplastic Agents	10
	Immunostimulants	1
	Immunosuppressants	12
Musculo-Skeletal System	Antiinflammatory And Antirheumatic Products	6
	Muscle Relaxants	1
Nervous System	Anesthetics	4
	Analgesics	14
	Antiepileptics	2
	Anti-Parkinson Drugs	2
	Psycholeptics	7
	Psychoanaleptics	5
	Other Nervous System Drugs	4
Respiratory System	Drugs For Obstructive Airway Diseases	15
	Antihistamines For Systemic Use	1
Various	All Other Non-Therapeutic Products	1

“dose linearity” to retrieve articles. Certainly, a publication bias might exist in selecting articles, but the 147 included articles describing 156 studies should still provide a useful overview of dose proportionality studies.

An early assessment of dose proportionality can help to guide the selection of doses for later trials and to determine the regimen for dosage adjustment. It is also useful to estimate the need for therapeutic concentration monitoring and the evaluation of the commercial viability of a new chemical entity [8]. Consequently, it

is imperative to explore dose proportionality as soon as possible in early clinical development, so that informed decisions can be made for long-term clinical studies. Some articles [8] proposed that dose-escalating phase I studies were ideal opportunities, and sometimes the only opportunity, for investigating dose proportionality because an extended dose range is investigated in phase I studies and the safety of the test subjects is closely monitored. Of the 147 studies included, 35 reported the stage of clinical development. Twenty-five studies were in phase I clinical trials, and 6 of them definitely declared that the study was first-time-in-humans. Because of low

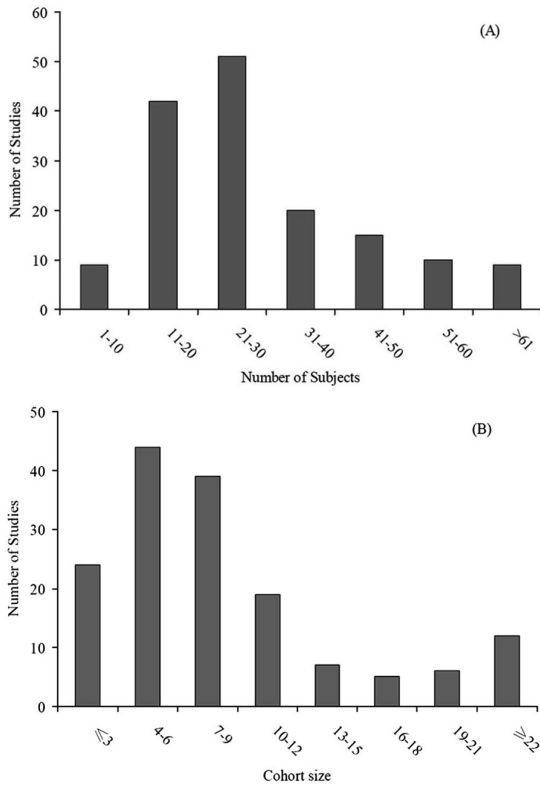


Fig. (5). Total number of subjects (A) and cohort size (B) in assessed studies. If cohort sizes in one study were not equal, the minimum cohort size was selected.

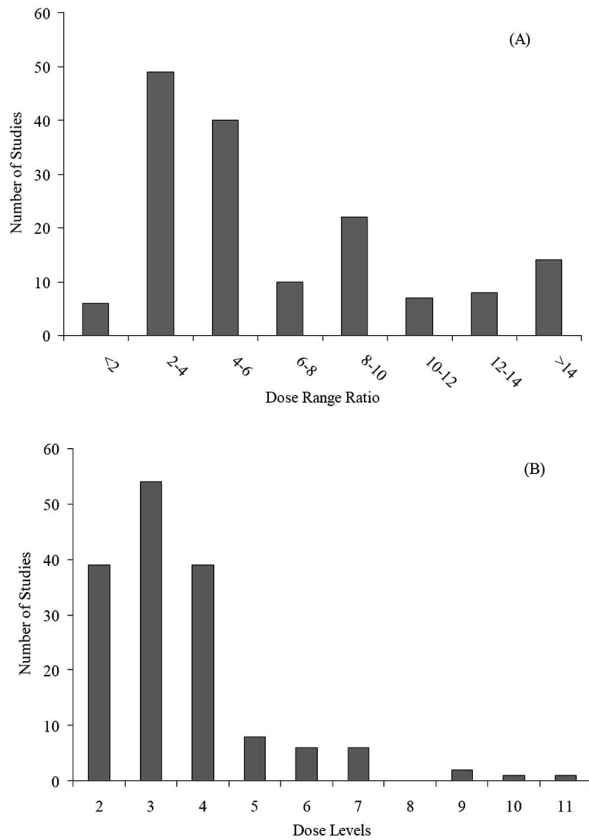


Fig. (6). Dose range ratio (A) and the number of dose levels (B) in dose proportionality studies.

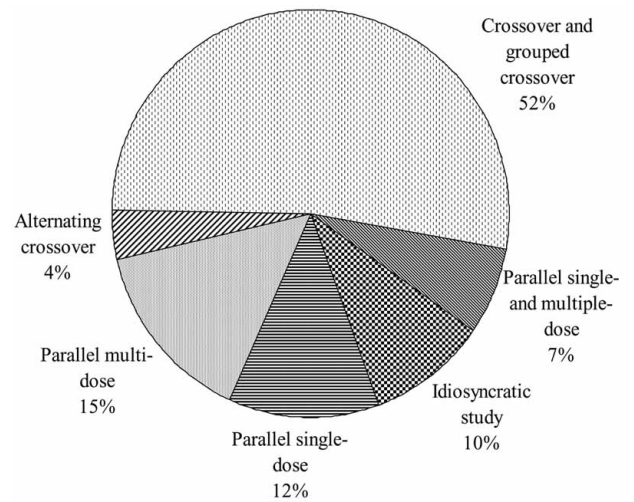


Fig. (7). Study design of dose proportionality studies.

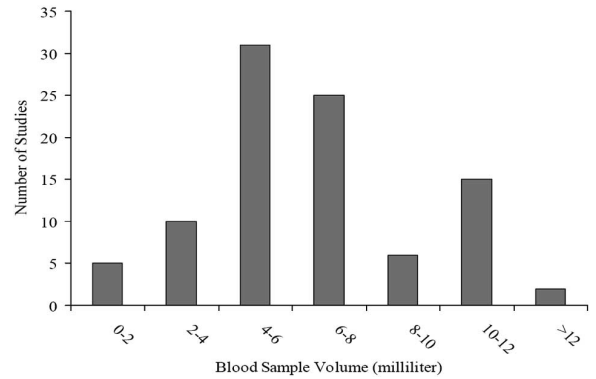


Fig. (8). Blood sample volume in dose proportionality studies.

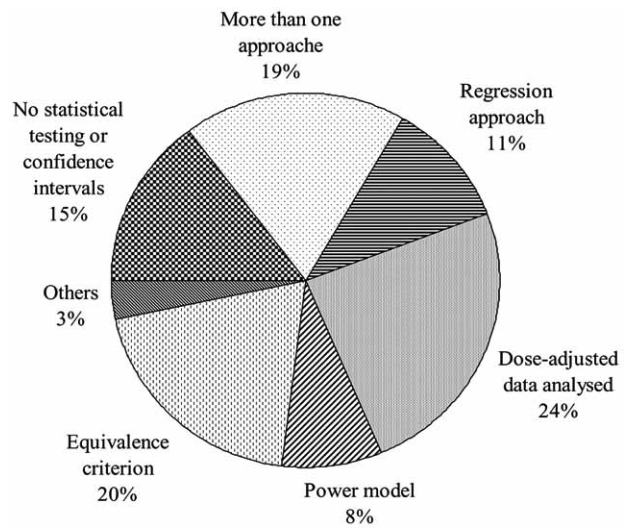


Fig. (9). Statistical approaches for dose proportionality assessment. In studies with more than one approach, the statistical approaches were composed of evaluating dose-adjusted PK parameters followed by hypothesis testing and other approaches (linear regression approach, 14; power model, 12; and equivalence criterion, 3).

power due to limited subject numbers treated at each dose level in early clinical studies, it was suggested that dose proportionality should be assessed at two different stages of the drug development process [157]. Dose proportionality could be approximately assessed from phase I studies and then confirmed in further clinical trials. In our analysis, only 10 studies were definitively reported to be in phase II or III. This might be caused by a lower publication rate for dose proportionality studies in late stage clinical trials (Phase IIb/III) because these trials are focused on efficacy and safety.

A variety of designs with varying reliability have been used to analyze dose proportionality. More than 50% of studies were performed using a crossover design; however, there were still remarkable differences within these studies. Some [14, 72, 75, 81] considered that the safety and tolerability of the higher dose and the lower dose might be afflicted by a potential carryover effect of the higher doses administered in the previous period; hence, the sequences of dose levels were designed in an escalating manner. Others [19, 93, 95, 115, 124] ignored the carryover effect or used a statistical method (a Latin squares or a balanced incomplete block design) to adjust for it such that the first dose in sequences of dose levels could be the higher dose. Within crossover design studies, a single study evaluating both single- and multiple-dose proportionality is very popular. A typical example is as follows: for each treatment period, the single doses were administered on study Day 1, followed by the same drug in multiple doses on Days 3–7. A washout period separated the last dose of the previous treatment period and the first dose of the next. This type of design was performed in 82 dose proportionality studies among the included studies. Alternative crossover design is more time efficient than other designs and requires fewer subjects without sacrificing safety concerns; thus, this design was recommended for investigating dose proportionality [8]. However, less than 5% of all included studies (6 studies) were undertaken using alternative crossover design. Because it allows for more information to be gathered using fewer subjects, thus saving time and money, dose proportionality studies should focus more on this design.

The distributions of the designs employed also varied depending on therapeutic areas (Fig. 10). Among two of the ATC groups ("Antiinfectives For Systemic Use" and "Antineoplastic And Immunomodulating Agents"), a crossover experiment was *not* the most frequent design for assessing dose proportionality. A small proportion of crossover design in these groups could be attributed

to the features of the investigated drug. As exemplified by antineoplastic and immunomodulating agents, the major objective of this kind of drug in early clinical study is to determine the maximum tolerance dose (MTD), and the studies are always performed in patients, so idiosyncratic design (3+3 design) is most frequently used.

Though many exploratory studies are included in this work, using 3 or fewer subjects per dose level, as occurred in 15% of the studies included, is still considered inadequate for investigating dose proportionality. For those studies in which cohort sizes were smaller than 6 active subjects, Buoem *et al.* [158] advised that there is much to gain in power with the inclusion of 1 extra subject. The weak correlation between the number of dose levels and dose range ratios was observed in our study (Fig. 11). Only two dose levels were investigated to assess dose proportionality in 25% of the studies. From a statistical perspective, treating half of the subjects at the lowest dose and half at the maximum tolerated dose is an efficient design [7]. However, the reliability of conclusions would be enhanced by collecting data from other levels because there may be a nonlinear pattern to the relationship between the PK parameters and dose levels. Practically, assessing the dose proportionality of a compound requires at least three doses.

Graphical representations of PK parameters versus dose level with statistical approaches are valuable in all assessments of proportionality. About one-third (49) of the studies used graphical plots to display dose proportionality. In these 49 studies, most of which were scatter plots of dose versus PK or dose versus dose-adjusted PK to show dose proportionality (Fig. 12). One study [145] represented a plot of mean dose-normalized plasma concentration versus time curves. The variation of the PK parameter (AUC and C_{max}) increases as the dose increases [159]. Therefore, displaying the PK parameter on a logarithmic scale, which was done in only two studies [128, 146], would be considered an appropriate plot for visual assessment of dose proportionality.

Several statistical methods for the assessment of dose proportionality were employed in these studies. Due to easy understanding and calculation, evaluating dose-adjusted PK parameters followed by hypothesis testing was the most frequent approach in dose proportionality studies. However, the method still has some disadvantages in that it treats the dose as a categorical variable, ignores the ordering of the doses and presents potential problems with multiple comparisons. According to the characteristics of dose proportionality, a linear regression approach is the simplest method for assess-

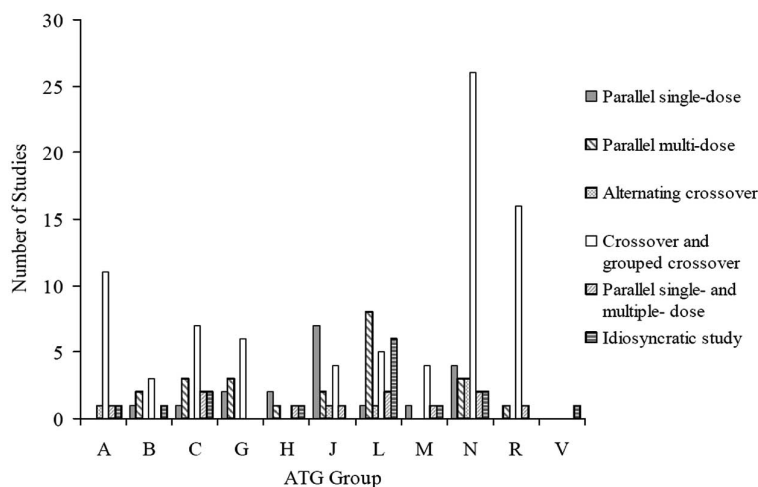


Fig. (10). The distributions of the designs employed within all therapeutic areas: (A) Alimentary Tract And Metabolism, (B) Blood And Blood Forming Organs, (C) Cardiovascular System, (G) Genito Urinary System And Sex Hormones, (H) Systemic Hormonal Preparations, Excl. Sex Hormones And Insulins, (J) Antiinfectives For Systemic Use, (L) Antineoplastic And Immunomodulating Agents, (M) Musculo-Skeletal System, (N) Nervous System, (R) Respiratory System, (V) Various.

ment. However, as the power of a linear regression approach is incapable of detecting departures from proportionality, this approach is a poor representation of the dose versus PK parameter relationship and should be avoided in dose proportionality study [3, 160].

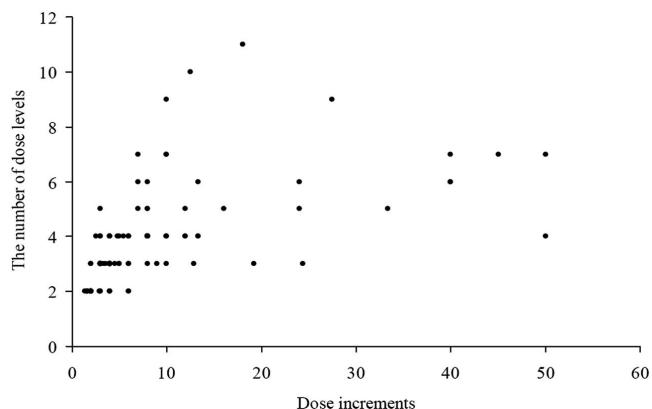


Fig. (11). The number of dose levels vs. dose range ratios.

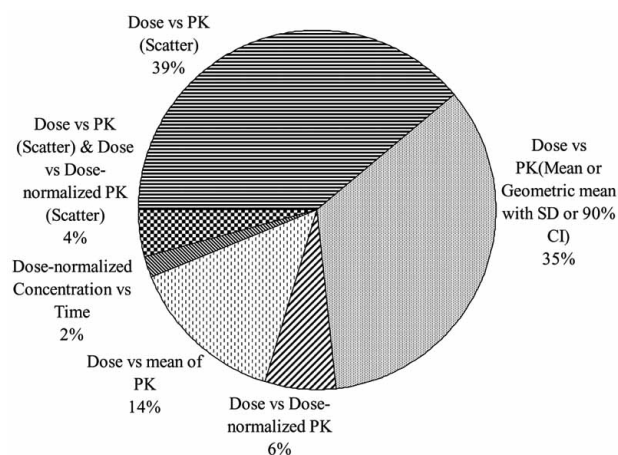


Fig. (12). Graphical representations for visual assessment of dose proportion

The power model has the ability to measure the degree of non-proportionality and associate confidence intervals and pre-specified critical regions for assessing proportionality. Because the standard deviation of a PK parameter (Y) often increases as the dose increases, the power model presents an appealing empirical relationship between the PK parameter (Y) and dose. The model can be described as: $Y = \alpha \cdot \text{dose}^\beta$. β equal to 1 implies perfect dose proportionality. α represents random subject effects, fixed period effects and errors. Then, the degree of nonproportionality can be measured by β together with its confidence interval. Compared with other statistical methods, more information can be obtained from the power model: an r^β -fold increase in AUC can be easily obtained when the dose is increased r -fold. The increase in dose for a given increase in AUC can be predicted by: $R = (Y_h/Y_l)^{1/\beta}$, where Y_h and Y_l correspond to the AUC for the highest dose and lowest dose, respectively. Therefore, the power model was recommended because it is well suited to detect nonproportional pharmacokinetic effects and to measure the departure from proportionality [3, 7]. However, this approach was used in 25 (16%) studies for dose proportionality assessment and should be applied more widely.

Gough *et al.* [3] reasoned that dose proportionality assessment is a problem of equivalence rather than hypothesis testing. When hypothesis tests were used, lack of dose proportionality could be

concluded by deciding against the null hypothesis and acceptance of the alternative hypothesis. However, failing to reject null hypotheses is not sufficient to announce dose proportionality. From a statistical viewpoint, however, the null hypothesis can never be proven. Hence, referring to the FDA guidance for testing average bioequivalence, Smith *et al.* [7] proposed proportionality assessment based on confidence intervals and equivalence regions. Then, dose proportionality is declared if the confidence interval for geometric means of a pharmacokinetic variable lies completely within the predefined acceptance interval.

A confidence interval criterion for the assessment of dose proportionality can be applied to many statistical models. When confidence interval criteria are coupled with a power model to define proportionality, the dose-proportional range is related to the dose ratio rather than to specific dose levels. In addition to assessing whether proportionality is attained, this approach also provides more valuable information. Once the equivalence criterion is specified, a maximal dose ratio can be calculated, below which proportionality is concluded, and a threshold ratio might also be calculated, above which nonproportionality is concluded. The values of these two ratios are occasionally larger or smaller than the ratio of the high to low dose in the actual dose range studied. Thus, the approach is not constrained to the exact dose levels studied and has the ability to support extrapolation beyond the studied dose range with caution.

With the advantages of the power model and equivalence criterion, a method combining the equivalence criterion and the power model enhances the information available from a dose proportionality study and was recommended in several articles [3, 7, 160]. Selecting the equivalence criterion is based upon safety, efficacy or drug registration considerations. The most common criterion was the interval of 0.8 to 1.25, which was suggested by the FDA and EMEA [161, 162] for the assessment of bioequivalence. Of the 156 included studies, 12 employed the equivalence criterion based on the power model to evaluate dose proportionality, and 11 used the standard limits of 0.80 to 1.25 as the acceptance interval. It should be noted that when the confidence interval comes from the power model, the equivalence criterion should be adjusted as following:

$$\text{Lower limit} = 1 + \ln(0.8)/\ln(r)$$

$$\text{Upper limit} = 1 + \ln(1.25)/\ln(r)$$

where \ln is the natural logarithm and r is the ratio of (highest dose)/(lowest dose).

Recently, this default equivalence criterion of 0.8 to 1.25 was questioned because it seems too strict in exploratory dose proportionality studies over the complete dose range, and a more lenient criterion of 0.5 to 2 has been proposed [5]. However, no study among all of the included studies adopted this criterion.

CONCLUSIONS

The dose proportionality study is very important in drug development, but its design and analysis are still very arbitrary. Based on the studies that we have examined, significant variations were seen in therapeutic areas, cohort sizes, number of dose levels, dose range ratios, total number of subjects and blood sampling; however, majorities of each criterion were within a certain range. Crossover design with some varieties was the most frequent design, and evaluating dose-adjusted pharmacokinetic parameters followed by hypothesis testing was the most common statistical approach in dose proportionality studies. For enhancing the information from a dose proportionality study using limited subjects, more focus should be given to the alternative crossover design and the power model statistical method. We hope that this work, which developed a profile of the manner in which studies were performed during the past decade, might serve as a point of discussion for debating the future direction of dose proportionality studies.

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