Biomedicine & Pharmacotherapy 163 (2023) 114823

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Design and statistics of pharmacokinetic drug-drug, herb-drug, and food-drug interaction studies in oncology patients

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ARTICLE INFO

Keywords:
Cross-over
Study design
Pharmacokinetics
Drug interaction
Oncology

ABSTRACT

Polypharmacy is becoming increasingly prevalent in society. Patients with polypharmacy are at greater risk for drug-drug interactions, which can influence the efficacy of treatment. Especially, in oncology this is a concern since neoplasms are increasing prevalent with age, as well as polypharmacy is. Besides drug-drug interactions, also herb-drug and food-drug interactions could be present. Knowledge of these interactions is of great importance for safe and effective anti-cancer treatment, because the therapeutic window of most of these oncologic drugs are small. To study pharmacokinetic interaction effects, a cross-over pharmacokinetic study is a widely used, efficient and scientifically robust design. Yet, several aspects need to be considered when carrying out an interaction study. This includes the knowledge of the advantages and disadvantages of a cross-over design. Furthermore, determination of the end point and research question of interest, calculation of the required sample size, analysis of the generated data with a robust statistical plan and consideration of the logtransformation for some pharmacokinetic parameters are important aspects to consider. Even though some guidelines exist regarding these key issues, no clear overview exists. In this article an overview of these aspects is provided and their effect is discussed.

1. Introduction

Polypharmacy is highly prevalent in daily clinical care and still increases every year. Worldwide, it is estimated that polypharmacy (defined as the use of 5 or more drugs) is present in 37% of patients [1]. Age is an important determinant for polypharmacy; in elderly patients (65 and over) polypharmacy is twice as prevalent (45%) as in patients younger than 65 years (25%) [1]. Since the prevalence of most malignancies increases with age, this is even more problematic in oncology [2]. Furthermore, cancer itself and various anticancer drugs cause symptoms and adverse reactions [3]. To treat these, multiple drugs are frequently prescribed and used simultaneously (*e.g.* anti-emetics, analgesics, steroids). Since most of the patients are treated with anticancer therapy, this could result in drug-drug interactions (DDI) [4]. In clinical practice, the intensity of cancer treatment (and subsequently therapeutic effect) is often limited by adverse events [5]. At least 20–30% of these adverse drug reactions are caused by DDIs [6] and one third of the oncologic patients are at risk for a DDI [7]. Apart from the limitation in the intensity of treatment, these DDIs are the cause of death in approximately 4% of cancer patients [8].

Besides DDIs, also herb-drug (HDIs) and food-drug interactions (FDIs) can influence treatment outcomes [9]. More than one third of the patients diagnosed with cancer uses food and herb supplements [10]. In most drug administration studies, high-fat meals are studied to compare bioavailability. However, also various food and herb supplements could influence absorption and metabolism of drugs. Therefore, post marketing interaction studies are important to discover drug interactions as this could optimize treatments and increase life expectancy.

Most interaction studies are performed with a cross-over design [11-13]. The advantage of this design is the robustness of the outcome,

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https://doi.org/10.1016/j.biopha.2023.114823
Received 1 March 2023; Received in revised form 27 April 2023; Accepted 30 April 2023
Available online 10 May 2023

since this is measured within the same patients under both mono- and combination therapy. A cross-over design requires limited sample sizes than parallel study designs (for this purpse) and is therefore more ethically justifiable from a perspective of no unnecessary harm. Although general guidelines exist for this type of study, several points need to be considered when designing such a study, including the statistical aspects of the trial [12,13]. A robust design and statistical analysis in any study is crucial, since the policy in health care is based on science. Therefore, an overview of statistical and methodological aspects for pharmacokinetic cross-over studies and their effects are provided in this article.

2. Pharmacokinetic parameters and log transformation

In cross-over pharmacokinetic interaction studies several pharmacokinetic (PK) parameters could be of interest. Usually, the total exposure (area under the curve; AUC), maximum concentration (C_{max}), time to maximum concentration (T_{max}), trough concentration (C_{trough}), clearance (CL), half-life ($T_{1/2}$) and volume of distribution (V_d), or a selection of these, are reported. Most of these parameters require dense sampling, but when this is not possible, fewer measurements can be taken and only C_{trough} or C_{max} could be reported.

In general, to analyze data of a cross-over study a logarithmic (log) transformation of the data is recommended [14]. There are several reasons for this. First, there is a clinical rationale. The FDA recommends to perform inferences on the ratio of the geometric means of several PK parameters. However, this is not straightforward when analyses are performed on the original scale. By using the logarithmic transformation, the difference between the two arithmetic means on the log scale can be studied. Then, the results (difference and confidence intervals) can be transformed back to the original scale by taking the exponent of the results on the log scale which then indicate inferences about the ratio of the geometric means on the original scale. Secondly, from a mathematical point of view, some of the PK parameters (*i.e.* AUC and C_{max}) implicate a multiplicative model [15]. Analyzing these parameters on the original scale would ignore this aspect, while it is taken into account when the log transformation is being used. Finally, non-compartmental PK parameters are often skewed [16], predominantly in the positive direction. To create a normal distribution of the data, which is a required condition for parametrical statistical tests, a transformation to the log scale is recommended [16].

3. Design

A cross-over study is a longitudinal study characterized by a 'within patient' comparison of treatments. In other words, each patient receives all studied treatments and the result of each treatment will be compared within the same patient (see Fig. 1). In comparison, in a parallel study design, each patient receives only one treatment and usually randomization is used to assign patients to one of the studied treatments. The main advantage of a within patient comparison is that this will (partially) eliminate potentially influencing factors which could alter the effect of a certain treatment, such as patient characteristics, genetics, and environmental factors. As environmental factors could change of over time and even between study periods of a cross-over trial, it may not be possible to fully eliminate their effects. However, elimination of these factors will lead to less variance in the outcomes and therefore a cross-over design requires fewer patients than a parallel design.

One of the influencing factors in DDI studies, especially in oncology, could be co-medication used by patients. Ideally, patients are upfront screened for known, or expected, interactions with co-medication, which are discontinued for the period of the trial if possible, since most DDI studies are relatively short . If co-medication cannot be interrupted (or certain interactions are not known yet), an advantage of the cross-over design, as already discussed, is the intra-patient comparison and therefore, the added effect of the co-medication is (partly) nullified in the overall effect.

Although a cross-over design has several advantages, there are some requirements for this design. Since patients undergo multiple treatments in consecutive periods in a cross-over study, the effects of those treatments have to be temporary. That is, the effects of an earlier treatment period should not influence the effects of the subsequent treatment period, *i.e.* there should be no carry-over effect. For instance, for studying the effect of a proton-pump inhibitor (PPI) in combination with targeted therapy a cross-over study may be a suitable design [17–20], since both agents have an elimination half-life of maximal a couple of hours up to a few days [21,22]. However, for interacting drugs with a relative long elimination half-life - such as for example amiodarone with a half-life of up to 142 days - a cross-over design is less suitable and a parallel design should be considered [14,23,12]. In addition, not all endpoints could be studied with a cross-over design. Only outcomes which can be observed relatively quick and outcomes which are reversible are suitable to study with this design, such as drugs concentrations or reversible side effects.

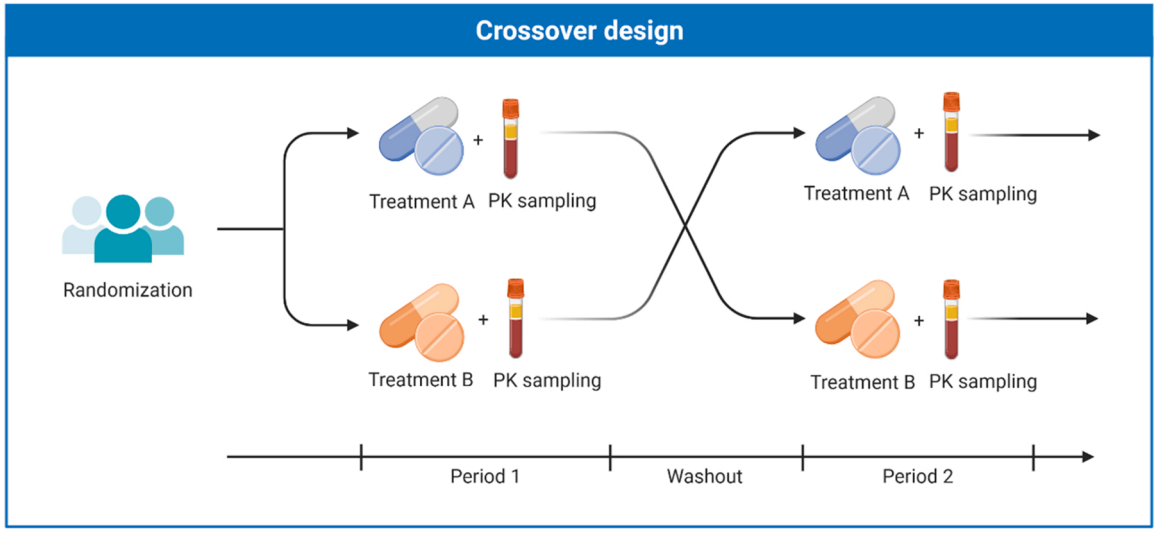

Fig. 1. A fictional two-period randomized pharmacokinetic cross-over trial. After allocation, patients are randomized to either of the two sequences A-B or B-A. In period one, patients will receive treatment A (monotherapy) and in period two, treatment B (combination therapy). Period one and two are separated by a washout period. In every period pharmacokinetics will be sampled. Abbreviations: PK = pharmacokinetics.

In every PK study, the length of sample time should be considered. Ideally, a relative wide range of 48–72 h could be considered to capture the absorption and elimination of most drugs. However, since every drug has its own PK properties (*e.g.* half-life of the drug), this range should be considered separately for every DDI study. Some drugs are administrated twice daily and thus sampling may be limited to a time of up to 12 h.

When FDIs are studied, a major challenge is to obtain a comparable food intake between patients. The investigated diets should therefore be as standardized as possible. Patients should be clearly instructed and guided thoroughly during the trial with for instance a dietary diary where all intake of food is documented. For example, this was done in the recent DIALECT study [24], where administration of alectinib (a novel targeted therapy for non-small cell lung cancer) with different diet types was studied in a cross-over setting.

Within a cross-over study it is preferred to randomize the sequence of treatments. Randomization minimizes confounding effects, *i.e.* unintended period, sequence, and carry-over effects. Although treatment periods are usually separated by a washout period, there is a risk that drug A influences the effect of drug B if the washout period between measurement points is not sufficiently long to clear out the effect of a concomitant drug (*e.g.* the interaction may prolong the elimination half-life). However, randomization is not always feasible for ethical or logistical reasons. For example, this was the case in a study where the exposure of the estrogen receptor antagonist tamoxifen was studied in combination with selective serotonin reuptake inhibitors (SSRIs) paroxetine and fluoxetine [25]. These SSRIs strongly inhibit the hepatic enzyme CYP2D6 that metabolizes tamoxifen into the clinically active endoxifen metabolite [26]. In this one-way cross-over PK study, endoxifen levels were investigated when patients switched from paroxetine or fluoxetine to an SSRI with a weak CYP2D6 inhibition. It was considered unethical to randomize between sequences, because all patients were already on paroxetine or fluoxetine at start of treatment; since these drugs lead to lower endoxifen levels than a 'weaker' SSRI and therefore less effect, this potentially increase the risk of (earlier) recurrence of breast cancer in these women [27]. Furthermore, it is known that switching between SSRIs results in a serious increased risk of depressive complaints with all possible consequences [28].

4. Superiority, non-inferiority and bioequivalence end points

Overall, most DDI studies are conducted to demonstrate, or to rule out, an interaction between drugs, food or herbs. Subsequently, the magnitude of the effect (and the associated clinical relevance) is evaluated. Usually, it is not explicitly mentioned whether the study will be evaluated in terms of superiority, non-inferiority or (bio)equivalence. In superiority studies the aim is to prove that there is a difference in the outcomes between treatments. For instance, Kletzl et al. [29] first demonstrated that when erlotinib was taken with a proton pump inhibitor (PPI) or H2-antagonist (to increase the pH in the stomach), the AUC of erlotinib decreased with 46–51%. Later, a proof-of-concept trial [20] was performed for patients with the need of a PPI during erlotinib treatment to improve the erlotinib availability. This was done by swallowing erlotinib together with a PPI and the acidic beverage cola during a period of time, and a period without cola. The AUC of erlotinib was compared after both time periods in these patients. This trial actually demonstrated a higher AUC, *i.e.* a superior effect (see A in Fig. 2), for the erlotinib + cola + PPI combination and is an example of a clinical study to improve PK.

As non-inferiority studies for investigating PK interactions are not common, the aim of these trials is to show that a combination of treatments or treatments with drugs or herbs, does not lead to lower PK levels as compared to monotherapy. To conclude non-inferiority, the lower boundary of the CI around the geometric mean ratio should not be lower than a pre-specified non-inferiority margin. This margin represents a pre-specified difference of PK between the investigated combination and the standard drug within which the effect of the investigated combination is considered not worse than the standard. As illustrated in G in Fig. 2, with margin 'δ'.

When an interaction between drugs has to be ruled out,

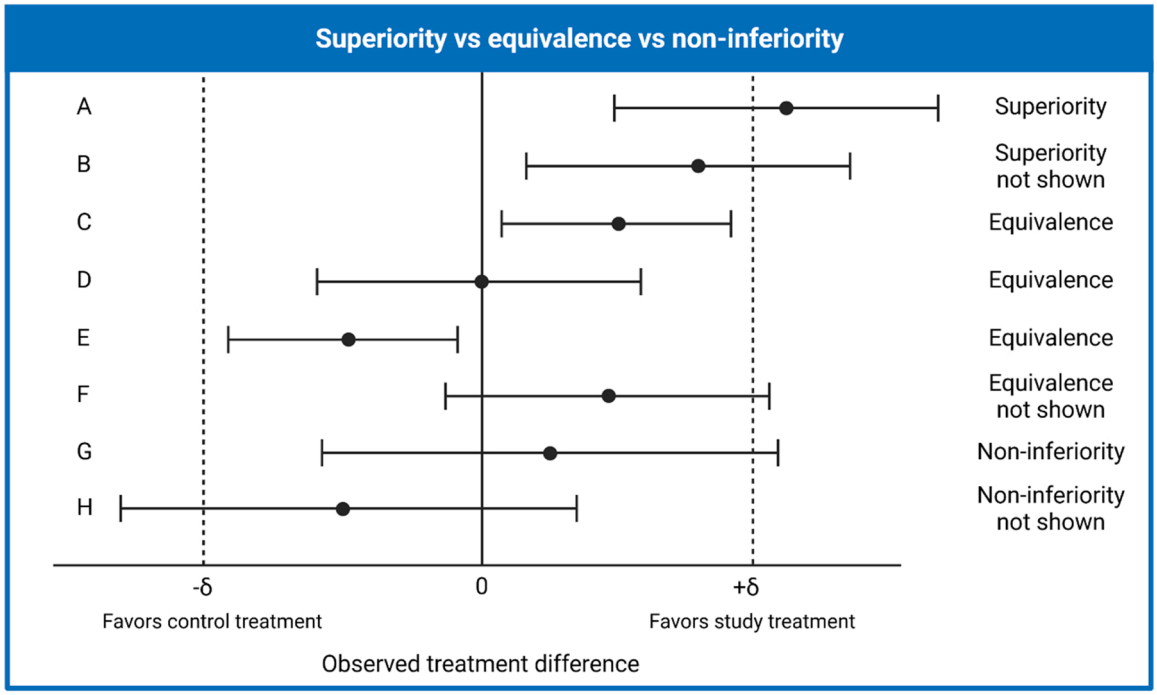

Fig. 2. Point estimates (dots) with clinical relevant margins (δ) of fictional trials indicating whether it is an superior, equivalence, or non-inferior effect. A: statistically significant and clinical relevant superior effect. B: statistically significant, but not a clinical relevant superior effect. C: statistically significant and equivalence shown. D: statistically not significant, but equivalence shown. E: statistically significant and equivalence shown. G: statistically no significant difference and non-inferiority shown. H: statistically no significant difference and non-inferiority not shown.

bioequivalence is studied. Equivalence means that the PK of a drug with monotherapy is equal to the PK when studied in combination. Therefore, the 90% CI of the geometric mean ratio should entirely fall within the pre-specified equivalence boundaries (usually 80–125%), as in C, D, or E in Fig. 2 [14,30]. This was for instance investigated in a study by Hussaarts, in which the combination of probenecid and sorafenib was studied [31].

5. Sample size calculation

Sample size calculations always rely on several key aspects of a trial: the design of the trial (*i.e.* randomization), type I and II errors (*i.e.* α and power), the type of comparison(*i.e.* superiority, non-inferiority or bioequivalence), the clinically minimal important difference to be detected and variance.

Typically, the power is set at either 80% or 90%, and indicates the chance to find a significant result if there is a true effect. Furthermore, in clinical studies α is usually set at 5%. However, it depends on the research question whether this is tested one- or two-sided. For superiority trials, two-sided testing is recommended, whereas non-inferiority is by definition a one-sided test (*i.e.* the interest is to know whether the effect is not inferior than the non-inferiority boundary).

For the minimal important difference, the research question is of relevance. In case of an equivalence trial, the 90% confidence interval (CI) around the geometric mean ratio should be between 0.80 and 1.25, and for non-inferiority the lower bound of the interval should be ≥ 0.80 [12,14]. In both cases, this translates into a relative difference of 20%. Hence, for a superiority trial the minimal important difference should generally be larger than 20%. This difference is considered to be clinically relevant by the FDA [12,14] and is used in several PK trials. Nevertheless, this difference is an arbitrary boundary and should not unquestioningly be adopted in every trial. Every drug has its own PK profile and its subsequent therapeutic window between optimal efficacy and tolerable toxicity. Finally, researchers and clinicians should argue whether an effect is, or is not, relevant to clinical care. The reason the geometric mean ratio of the CI is not symmetrical around 1 is inherent to the fact that it is a ratio. When the data are transformed to the log scale, the CI around the difference between the means will be symmetrical around zero. That is, if the CI boundaries are 0.80 and 1.25 around the geometric mean ratio, the CI around the difference on the log scale will be -0.223 and $+0.223$; see Fig. 3 for an illustration.

Since log-transformation is recommended when analyzing PK data, this should also be taken into account when calculating the required sample size. This means that if the minimal important difference is set at 20%, the (absolute) log of 0.80, *i.e.* $|\log(0.80)| = 0.223$, should be used in the sample size calculation (rather than 0.20).

The final required information for sample size calculations is the variance. Most frequently a measure of variance is available in the literature for the reference treatment (usually monotherapy of the compound of interest). Hereto, one can search for the coefficient of variation (CV) that is (often) reported along the geometric mean of the PK parameter of interest. The CV is usually expressed as a percentage. This can be used in the sample size calculation by dividing it by 100. Although the CV may not fully cover the within- and between-subject standard deviation needed for some of the calculators, it may be the best estimate to obtain from the literature as standard deviations are rarely reported.

In case of a one-way cross-over design, the sample size can be calculated based on the formula for a paired t-test. However, in case of a randomized cross-over trial, one should take accompanying aspects into account since the eventual analyses will take these aspects into account as well (*i.e.* period and sequence effects). The sample size for a common cross-over design can be calculated in most software packages. However, currently, also various online tools are available to calculate a valid sample size in cross-over trails, such as the tool developed by Schoenfeld, Harvard University (Cambridge, MA) [32].

According to the FDA and EMA, a minimum sample size of 12 patients is required when performing a bioequivalence study [14,30] though the actual required number of patients will depend on all factors mentioned above. In the previous discussed examples, sample sizes between 10 and 29 were used, although trials with fewer than ten patients have also been published (see Table 1). For example, this was the case in a study investigating the effect of St. John's wort, a frequently used herbal with antidepressant activity, on irinotecan chemotherapy PK

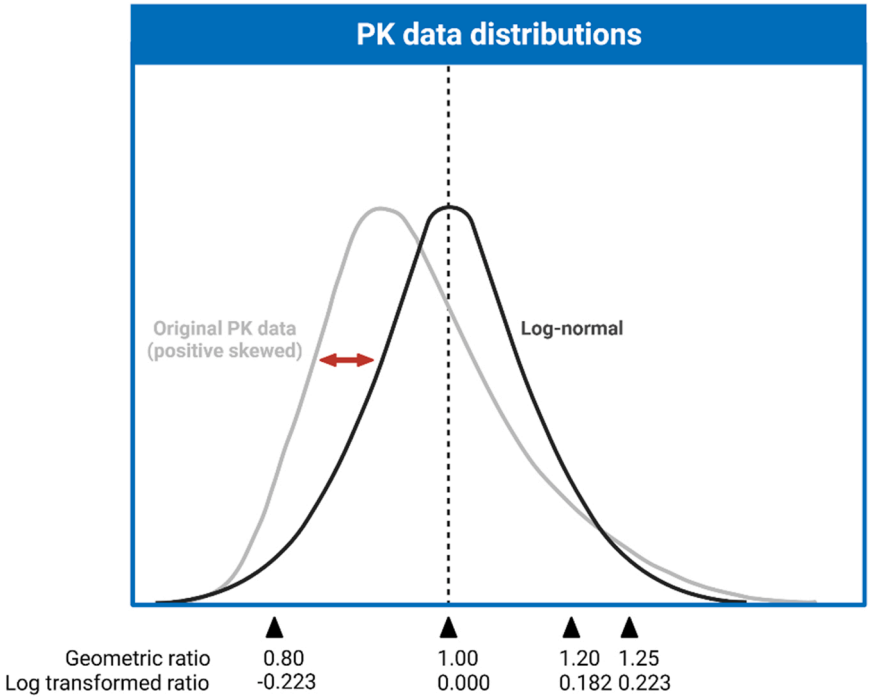

Fig. 3. Distributions of pharmacokinetic data; original and log-normal transformed. Provided with the geometric mean ratios and the log-transformed ratios. Abbreviations: PK = pharmacokinetics.

Table 1
Overview of the discussed PK studies in this paper with the reference, objective, suggested mechanism of interaction and details regarding design and statistics. Abbreviations: PK = pharmacokinetics, BE = BioEquivalence, S = Superiority, LMM = Linear Mixed Modelling, NA = Not Available, CYP = Cytochrome-P450, SSRI =Selective Serotonin Reuptake Inhibitor, OAT6 = Organic Anion Transporter 6.

Article	Study objective (s)	Suggested mechanism	No. of comparisons	Required no. of patients	Evaluable no. of patients	Statistical method	BE/S design	Randomized?
Van der Bol[15]	Effect of omeprazole on the PK and toxicity of irinotecan.	pH-dependent solubility	1	14	14	Paired t-test	NA	Yes
Van Doorn[16]	Effect of esomeprazole on the PK and toxicity of capecitabine.	pH-dependent solubility	2	22	22	LMM	BE	Yes
Veerman[17]	Effect of esomeprazole and milk on the PK of erlotinib.	pH/fat-dependent solubility	3	28	29	LMM	S	Yes
Van Leeuwen[18]	Effect of cola, with or without esomeprazole, on the PK of erlotinib.	pH-dependent solubility	2	28	28	LMM	S	Yes
Lanser[22]	The influence of food with different fat concentrations on alectinib exposure: a randomized cross-over pharmacokinetic trial.	Fat-dependent solubility	3	20	20	LMM	S	Yes
Binkhorst[23]	Effect of a strong *vs* weak CYP2D6 inhibiting SSRI to the PK of endoxifen.	Inhibiting CYP2D6 metabolism	1	13	10	Wilcoxon signed rank test	NA	No
Stearns[24]	Effect of paroxetine (SSRI) on the PK of tamoxifen and metabolites.	Inhibiting CYP2D6 metabolism	1	NA	12	Paired t-test	NA	No
Hussaarts[28]	Effect of probenecid on the PK of sorafenib.	OAT6 inhibition	1	16	16	Paired t-test	BE	No
Mathijssen[31]	Effects of St. John's wort on irinotecan PK.	Inducing CYP3A4 metabolism	1	NA	5	Student's t-test	NA	Yes

[33]. In this study with only five patients, a deleterious effect on the plasma irinotecan PK was demonstrated, indicating a clinical relevant interaction. Consequently, St. John's wort is nowadays discouraged to use in combination with CYP3A4 metabolized chemotherapies.

6. Statistical analysis

Most of the PK parameters are continuous variables, with the exception of time to maximum concentration (T_{max}). The FDA suggests that both arithmetic means (with standard deviations of CVs) and geometric means should be reported per treatment for the continuous PK parameters, while for T_{max} the median and interquartile range (or first and third quartile) should be reported. Furthermore, the main interest is in the geometric mean ratio together with a confidence interval, where the ratio should be T over R, *i.e.* the geometric mean of the test treatment (usually the combination) over the one of the reference (usually monotherapy of the compound of interest).

Analyses of the continuous PK parameters can be performed by the paired t-test in case of a one-way cross-over design. However, in case of a randomized cross-over design the sequence and period effects need to be taken into account. Hereto, general linear model procedures such as analysis of variance (ANOVA) or linear mixed effects models can be used. The model usually includes the factors sequence, subjects nested in sequences, period, and treatment. In case of a linear mixed effect model treatment, sequence, and period are included as fixed effects and subject within sequence as a random effect [34]. In order to account for the often limited number of patients, it is advised to estimate variance components based on restricted maximum likelihood (REML) methods, and to use the Kenward-Roger method of computing the denominator degrees of freedom [34].

The results for the treatment effect obtained from any of these analyses can be translated back to the original scale by taking the exponent of the difference and CI bounds in order to obtain the geometric mean ratio and the corresponding CI. For equivalence and non-inferiority studies, the 90% CI should be used, whereas the 95% CI is commonly used for superiority studies.

The analysis of T_{max} can be performed by means of the Wilcoxon signed rank test, since the T_{max} is a categorical ordinal variable due to the unequally spaced time points between sample withdrawal.

7. Conclusions

PK studies evaluating potential interactions with drugs are important, particularly in oncology where polypharmacy is common and supplements are popular. A cross-over study is a comprehensive and efficient design to evaluate potential pharmacological relevant interactions. However, some important considerations like reporting important PK parameters, determining the end point of interest and statistical plan have to be taken into account when considering the design, sample size, and data analysis of such trials.

Ethics approval

For this literature study, no ethics approval was requested since no patients participated in this study.

Consent to participate

Not applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

DACL: Conceptualization; Literature Search; Investigation; Visualization; Writing – original draft. **MBAvdK:** Investigation; Writing – review & editing. **GDMV:** Supervision; Writing – review & editing. **NS:** Supervision; Writing – review & editing. **ADRH:** Supervision; Writing – review & editing. **RHJM:** Conceptualization; Literature Search; Investigation; Supervision; Writing – original draft/review & editing. **EOdH:** Conceptualization; Literature Search; Investigation; Supervision; Writing – original draft/review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare. All co-authors

have seen and agree with the contents of the manuscript and there is no financial interest to report.

Data availability

Not applicable.

References

[1] M. Delara, L. Murray, B. Jafari, A. Bahji, Z. Goodarzi, J. Kirkham, et al., Prevalence and factors associated with polypharmacy: a systematic review and Meta-analysis, BMC Geriatr. 22 (1) (2022) 601.

[2] Cancer incidence by age: Cancer Research UK; [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero.

[3] F. Batalini, M. Gomes, I.F. Kuwae, F. Macanhan, G. Pereira, JLB. Cancer complaints: the profile of patients from the emergency department of a Brazilian oncology teaching hospital, *F1000Res.* 6 (2017) 1919.

[4] R.W.F. van Leeuwen, F.G.A. Jansman, P. van den Bemt, F. de Man, F. Piran, I. Vincenten, et al., Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions, Ann. Oncol. 26 (5) (2015) 992–997.

[5] J. Chang, Chemotherapy dose reduction and delay in clinical practice. evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer, Eur. J. Cancer 36 (Suppl 1) (2000) S11–S14.

[6] G.I. Köhler, S.M. Bode-Böger, R. Busse, M. Hoopmann, T. Welte, R.H. Böger, Drug-drug interactions in medical patients: effects of in-hospital treatment and relation to multiple drug use, Int J. Clin. Pharm. Ther. 38 (11) (2000) 504–513.

[7] R. Riechelmann, D. Girardi, Drug interactions in cancer patients: A hidden risk? J. Res Pharm. Pr. 5 (2) (2016) 77–78.

[8] I. Buajordet, J. Ebbesen, J. Erikssen, O. Brørs, T. Hilberg, Fatal adverse drug events: the paradox of drug treatment, J. Intern Med 250 (4) (2001) 327–341.

[9] G.D.M. Veerman, K. Hussaarts, F.G.A. Jansman, S.W.L. Koolen, R.W.F. van Leeuwen, R.H.J. Mathijssen, Clinical implications of food-drug interactions with small-molecule kinase inhibitors, Lancet Oncol. 21 (5) (2020) e265–e279.

[10] M. Bahall, Prevalence, patterns, and perceived value of complementary and alternative medicine among cancer patients: a cross-sectional, descriptive study, BMC Complement Alter. Med 17 (1) (2017) 345.

[11] B. Sibbald, C. Roberts, Understanding controlled trials, Cross Trials *Bmj.* 316 (7146) (1998) 1719.

[12] M12 Drug Interaction Studies, Food and Drug Administration (FDA), 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m12-drug-interaction-studies.

[13] Investigation of drug interactions - Scientific guideline, European Medicines Agency (EMA), 2012. [Available from: https://www.ema.europa.eu/en/investigation-drug-interactions-scientific-guideline.

[14] Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, Food and Drug Administration (FDA), 2002. [Available from: https://www.fda.gov/files/drugs/published/Guidance-for-Industry-Bioavailability-and-Bioequivalence-Studies-for-Orally-Administered-Drug-Products—General-Considerations.PDF.

[15] Statistical Approaches to Establishing Bioequivalence. Food and Drug Administration (FDA), 2001. [Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-approaches-establishing-bioequivalence.

[16] L.F. Lacey, O.N. Keene, J.F. Pritchard, A. Bye, Common noncompartmental pharmacokinetic variables: are they normally or log-normally distributed? J. Biopharm. Stat. 7 (1) (1997) 171–178.

[17] J.M. van der Bol, W.J. Loos, F.A. de Jong, E. van Meerten, I.R. Konings, M.H. Lam, et al., Effect of omeprazole on the pharmacokinetics and toxicities of irinotecan in cancer patients: a prospective cross-over drug-drug interaction study, Eur. J. Cancer 47 (6) (2011) 831–838.

[18] L. van Doorn, N. Heersche, F.M. de Man, P. de Bruijn, I. Bijl, E. Oomen-de Hoop, et al., Effect of the Proton Pump Inhibitor Esomeprazole on the Systemic Exposure of Capecitabine: Results of A Randomized Crossover Trial, Clin. Pharm. Ther. 111 (2) (2022) 455–460.

[19] G.D.M. Veerman, K. Hussaarts, R. Peric, E. Oomen-de Hoop, K.D. Landa, C.H. van der Leest, et al., Influence of Cow's milk and esomeprazole on the absorption of erlotinib: a randomized, crossover pharmacokinetic study in lung cancer patients, Clin. Pharm. 60 (1) (2021) 69–77.

[20] R.W. van Leeuwen, R. Peric, K.G. Hussaarts, E. Kienhuis, P. de Bruijn, N. S. IJzerman, Influence of the acidic beverage cola on the absorption of erlotinib in patients with non-small-cell lung cancer, J. Clin. Oncol. 34 (12) (2016) 1309–1314.

[21] N. Eckstein, L. Röper, B. Haas, H. Potthast, U. Hermes, C. Unkrig, et al., Clinical pharmacology of tyrosine kinase inhibitors becoming generic drugs: the regulatory perspective, J. Exp. Clin. Cancer Res 33 (1) (2014) 15.

[22] K.M. Fock, T.L. Ang, L.C. Bee, E.J. Lee, Proton pump inhibitors: do differences in pharmacokinetics translate into differences in clinical outcomes? Clin. Pharm. 47 (1) (2008) 1–6.

[23] P. Vassallo, R.G. Trohman, Prescribing amiodarone: an evidence-based review of clinical indications, *Jama* 298 (11) (2007) 1312–1322.

[24] D.A.C. Lanser, S.P. de Leeuw, E. Oomen-de Hoop, P. de Bruijn, M.S. Paats, D.W. Dumoulin, et al., The influence of food with different fat concentrations on alectinib exposure: a randomized cross-over pharmacokinetic trial, J. Natl. Compr. Canc Netw. (2023), https://doi.org/10.6004/jnccn.2023.7017.

[25] L. Binkhorst, M. Bannink, P. de Bruijn, J. Ruit, H. Droogendijk, R.J. van Alphen, et al., Augmentation of Endoxifen Exposure in Tamoxifen-Treated Women Following SSRI Switch, Clin. Pharm. 55 (2) (2016) 249–255.

[26] V. Stearns, M.D. Johnson, J.M. Rae, A. Morocho, A. Novielli, P. Bhargava, et al., Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine, J. Natl. Cancer Inst. 95 (23) (2003) 1758–1764.

[27] L. Madlensky, L. Natarajan, S. Tchu, M. Pu, J. Mortimer, S.W. Flatt, et al., Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes, Clin. Pharm. Ther. 89 (5) (2011) 718–725.

[28] N. Keks, J. Hope, S. Keogh, Switching and stopping antidepressants, Aust. Prescr. 39 (3) (2016) 76–83.

[29] H. Kletzl, M. Giraudon, P.S. Ducray, M. Abt, M. Hamilton, B.L. Lum, Effect of gastric pH on erlotinib pharmacokinetics in healthy individuals: omeprazole and ranitidine, Anticancer Drugs 26 (5) (2015) 565–572.

[30] Guideline on the investigation of bioequivalence. European Medicines Agency (EMA), 2010. [Available from: https://www.ema.europa.eu/en/investigation-bioequivalence-scientific-guideline.

[31] K. Hussaarts, L. van Doorn, K. Eechoute, J. Damman, Q. Fu, N. van Doorn, et al., Influence of Probenecid on the Pharmacokinetics and Pharmacodynamics of Sorafenib, Pharmaceutics 12 (9) (2020) 788.

[32] Schoenfeld D. Statistical considerations for a cross-over study where the outcome is a measurement: MGH Biostatistics Center, Havard; 2015 [Available from: http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html.

[33] R.H. Mathijssen, J. Verweij, P. de Bruijn, W.J. Loos, A. Sparreboom, Effects of St. John's wort on irinotecan metabolism, J. Natl. Cancer Inst. 94 (16) (2002) 1247–1249.

[34] B. Jones, M.G. Kenward. Design and Analysis of Cross-Over Trials, Chapman & Hall/CRC monographs, 2003.