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CONFERENCE REPORT

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Practical experience and issues in designing and performing population pharmacokinetic/pharmacodynamic studies

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Abstract An expert meeting to discuss issues relating to the design of population pharmacokinetic/pharmacodynamic (PK/PD) studies was held in Brussels in March 1995, under the auspices of the European Co-operation in Science and Technology (COST), Medicine (B1) programme. The purpose of the meeting was to discuss the experts' experience in designing and performing population PK/PD studies. The topics discussed were current practice, logistical issues, ensuring the accuracy of data, covariate assessment, communication, and protocol design.

The main conclusions from the meeting were: 1) a population PK/PD analysis should be one of the objectives of a clinical trial and should not compromise the other objectives; 2) it is particularly important to communicate the purpose of the population PK/PD analysis to the investigators and to convince them of the importance of accurately recording dosing and sampling times; 3) some prior knowledge of the PK and PD models and covariate relationships is necessary for the analysis of sparse phase III data; 4) computer simulation and optimal design measures may be useful in defining sampling times; 5) population methods and objectives must be specified as completely as possible in the protocol.

Key words Population pharmacokinetics, Pharmacodynamics; experimental design, drug development, clinical trials

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The views expressed by the participants do not necessarily reflect those of the organizations they represent.

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An expert meeting to discuss issues relating to experimental design in population pharmacokinetic/pharmacodynamic (PK/PD) studies was held in Brussels in March 1995, under the auspices of the European Co-operation in Science and Technology (COST), Medicine (B1) programme. The meeting was the second meeting organized by the COST-B1 working party on population approaches, the previous one being concerned with population PK/PD software [1]. The purpose of the second meeting was to discuss current experience in the design and performance of population PK/PD studies. We were especially interested in information and ideas that would not normally be published. A questionnaire was devised and circulated to the experts before the meeting and the meeting evolved from the responses to that questionnaire. Because the topic of design with all its ramifications is so diverse, it was not possible to produce a consensus document, as was done with PK/PD software [1]. The main reason for the lack of consensus in some areas was lack of experience rather than

divergent opinions. Nevertheless, we report here a summary of the meeting together with general recommendations. Discussion focused on the following topics: current practice, logistical issues, ensuring the accuracy of data, covariate assessment, communication, and protocol design.

Current practice

The population approach has frequently been implemented in phase II and III studies to obtain additional information about the PK/PD model in a representative sample of patients. However, it was generally recognized that the primary purpose of phase III clinical trials was not PK/PD, and that any attempt to interfere grossly with the design of such studies would meet, justifiably, with great resistance from clinical development teams. Consequently, population PK/PD studies must be carefully interwoven with existing protocols and every effort made to convince clinical investigators of their relevance. Three areas in which population PK/PD might be useful were identified: the estimation of covariate effects, the design of *a priori* dosing regimens, and the exploration of concentration/effect relationships. In the latter context, pharmacodynamics was taken to mean any measurable effect produced following drug administration, including efficacy and safety endpoints. In addition it was recognized that when only sparse data are available, for example in studies on neonates, the population approach represents the only way to define the PK/PD model of the drug. To date, population PK/PD has been used with drugs indicated in a wide variety of therapeutic areas, including cardiovascular and CNS disorders, rheumatoid arthritis, cancer, migraine, Alzheimer's disease, allergy, infection, and asthma; using single-dose treatment and multiple dosage regimens; and various routes of administration, including intravenous, oral, and subcutaneous.

It was generally acknowledged that the structural model used for population PK/PD analysis of sparse phase III data may well be less complicated (for example, one-compartment as against two-compartment) than that used for the analysis of phase I and II (rich) data. Therefore some prior knowledge of the PK and PD models and covariate relationships (where available) was deemed necessary for the analysis of sparse phase III data. No consensus was reached on whether to mix 'data-rich' phase I and II studies with 'data-poor' phase III studies. However, data-rich phase I and II studies are the basis for the analysis of phase III studies. It was agreed that this was an area for further investigation.

The questions of the numbers of subjects, the number of measurements per subject, and the timing of the measurements were extensively discussed. No generally valid rules are available for the number of subjects necessary for a population PK/PD analysis, since this will depend on interindividual variability, the number of clinically relevant covariates, and the nature of the PD response. In addition, the study population needs to be representative of the target population. However, in general, the choice of the number and nature of the subjects in a phase III clinical trial is made in relation to the primary goal of the study, which is usually concerned with the demonstration of efficacy and assessment of safety. Computer simulation and optimal design measures (regression) have been used to plan the timing of measurements, and the idea of a sampling window (that is, a range of times rather than a particular time) has been widely used, as it helps to structure the sampling process and ensure that an adequate description of the PK/PD profile is obtained. The use of random sampling was also advocated, particularly as it 'robustified' the design. A figure of 3 samples per patient, one of which would inevitably be at the trough, was generally agreed to be reasonable from the point of view of logistics and information content. Of course, data from subjects with only one or two measurements would not be discarded *a priori*. In long-term studies, measurements are often made on different days, even though they were often analysed as if taken within the same dosing interval. However, the failure to recognize inter-occasion variability or systematic changes in PK/PD parameters could severely bias the estimation of interindividual variability. Nevertheless it was felt important to collect samples early in a study, as well as later, to allow for the detection of changes in PK/PD parameters over the course of the study.

The main purpose of the meeting was to discuss design issues in clinical drug development. However, several participants stressed the potential relevance of the population approach to pre-clinical drug development, particularly toxicokinetic studies.

Logistical issues and ensuring the accuracy of the data

Many anecdotal disasters were described by the experts, such as the failure to record dosing and sampling times and the loss of samples in transit. Logistical problems, which could be solved with more efficient management, arose at the level of sample handling and of data management. It is paramount for good compliance of both the patient and the investigator that the protocol should not be overcomplicated. Patients do not like excessively invasive procedures and the sample schedule should be made as convenient as possible. Furthermore, the necessity of the sampling, should be explained to the patient. The need for increased or better communication, with respect to the purpose of the study, between the PK/PD staff or the development team and the attending physician, as well as between the attending physician and the patient, was clearly stressed by several participants.

Clear instructions should be provided for the investigator, backed up by adequate monitoring. Labels

should not be ambiguous, and instructions for handling the samples should be explicit. If necessary, handling should be performed by a third party. Adequate resources must be made available for ensuring optimal sample preparation and storage at the investigator site, transport, and pre-analytical storage of biological samples. Some concern was expressed about the use of PD measures based on subjective observer assessment. Objective assessment was preferred; if necessary, subjective assessment should be performed by the minimum number of observers. The problem of recording PK and PD information in different databases was discussed. Ideally it should be possible to merge these two databases electronically. In addition it is necessary to be able to conveniently extract the required data for input to population software packages. The problem of unblinding before the end of the study to perform the PK/PD analysis was seen as surmountable.

Compliance was a major concern. Special care needs to be taken to use methods that are as objective as possible to reconstruct dosing history. Electronic monitoring devices, patient diaries, tablet counts can all be used to monitor compliance. Several companies use nurses or clinical research associates to visit patients to ensure compliance. One company suggested that patients could be contacted by telephone to remind them to take their medication. Everyone felt that the additional costs in these measures were not a significant obstacle to their implementation. Investigator motivation was also seen to be crucial in improving certain aspects of compliance.

Sample timing and dosing history is fundamental to PK/PD analysis. Therefore, special attention should be paid to the design of case record forms (CRF) and adequate space should be allowed for the recording of the times of specific events, such as drug intake, blood sampling, measurement of effect, and the occurrence of adverse effects. Some experts advocated the use of a separate CRF specifically for the purpose of recording of timings in population PK/PD studies.

Covariate assessment

Covariates which are likely to influence PK/PD parameters include demographic variables, laboratory values, co-medications, environmental factors, and disease states. The size of study necessary to detect important covariate effects was extensively discussed. Although a figure of 20 subjects per covariate was proposed, this figure will obviously depend on the variability and magnitude of the parameter-covariate relationship and on confounding between covariates. It was also thought important to distinguish between clinically relevant, that is having an impact on labelling, and statistically significant covariate effects. The consensus was that potentially important covariates, based on a careful examination of all data, should be defined in the protocol. Therefore, some degree of stratification of the experimental design into subgroups was thought to be desirable. The alternative of *ad hoc* subgroup analysis is liable to create false positives, and should be avoided if possible. However it was recognized that, because of safety issues, certain covariate relationships, for example severe renal or hepatic impairment, may have to be investigated in a separate well-defined subpopulation.

The recording of covariate information should be subject to quality control. Care needs to be taken in the design of CRFs and data entry should be closely monitored. Transfer of such data to electronic databases needs to be validated. Where laboratory measurements are required, centralized laboratories should be used, as far as possible. All necessary methods should be described fully in the protocol. Missing data and covariates that change over time represent particular problems. Although every effort should be made to ensure complete collection of covariate information, such as collecting this information at times when other data are collected, it was acknowledged that typically covariate information will be incomplete. If covariate measurements change over time, several measurements will need to be made during the course of the trial, and if this information is incomplete model-based techniques may be used for interpolation. If a covariate needs to be calculated from raw data, for example creatinine clearance from serum creatinine, then an adequate description of the calculation and how to handle missing data should also be described in the protocol.

Co-medication presents a particular challenge, owing to the heterogeneity in the medications that a patient is likely to receive, although some pre-assignment may be possible. Therefore, it will be very difficult to identify individual drug-drug interactions. Co-medications could be grouped according to therapeutic class or to pharmacokinetic behaviour, such as induction, inhibition, or binding to plasma albumin. It was felt that much of the information on likely drug-drug interactions should be known from pre-clinical and *in vitro* studies.

The problems associated with multicentre studies were also discussed. Differences between centres can arise because of differences in study populations, observers, sample handling, and data handling. Although centre as a covariate was thought to be pointless for predictive purposes, it was generally agreed that failure to take it into account could result in confounding between centre and treatment effects. There was no consensus on how data arising from several centres should be analysed: that is how such data should be combined. This is an important area for future research.

Communication

Any activity in drug development needs communication and education. One of the major problems with

population PK/PD studies is that the members of the development team do not necessarily fully understand the importance of modelling and are worried that additional protocol requirements may jeopardize the major objectives of the trial. In addition, senior management needs to appreciate and be convinced of the cost/benefit ratio of the population PK/PD component of the study.

One reason for difficulty in communication is that people involved in the process of application of the population approach in clinical trials have very different backgrounds, for example medicine, statistics, analytical chemistry. To promote the population approach within a pharmaceutical company one has to present the advantages and potential of this approach to people responsible for clinical trials. Management is likely to be convinced of the approach when it can be shown that the approach can produce useful results for registration or when classical studies are not possible, such as in studies of neonates. In addition, there is now pressure from regulatory bodies, such as the FDA, to conduct pharmacokinetic screens in phase III clinical trials.

As has been mentioned previously, it is necessary to convince the clinical staff involved in the study of the importance of accurately recording dosing and sampling times. This can best be achieved by informing the investigators about the purposes of the population PK/PD component of the study. Indeed, one European regulatory authority requires education as part of good clinical practice (GCP). It was suggested that a population specialist should be part of the development team to facilitate the implementation of those parts of the protocol related to the PK/PD analysis. An added benefit of increased communication between the clinical staff and the PK/PD staff is that the investigators are likely to become more motivated, eventually resulting in data of higher quality.

Protocol design

Population methods must be part of the protocol if they are implemented in a study. They should be handled in a similar way to statistical methods. It must, however, be kept in mind that population methods are still usually of an exploratory nature. As a consequence, they cannot be described *a priori* with the same precision as statistical methods used to assess efficacy issues. Nevertheless, it was agreed that important problems related to population PK/PD analysis need to be addressed in the protocol.

The data that are going to be used for the PK/PD analysis have to be defined: which patients and which subgroups are going to be used; what measurements (plasma concentration, efficacy, toxicity) are going to be considered; which covariates will be measured. In addition the individual sampling design has to be specified, and any subgroup stratification should be defined. An important and often neglected part of the protocol is the description of the data analysis. Procedures for handling missing data and data anomalies, involving for example deletion or estimation, should be clearly described in the protocol. The experts were sensitive to over-prescribing the data analysis and desired it to be as flexible as possible. However, the plan of the analysis, at the least, should be described in advance in the protocol as accurately as possible. The same applies to the methods to be used to validate the results of the analysis.

Conclusions

The population approach is gaining more support in drug development. It now needs to be formalized within the drug development plan. The main purpose of the meeting was to consider issues related to designing population PK/PD studies and integrating those studies in the development plan. It is perhaps still too early to have a consensus on all aspects of design relating to population PK/PD studies, and these issues will always have to be considered on a case-by-case basis. Nevertheless, several important conclusions arose from the meeting.

- When participating in the design of a new study, the population approach group must be careful not to include sampling or data collection items that would compromise the main objectives of the clinical trial.
- It is particularly important to communicate the purpose of the population PK/PD analysis to the investigators and to convince them of the importance of accurately recording dosing and sampling times.
- Some prior knowledge of the PK and PD models and covariate relationships is necessary for the analysis of sparse phase III data.
- Subject numbers are often dictated by the main objective of the clinical trial. However, computer simulation and optimal design measures may be useful to define sampling times.
- Population methods must be specified in the protocol. Although population PK/PD analysis is often exploratory, the data analysis strategy should be specified as fully as possible.

References

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