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Pharmacokinetic/pharmacodynamic modelling approaches in paediatric infectious diseases and immunology☆

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ABSTRACT

Pharmacokinetic/pharmacodynamic (PKPD) modelling is used to describe and quantify dose–concentration–effect relationships. Within paediatric studies in infectious diseases and immunology these methods are often applied to developing guidance on appropriate dosing. In this paper, an introduction to the field of PKPD modelling is given, followed by a review of the PKPD studies that have been undertaken in paediatric infectious diseases and immunology. The main focus is on identifying the methodological approaches used to define the PKPD relationship in these studies. The major findings were that most studies of infectious diseases have developed a PK model and then used simulations to define a dose recommendation based on a pre-defined PD target, which may have been defined in adults or in vitro. For immunological studies much of the modelling has focused on either PK or PD, and since multiple drugs are usually used, delineating the relative contributions of each is challenging. The use of dynamical modelling of in vitro antibacterial studies, and paediatric HIV mechanistic PD models linked with the PK of all drugs, are emerging methods that should enhance PKPD-based recommendations in the future.

Contents

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1. Introduction

Pharmacokinetic/pharmacodynamic (PKPD) modelling seeks to quantify the dose–concentration–effect relationship with a mathematical model. It can be used in both pre-clinical and clinical study designs. The statistical aspect to PKPD modelling seeks to quantify variability in the data, and following suitable evaluation, simulate the predicted behaviour of the system. This so-called pharmacometric approach is increasingly recognised as being an important supplement to randomised control trial (RCT) data [1], particularly in patient groups where recruitment to RCTs is problematic, such as in children and neonates.

During model development, when fitting a PKPD model to data from in vitro and/or in vivo sources, there will always be some element of 'noise' whereby the model does not fit the exact data points, since by definition a mathematical model is a simplification of reality. The mathematical PKPD model is therefore extended to include a statistical component which models this noise; typically the central tendency of the noise is assumed to have a mean of zero (so that model predictions go through the middle of the data) and the noise magnitude (its variance) is estimated. Typical use of a PKPD model is to make inferences on whether and to what extent a drug's dose and concentrations are associated with markers of disease.

One difficulty in properly conducting clinical PKPD studies is the fact that the experimental units (patients) are not homogenous. For this reason, care is needed when modelling data from more than one subject, because it is known a priori that individuals differ from one another; this is true for both PK and PD outcomes. Indeed, fitting a single model to all data (the naïve pooled or data averaging approach), and to a lesser extent fitting the model to each individual and then averaging parameter estimates (two-stage approach) are methods known to bias parameter estimates [2]. Fortunately, over the past 30 years clinical pharmacology has been at the forefront of implementing the so-called 'population approach' using the statistical method known as nonlinear mixed effects (NLME) modelling. By fitting a single model to all individuals simultaneously, whilst allowing for two levels of random effects (noise), estimates can be made of both the model parameter typical values and their inter-individual variability, in addition to the residual variability. By splitting the variability in this way, and so allowing model parameters to take different values in each individual, unbiased estimates can be obtained. A further benefit is that by taking this population-level approach, individual subjects can contribute differing amounts of data, making opportunistic sampling designs a possibility. An introduction to the field of population PKPD modelling is described elsewhere [2–7].

For the majority of antimicrobial agents there tends to be some published PK which, although may not cover all paediatric age groups, is usually sufficient to predict paediatric PK across ages using knowledge of developmental differences [8]. Knowledge of PK alone is, however, insufficient to define a dose recommendation. In order to develop guidance on dosing, the dose–concentration–effect relationship needs to be understood and this means going beyond PK, to make extrapolations as to how these concentrations link with effect (PD). There are two main approaches that make the link from PK to PD in infectious diseases research. The most common approach uses simulations from the PK model to determine a dose which yields a pre-defined endpoint, which is thought to translate to the desired effect. Such endpoints are often derived from in vitro concentration–effect experiments [9], although in vivo animal PKPD outcomes or previous clinical PKPD studies can be used [10]. A major disadvantage of this approach is that assumptions have to be made about factors such as the circulating drug concentration being proportional to that at the site of pathogen load, or the transferability of outcomes between different studies. The second, and more challenging approach, is to collect and model both PK and PD information in the same patient, thereby eliminating the need for extrapolations. Whilst the data generated from this approach could be considered gold standard, the difficulty lies in defining a suitable PD endpoint, recruiting patients to such studies (e.g. many neonates treated with antimicrobials do not have proven infection) and obtaining stable estimates of a joint PKPD model. This review is focused on summarising the PKPD information available in paediatric infectious diseases and immunology, the modelling approaches taken, and identifying potential avenues for future PKPD research. The PubMed database search terms included the generic drug names and classes of antimicrobials, pharmacokinetics, pharmacodynamics, paediatric/pediatric and neonatal, and disease states where relevant: titles and abstracts of papers available in English were reviewed, and selected for inclusion if they contained relevant or new information.

2. Infectious diseases

2.1. Bacterial infections

The PKPD indices of most antibacterial agents have been defined from both in vitro and animal and human in vivo studies. A summary of these is given in Table 1. Typically a breakpoint for susceptibility will be set based on the minimum inhibitory concentration (MIC) of the antibacterial, that is to say the minimal concentration required to inhibit growth in strains considered sensitive. This breakpoint is then compared to either circulating maximum (C_{max}) concentrations, area under the curve (AUC), or circulating time above MIC (T>MIC) depending on the antibacterial mode of action.

2.1.1. Beta-lactam antibiotics

The beta-lactam agents act principally by causing irreversible inhibition of bacterial cell wall synthesis, achieved by covalent binding to penicillin-binding proteins [11,12]. Beta-lactams are renally cleared, and have a wide therapeutic index [13]. On the basis of in vitro and in vivo data, the pharmacodynamic target for beta-lactam therapy is the fraction of time per dosing interval that the free drug concentration exceeds the minimum inhibitory concentration (MIC) of the organism (denoted by %T>MIC) [14]. This is thought to be due to the fact that the penicillin binding protein requires near saturation before cytotoxicity occurs, implying that the minimum concentration required for effect is close to the maximum possible effect. The standard therapeutic goal for penicillins is %T>MIC of 30–40% which has generally been derived from observing that this value leads to decrease in bacterial load either

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