Can Pharmacokinetics/Pharmacodynamics Replace Clinical Trials?

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When the path to discovery of a drug has reached the stage that use and application in humans is feasible, the traditional road to registration is a phase 1 clinical trial followed by phase 2 and phase 3 trials. While the phase 1 trial is primarily aimed at the behaviour of the drug in humans including pharmacokinetics and a rough idea of toxicity, phase 2 and phase 3 trials are aimed at dose finding or proof of concept and efficacy versus a golden standard or other comparison, respectively. However, the single most important feature of antimicrobials compared to all other drugs, clearly segregating them from all other drugs, is that the action of an antimicrobial is not directed at receptors in the human but at those in micro-organisms. Antimicrobials are designed to interact (kill) bacteria, that is what they are supposed to do and that is all they can do. Antmicrobials can not cure patients by themselves. They can however, by killing infectious micro-organisms, make recovery of patients more likely.

The effect or interaction of any drug with its target can be described by a concentration - effect relationship. In microbiology, the drug is the antimicrobial and the effect site is the micro-organism. This is in sharp contrast to virtually all other drugs - those interact with human receptors. It offers a unique opportunity for these agents because concentration-effect relationships between bug and drug can be studied in the lab or in animals or elsewhere and not necessarily in humans. If the concentration-effect relationship between drug and bug is known the effect in vivo can be completely predicted if the concentration at the site of the receptor or, more broadly speaking a micro-organism, is known.

Although at present the exact concentration - effect relationships of antimicrobials at the receptor site are not always know, a number of surrogate markers and their relationship with antimicrobial and clinical effect have been studied intensively over the last decade. From these studies, very consistent patterns of activity have emerged. In fact, the patterns show such consistency that the effect of a drug can be reasonably well predicted from its pharmacological properties and pharmacokinetic/ pharmacodynamic (pk/pd) relationships. This is especially true for antimicrobials for which the class effect is already known. An example is the pk/pd relationship for quinolones : if a new quinolone were to be investigated the effect of treatment in human infections can be, and has been, completely predicted by its pk/pd properties.

With current knowledge, the answer to the question expressed in the title could be the following.
Phase 1 Clinical trials are necessary in all cases to determine the complete pharmacokinetic profile of the antimicrobial, including protein binding, distribution over various body sites, important toxic effects and population pharmacokinetics.

From studies in animals or in other models, the dose resulting in a favorable pharmacokinetic profile can then be determined from the pk/pd relationship. The extent of phase 2 and 3 trials may depend on the present state of knowledge of the class. In principle, what is needed are proof of concept studies only - with the difference between agents from an established class and a new class that the proof of concept in the established class is better known, and therefore easier to achieve. Of prime importance however, is that because optimization of effect is (or should be) the final goal of these studies, trial design should be based on concentration-effect relationships instead of the current paradigm of cure versus no cure. Using current trial design, the dichotomous nature of the outcome results in a low discriminatory power, and thus the need of many patients to show effect; in addition the information obtained does not tell us whether the dose or dosing regimen used is the optimal dosing regimen available. In contrast, a well designed trial using quantitative effect measures could show the efficacy of an antimicrobial in as few as 15 to 30 patients- as has recently been demonstrated in several cases.

The question of toxicity can not be answered using this approach. It can not be answered by the 'classical' approach either, because too few patients will have received the drug in clinical trials to discover infrequent adverse events. To that purpose, a new system of adverse event registration is needed - before and after registration.

To summarize, phase 2 and phase 3 trials should be redesigned taking pk/pd properties into account. The advantages of that approach are that more insight is gained in the dose-effect relationships in humans including optimization of dosing schedules, far fewer patients are needed too show the efficacy of an antimicrobial, and that the time to registration and costs are drastically reduced. A new system for registration of adverse events should be set up and evaluated to monitor possible toxic effects.