

PERSPECTIVE

Challenges faced when modeling clinical toxicology and toxinology events

The discipline of pharmacometrics encompasses a wide range of mathematical and statistical approaches, including quantitative systems pharmacology, physiological-based pharmacokinetics, and compartmental modeling, that yield predictive models and mechanistic insight into the pharmacokinetic/pharmacodynamic (PK/PD) profile of a drug. Although these methods have been well-characterized for data that arises from clinical pharmacology studies, they have been less well-studied for data from clinical toxicology or toxinology studies which are hampered by additional challenges, such as missing data.

For clarity, we provide definitions of clinical pharmacology, toxicology, and toxinology in Table 1. Data arising from all clinical study types (whether clinical pharmacology, toxicology, or toxinology) may include missing data relating to the independent variables, including dose, dosing rate, and schedule and sample timing.¹ In general, early phase clinical trials are tightly managed by the sponsor and tend to be subject to minimal protocol violation and missingness. Later phase clinical trials, in which the patient may take the drug autonomously for a significant period of time, increase the risk of inadvertent protocol violation. Various methods have been proposed to handle missingness of data^{1,2} with perhaps the most common solution being to assume the nominal schedule as true, albeit incorrect. In contrast to clinical pharmacology studies, those in clinical toxicology and toxinology arise from uncontrolled settings, in which there is little if any data management. In these settings, the patient may deliberately or unintentionally become exposed to a toxic substance or be envenomed, which leads to significant uncertainty about the independent variables (Table 2). Essentially, these study types are an exercise in handling missingness. What makes this observation particularly powerful is that, in some circumstances, accurate determination of an overdose occurrence is the necessary first step to intervention with either a specific antidote or non-specific decontamination procedure.

Perhaps the first study to directly account for missingness in clinical toxicology was described by Friberg³ in which data were available following patients who deliberately self-poisoned with citalopram. In this study, a five-point veracity scale was used to describe the credibility of the patient history, with zero being an excellent history and four being a very poor history. Friberg then considered the dose to be a random variable and linked this measure of veracity into the prior distribution of the reported dose, in which a veracity score of zero applied the patient recall of dose as exact and higher scores with greater imprecision on the distribution of doses. Similarly, the time of dose was assumed to be a random variable within defined bounds often provided by first-responders, patient recall, or relatives and friends. This work identified and quantified the benefits of gastric decontamination with activated charcoal, which was found to beneficially reduce the probability of QT prolongation.⁴ The influence of activated charcoal was then confirmed in a later clinical study⁵ and as guidelines.⁶

Perhaps not unexpected there are far fewer PK/PD analyses of snake envenomation. Snake envenomation in the rural tropics is now being recognized as a World Health Organization neglected tropical disease. In all cases, the injected dose by snake envenomation is unknown and the composition only known approximately (to the level of the species of snake, if this has been correctly identified by the patient).⁷ Snake venoms contain four dominant toxin families, up to six secondary toxin protein families, with small amounts of uncommon toxins.⁷ These toxins have varying molecular weights and a corresponding anticipated variable range of clearance values.⁸ In a simulation-estimation study, it was found that even with 40-fold variability in toxin molecular weights, a maximum of three dominant time course profiles could be identified.⁸ In subsequent PK⁹ and PK/PD¹⁰ studies of *Pseudechis porphyriacus* (red bellied black snake) envenomation, in which the venom dose was treated as nominally one unit, the variability in

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TABLE 1 Definitions

Discipline	Scope	Example
Clinical pharmacology	The study of therapeutic or diagnostic substances when administered to the species of interest	Therapeutic (or diagnostic) dose of a therapeutic (or diagnostic) substance (e.g., 1000 mg of acetaminophen to an adult)
Clinical toxicology	The study of substances that are not intended for therapeutic or diagnostic use when administered to the species of interest	Overdose of a therapeutic substance for nontherapeutic purposes (e.g., 10 g of acetaminophen). Exposure to a nontherapeutic substance (e.g., lead poisoning).
Clinical toxinology	The study of xenobiotic substances that are produced naturally by a species when administered to the species of interest	Envenomation (e.g., snake bite, <i>urtica dioica</i> [stinging nettle])

Note: Clinical = species of interest (typically human but can be other species in the case of veterinary medicine).

TABLE 2 Missing data pertinent to discipline

Data knowledge	Clinical pharmacology	Clinical toxicology	Clinical toxinology
That a drug was taken/administered	Known	Known	Known
Details of the drug and formulation	Drug = known Formulation = known	Drug = uncertain Formulation = uncertain Notes: The patient may take a cocktail of drugs, exact details on each drug may not be available. If a single drug ingestion, then both drug and formulation are generally known.	Drug = known (particular snake venom) Formulation = uncertain (what is in the venom) Notes: The type of snake is known but there is less quantitative information on the mixture (types and amounts) of toxins within the venom.
Dose/dose rate	Known nominally	Uncertain Known within a window (from no dose up to maximum dose [e.g., whole packet, whole bottle])	Unknown
Dose timing/ schedule	Known nominally	Uncertain Known within a window (not before patient was seen previously and [usually] not after patient arrives at hospital)	Uncertain Known within a window (not prior to entering risk area, not after symptoms arise). Often better known than overdose as event and symptoms are usually clearly evident.

the relative bioavailability across the population was estimated at 141%. Importantly, the influence of antivenom (a specific treatment made up of antibodies or antibody fragments raised against the relevant snake toxins) could be estimated accurately. However, carrying this forward into an evaluation of the influence of venom PK on myotoxicity, it was not possible to confirm the overall venom PK profile as the driver for myotoxicity, and it was seen that a kinetic PD (KPD) model performed better than a PK/PD model,¹⁰ with an estimated putative half-life of the causative toxin from the KPD model of twice that estimated by the venom PK (a mixture of toxins) itself. This

suggested that the myotoxin was not a highly abundant toxin within the venom mixture. In addition, the severity of the myotoxicity could not be described by either the KPD or PK/PD model, which indicates that other snake or patient factors must contribute to this story. These examples highlight that missingness of explanatory variables plays a major role in both clinical toxicology and toxinology studies.

In addition and in contrast to clinical pharmacology studies, clinical toxicology and toxinology studies are also hampered because they usually lack (1) treatment controls, for instance, the standard of care can differ dramatically

between treatment centers making an equipoise comparator problematic, (2) rigorous experimental conditions in that each patient presents following their own unique experimental protocol, (3) prospectively defined data management, typically data are collected by convenience rather than per protocol and data collection processes may vary dramatically between centers, and (4) randomization is either impossible (i.e., to randomize the toxicological/toxinological insult) or impractical for evaluation of an intervention due to the acuteness and variability of the clinical presentation. Essentially, all of these issues mean that the normal levels of evidence that are adhered to in clinical studies are essentially impractical or near impossible or just very rare in this setting. Prospective cohort studies are generally the highest level likely to be achieved in most of these settings. These limitations increase the risk of bias and confounding, which are not necessarily explicable or accountable by pharmacometric modeling approaches.

It is fortunate, although perhaps not for the patient, that the signal from the clinical toxicology/toxinology insult is generally strong such that antidotes and decontamination have the potential to cause a large clinical benefit. Hence, despite the limitations of missingness, it remains possible to evaluate dosing protocols and evaluate guidelines for care based on pharmacometric principles.

CONFLICT OF INTEREST

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