Meta-analysis of Ketamine Pharmacokinetics

Lots of Work Done but Still Lots to Do

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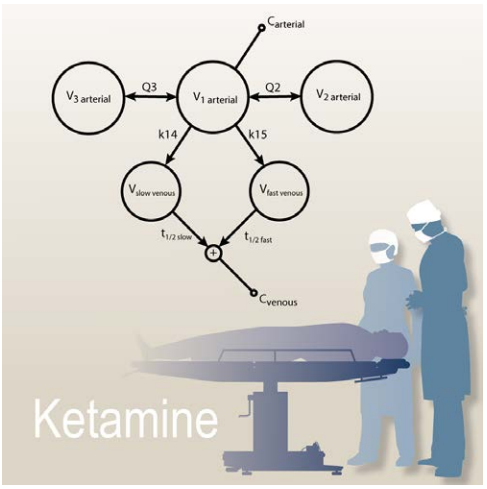
Ketamine is an "old" drug and has been in use for more than a half-century. It is perhaps older than many of those administering it. It has a wide range of clinical effects and notoriously complex molecular actions,[1] many of which are not fully understood. A first step toward obtaining the greatest benefit from ketamine administration is to understand what the body does to ketamine after dosing. If we can predict the time course of ketamine concentrations in the body after dosing using a robust pharmacokinetic model, then it can play a role toward finding infusion schemes maximizing beneficial effects and minimizing detrimental effects. It is this challenge to develop a pharmacokinetic model for ketamine taken by Kamp *et al.*[2] with their meta-analysis in this edition of Anesthesiology.



"Data sharing leverages the costs and effort of designing, performing, and executing [large pharmacokinetic] studies."

Numerous pharmacokinetic models for ketamine are available in the literature, so why do we need another one? Most of the published studies of ketamine pharmacokinetic are "small" in the sense that they focus on a specific patient group or dosing scheme, are limited to the context of a particular clinical intervention, or include a low number of studied individuals. While it might seem a good state of affairs that clinicians and researchers can choose between 20 and 30 published pharmacokinetic models to select the "right" pharmacokinetic model, this is actually a very difficult task even for experienced researchers. Matching the clinical and patient conditions at hand with the documented study conditions and patient groups is by no means straightforward. Each of the study results are slightly different, and sometimes the findings are incompatible. The variability across patient and clinical conditions is often considerably greater than that of the published studies, so finding a match may be impossible. Even if a match is found, a low number of individuals studied can introduce inaccuracy due to population random sampling error. Older studies can be difficult to evaluate because relevant diagnostics may not be included in the study publication. Recognizing these difficulties, it seems reasonable that clinicians and researchers would benefit from a robust ketamine pharmacokinetic model that "just works," with broad support across patient groups and clinical conditions.

Meta-analysis is a quantitative approach to making sense of a diverse ecosystem of medical research. The study by Kamp *et al.*[2] is unique in that it considers two different approaches for meta-analysis. Along with the classical study-level meta-analysis, in which study results are weighted by quality criteria and combined, the authors also performed a data-level meta-analysis by obtaining the raw data from numerous pharmacokinetic studies and estimating a single population model from the combined data. This data-level method would likely have been impractical a number of years ago, but the incredible increases in computing power in recent years have made it a workable approach. These are sometimes referred to as "second-generation"[3] pharmacokinetic models, and some recently published general purpose models have appeared for propofol,[4] remifentanil,[5,6] and vancomycin.[7]

Estimating pharmacokinetic models from large collections of data can hardly be called "simple," but it does solve a number of issues inherent to the classical study-level meta-analytic approach. Study weighting factors are

Image: Getty Images.

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not necessary, and one does not have to rely on the (good or bad) quality of the numerical methods and approach to model building used in the original analysis. Different studies can find differing pharmacokinetic model structures to be optimal, and this complicates the synthesis of a singular best model from diverse and sometimes incompatible study results. Data-level meta-analysis allows modern population estimation numerical methods to be applied and the best diagnostics methods used to evaluate the final model. This "lets the data speak" as well as current statistical methods and tools can understand.

It might be reassuring that Kamp *et al.*[2] found roughly similar results between classical study-level and data-level meta-analysis approaches. However, if these two methods had produced substantially different results, then it seems rational to prefer the latter as it seems to be more objective and relies on fewer assumptions. Only if the raw data were not available might a study-level meta-analysis be the best choice.

It is exceedingly efficient to utilize large data sets contributed by the work of others. Data sharing leverages the costs and effort of designing, performing, and executing the contributing studies. Nevertheless, it does not replace the design, performance, and execution of the studies that make those data possible. Initiatives have been started with the goal of promoting standardized data sharing, such as GO FAIR[8]. The actual data sharing requires negligible effort because data files and documentation are often quite small. However, there are regulatory and administrational burdens introduced by recent data security and privacy legislation. Effort must also go into locating where the data are stored, determining what rights and responsibilities are associated with the data (*i.e.* who "owns" it), and converting the data format to those suitable for the analysis tools. As we reflect on the value of second-generation pharmacokinetic models, we must understand the effort that underlies those models. The great majority of work was performed by the researchers in the predicate investigations that generated the data used in the second-generation analysis. The sum total of effort underlying the meta-analysis of ketamine pharmacokinetics by Kamp *et al.*[2] is exceedingly large, much greater than that of Kamp *et al.* themselves.

A pharmacokinetic model, by itself, has rather limited usefulness. Its potential lies in that it can be combined with a pharmacodynamic model so that dosing schemes can be connected to expected drug effects over time. The most robust approach is to obtain pharmacokinetic and pharmacodynamic data from the same population, although alternatives exist.[9] Target-controlled infusion systems can be applied to translate from simple selections of target concentrations into complex infusion profiles. With these tools, dosing schemes can be proposed, tested, and optimized. The logical next steps are validation of the Kamp *et al.*[2] pharmacokinetic model for ketamine and development of pharmacodynamic models for relevant clinical endpoints. Lots of work has been done, but there is still much needed to get the dose of ketamine "right" and better understand its complex pharmacodynamic characteristics to ultimately improve clinical outcomes for patients.

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Competing Interests

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