Target-controlled-infusion for special populations

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EDITORIAL

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Target-controlled-infusion for special populations: How different is different enough?

Target-controlled-infusion (TCI) is a well-tested and mature technology[1] that allow clinicians to raise or lower drug concentrations of intravenous anaesthetics in patients, mimicking the convenient properties of a vaporizer. They use an internal drug-specific pharmacokinetic (PK) or pharmacokinetic-pharmacodynamic (PK-PD) model to predict drug elimination and transport to and from peripheral compartments. Once these drug transports are known, a compensating drug infusion can be calculated and applied to stabilize drug concentration at a target set by a clinician. An appropriate target concentration can be determined by scientific studies.

Because TCI systems rely on an internal PK or PK-PD model to calculate drug administration, it is imperative that the model reflect the true characteristics of each individual as accurately as possible. Otherwise, misprediction of drug concentrations and infusion rates can cause patient drug concentrations to vary over time, making accurate patient treatment more difficult. These systems typically individualize the models based on patient weight but may also use age, sex, BMI, or membership in special populations.

This issue of Acta Anaethesiologica Scandinavica presents a study by Jung-Min[2] in which propofol PK models are evaluated for their predictive performance for a special population, underweight Korean patients. General purpose models (Eleveld model[3]) as well as adult models (Marsh[4] and Schnider[5]) were compared to a PK model specialized to that same population (Choi model[6]), which was recently developed with data exclusively from underweight Korean patients. One might expect that a specialized model, focused on that particular population, would perform better under those conditions. A general purpose model must balance between the diverse characteristics of a broader population.[7] Presumably this broad generalizability would be detrimental to accuracy in a specialized population. On the other hand, general purpose models are typically developed with larger data sets and this may reduce the influence of random sampling variation, resulting in a better estimation of the "correct" final model.

The important finding of the Jung-Min study is that all of the propofol PK models tested were judged as clinically acceptable. This is often defined as bias of less than 10%-20% and an accuracy of between 20%-40%.[8,9] While the Choi model showed the lowest bias, the general purpose Eleveld model has slightly better overall accuracy, as well as better wobble and divergence. This result should come as a relief to propofol TCI system users because it can make their daily work easier. They are not required to (a) correctly identify each patient as underweight Korean or "other" and (b) to select the correct PK model via a computer interface, if they are to obtain acceptable performance in their TCI systems and PK models.

1 | HOW DIFFERENT IS DIFFERENT ENOUGH?

While the study of Jung-Min does not support the clinical necessity of a specialized PK model for underweight Korean patients, it does raise an important question:

1.1 | How different does some population need to be for it to require a specialized TCI model?

A number of things need to be considered:

1. Is the predictive performance of a general purpose model acceptable on the special population? If so, then the additional complexity to a TCI system does not seem desirable for a small benefit.
2. Can simple adjustments in TCI target concentrations result in acceptable performance in the special population? If so, then this represents only a small burden to clinicians because they already adjust TCI target concentrations in each individual as necessary to compensate for PK and PD inter-individual variability.

If the answer to (1) and (2) are both no, then it is reasonable to suggest that a specialized PK or PK-PD model focused on that population would be advantageous. It seems likely that for many drugs the presence of significant renal, liver, cardio-vascular or brain disease, acute trauma, or strong drug interactions would significantly change the PK and there would be a demonstrable benefit from a specialized TCI model. This is an important avenue for future research.

2 | TCI SYSTEM DESIGN CONSIDERATIONS

The design of any product involves understanding how it can be used and potentially misused. This is especially true of medical devices which can have a great impact on the health of patients. Engineering students are often required to study the history of the THERAC-25[10] computer-controlled radiation therapy machine. The

device was used successfully many times but was involved in at least six accidents between 1985 and 1987, in which patients were inadvertently given massive overdoses of radiation. One of the core lessons is that complex devices consist of subsystems and the design of each subsystem influences others because they must interoperate. The design choices made for each subsystem determine the benefit and the faults of the device as a whole.

Since the appearance of TCI systems in clinical practice, investigations of drug PK have, beyond the scientific knowledge gained, also become an element of TCI subsystem design. If a specialised PK model is proposed for a special population then we should consider the consequences of offering this option to TCI system users. Because of the dependency of TCI system performance on a chosen PK model it is wise to consider the potential consequences of a mistaken choice. If a TCI system would offer the user the choice to use the Choi propofol PK model, then what consequences would patient misidentification have on propofol dosing and further treatment? It is currently not possible to answer this question because it depends on the specific patient being treated and the characteristics of the model for extrapolation. These properties of the Choi model have not yet been explored. On the other hand, what consequences are likely if a general purpose model is used in the special population, in this case underweight Korean patients? The study of Jung-Min suggests that moderate bias would occur, and correcting for this bias is straightforward by adjusting target concentrations. This should not unduly burden clinicians as they already adjust target concentrations based on individual response.

Scientific progress does not occur in a vacuum. There are a multitude of consequences, both understood and not, seen and unseen, that result from the choices made in a seemingly abstract scientific investigation. For drug PK studies, the existence of TCI systems and their reliance on PK models, should prompt us to consider likelihood that the PK model may become a TCI subsystem and keep that in mind in the design and execution of the PK study analysis. In this way, we optimize research to result in better TCI devices and ultimately to improved outcomes for patients.

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