Moving from dose to concentration: as easy as TCI!

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To encourage a favourable stance from regulatory agencies such as the US Food and Drug Administration (FDA), advocates of target-controlled infusion (TCI) systems have been exclaiming for years that TCI systems administer 'approved drugs by approved routes at approved doses for approved indications'.[1] In a recent issue of *British Journal of Anaesthesia*, Eleveld and colleagues[2] provide sophisticated, albeit expected, evidence that TCI systems do indeed deliver doses consistent with the Summary of Product Characteristics (known as the Product Label in the USA) for three contemporary remifentanil pharmacokinetic models.[3–5] Going forward, this observation has important implications for regulation of TCI systems as it relates to both the initial approval of TCI devices and to the incorporation of new drugs and new models (for existing drugs) into TCI systems. This new evidence should also be reassuring to physicians who are not yet familiar with TCI technology and who are accustomed to practicing in the dose domain.

TCI systems, a form of open loop control,[6] deliver intravenous anaesthetics according to their pharmacokinetic behaviour using an infusion pump controlled by a computer.[7] The computer's pump control algorithm calculates the infusion rate that is necessary to achieve a user-designated drug concentration (the 'target') in the plasma or theoretical effect-site according to a pharmacokinetic model for the drug.[8] In simple terms, TCI systems enable clinicians to move from the dose to the concentration domain for intravenous drug delivery, approximating the delivery paradigm to which they are accustomed when administering volatile anaesthetics with a vaporiser.[6]

As shown in Figure 1, rational use of a TCI system requires a different physician knowledge base compared with practice in the dose domain.[7] To operate a TCI system the physician must be familiar with the available pharmacokinetic models, the therapeutic windows for various procedures and anaesthetic techniques, the distinction between plasma and effect-site control, and how covariates (e.g. body weight, age, among others) affect drug disposition and effects. In addition to clinical and electronic assessment of drug effect via physical examination and standard monitoring technology (ideally including the raw and processed EEG),[9] the TCI user must also be acquainted with interpreting a pharmacokinetic simulation (ideally including an understanding of decrement times, drug interaction response surfaces, and isoboles).[6,10,11]

It is important to emphasise that modern TCI systems simplify these pharmacologic complexities with a user-friendly interface, automating much of their operation. Although understanding the fundamental principles of TCI is essential to using the systems intelligently, the potential user need not be intimidated by the knowledge base incorporated into the TCI 'black box'. As evidenced by the existence of tens of thousands of enthusiastic TCI users in numerous countries across the world, the TCI system user experience is remarkably straightforward and has been well received in the trenches of everyday anaesthesia practice.[12] As the knowledge base underpinning the successful use of TCI technology begins with an understanding of how dose relates to concentration, the new evidence provided by the Eleveld and colleagues[2] simulation study should be enlightening to novice TCI users.

However, the implications of the study by Eleveld and colleagues[2] are perhaps even more relevant to TCI regulation by government agencies. TCI systems are approved and well entrenched in most of the developed world, where the technology has proven remarkably safe and robust.[12,13] The USA is a notable exception.[14] An application for Premarket Notification (PMN), also referred to as 510(k) by the FDA, made in 1995 by a pioneer in TCI development remained incomplete and was ultimately withdrawn by the sponsor 9 yr later.[15] Since then, apparently no company has applied for market registration of TCI technology with the FDA.[16]

At first glance, this situation appears astonishing but might be best explained by the current dilemma. Given that propofol, remifentanil, and TCI technology are beyond their proprietary
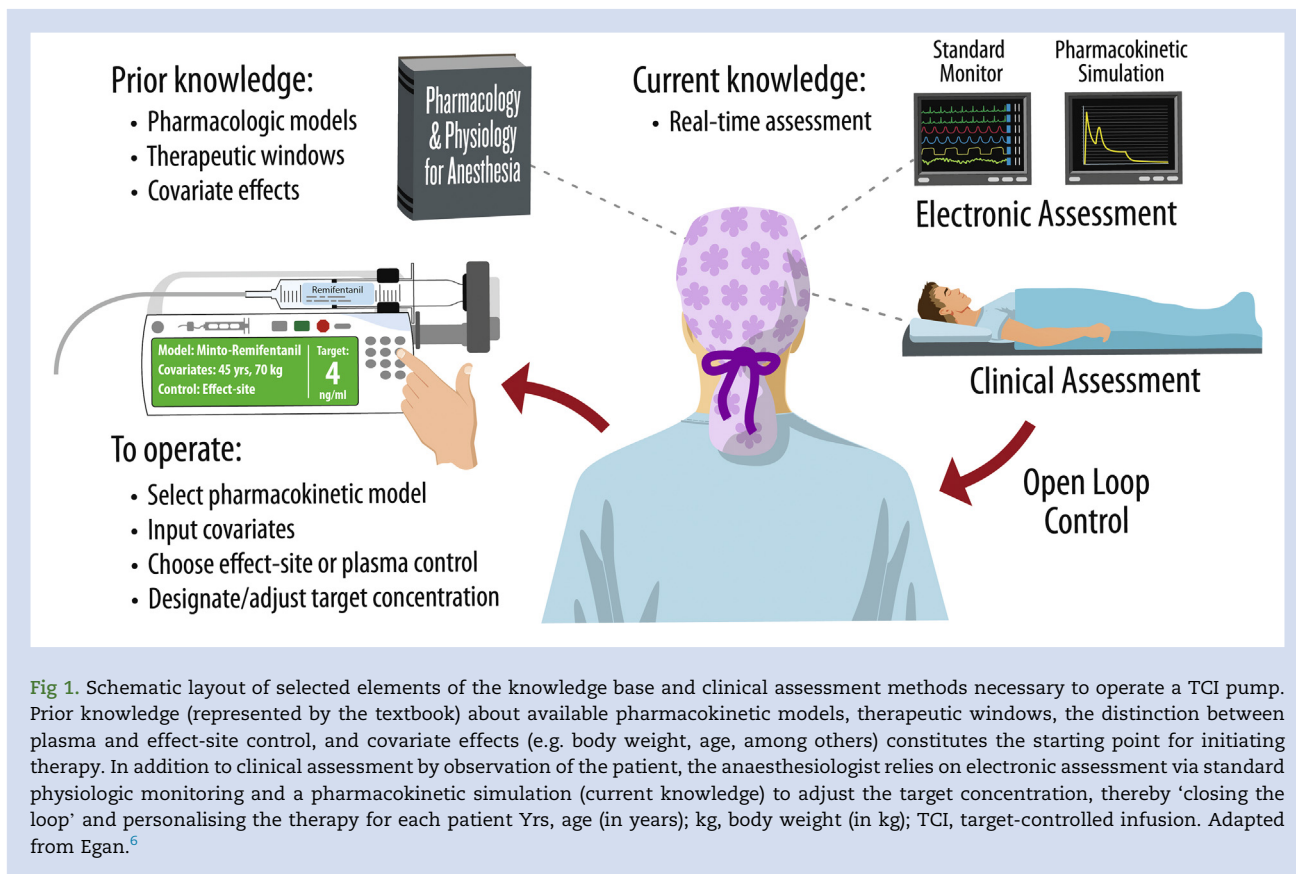

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Fig 1. Schematic layout of selected elements of the knowledge base and clinical assessment methods necessary to operate a TCI pump. Prior knowledge (represented by the textbook) about available pharmacokinetic models, therapeutic windows, the distinction between plasma and effect-site control, and covariate effects (e.g. body weight, age, among others) constitutes the starting point for initiating therapy. In addition to clinical assessment by observation of the patient, the anaesthesiologist relies on electronic assessment via standard physiologic monitoring and a pharmacokinetic simulation (current knowledge) to adjust the target concentration, thereby 'closing the loop' and personalising the therapy for each patient Yrs, age (in years); kg, body weight (in kg); TCI, target-controlled infusion. Adapted from Egan.[6]

life cycle (i.e. off patent) in the USA, it is a peculiar situation for any company wanting to apply for a market registration of TCI technology with the FDA. A 510(k) application seems impossible, as there is no substantially equivalent predicate product available in the US market. The other potential registration pathway, a Premarket Approval (PMA), would require the conduct of a clinical registration trial (i.e. 'pivotal clinical trial') and thus a considerable financial investment by the applicant. Such investment would be difficult to recoup, especially in the absence of the patent protection necessary to establish a legal monopoly for a period of time. As more than 500 peer-reviewed research manuscripts on TCI have been published to date, aside from the financial implications, a pivotal trial just for the sake of a registration process would be difficult to justify both from a scientific and an ethical point of view.

Could there be a solution to this impasse? In fact, there is an uncommon third regulatory pathway, the so called *de novo* petition, which lies somewhere in between the PMN and PMA pathways in terms of costs, ease, and timelines. This path implies a reclassification of a Class III medical device to a less risky Class II device and could be justifiable if the TCI system is to be used exclusively with approved drugs according to their labels.[16]

This is why the study by Eleveld and colleagues[2] has important regulatory implications. The study demonstrates that TCI administration of remifentanil by three different pharmacokinetic models conforms to the dosing guidelines approved by regulatory bodies. The TCI administration of drugs outside their existing labels would presumably require not only a PMA approach to approval, but also a label change of

the corresponding drug, a challenge that presents tremendous difficulty for the pump manufacturer who does not typically own the rights to develop or market the corresponding drug(s).

In view of this reality, and to limit the overall burden of a regulatory application, a rational plan for TCI pump developers is to focus on administration of drugs according to their respective labels.[16] If endorsed by the FDA, such a regulatory strategy could represent a 'goal-directed', workable option. Owing to the uncommon nature of the *de novo* registration pathway, however, the outcome of such a strategy is admittedly perhaps less predictable in comparison with the classical PMN and PMA pathways.

In the case of the US FDA where TCI would be evaluated as a 'combination product' (a drug–device combination), because the novelty of TCI lies in the medical device rather than the drugs administered by it, the review would be expected to be led by the Center for Devices and Radiological Health (CDRH), whereas the final approval would presumably come from both CDRH and the Center for Drug Evaluation and Research (CDER). To define the way forward, direct communication with the FDA would be recommended to align on the regulatory submission type and the studies that would be required to demonstrate a reasonable assurance of safety and effectiveness (and perhaps a 'human factors' study to confirm the usability of the technology).[16]

Were the FDA to endorse such a *de novo* regulatory pathway, it is conceivable that we could finally welcome the introduction of TCI technology into the USA sometime in the near term. However, if not, the study by Eleveld and colleagues[2] is nonetheless likely to have positive impact on how new

pharmacokinetic models and new drugs are incorporated into existing TCI platforms in countries where the technology is already approved. New pharmacokinetic models appear with some frequency for both existing and novel drugs.[17] Demonstrating through simulation that TCI drug delivery with a new model (for an old or novel drug) conforms to the product labelling will alleviate some regulatory concerns. Furthermore, in this way, clinicians who are somewhat new to TCI technology can rest assured that the innovative pumps are delivering drugs at doses similar to traditional calculator pumps but in a more sophisticated way. To extend this line of research, a similar analysis for commonly used propofol models is a logical next step. In any case, in moving drug delivery from the dose to the concentration domain, clinicians and regulators alike should remember 'It's as easy as pie, or TCI!'

Authors' contributions

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Writing of the initial draft: TDE
Curation of revisions of co-authors: TDE
Contributed to the initial draft: MW
Critical revisions to the manuscript: MW, CFM, TWS
All authors made a substantial contribution to conception of the editorial; drafted or revised it critically for important intellectual content; provided final approval of the version to be published; and agree to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations of interest

TDE has no conflicts related to this manuscript. TWS was involved in the development of a TCI system for CODAN ARGUS AG, Switzerland. He receives royalties from TCI pump sales. MW is Chief Medical Officer and a shareholder of Fresenius, a global company that has propofol and TCI pumps in their portfolio. CFM was involved in the development of a TCI system for CODAN ARGUS AG, Switzerland. He receives royalties from TCI pump sales.

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