Target Controlled Infusion in the ICU

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Target Controlled Infusion in the ICU: An Opportunity to Optimize Antibiotic Therapy

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38.1 Introduction

Infection is a common yet important problem for patients admitted to intensive care units (ICUs) around the world and is a major cause of morbidity, mortality and costs [1]. Appropriate antibiotic therapy is a key element in the management of severe infections and it is important to achieve an adequate dose of the appropriate antibiotic at the site of infection. Treatment outcomes for severe infections remain poor, with critically ill patients having the highest mortality rates [2]. There are two important contributors to this worse outcome in critically ill patients. First, infection paradigms are largely based on infection models and clinical data that do not specifically compensate for the altered antimicrobial pharmacokinetics (PK) and severity of illness of these patients, which can lead to inadequate antibiotic dosing. Second, infections in ICU patients are increasingly caused by multidrug resistant (MDR) pathogens, which are associated with even worse outcomes [3]. This makes appropriate antibiotic therapy very challenging in critically ill patients and exemplifies the need for individualized antibiotic therapy in order to increase the accuracy of dosing and optimize outcomes [4].

In recent years, several solutions have been proposed to improve antibiotic dosing. Several studies have described the variability of antibiotic concentrations after standard dosing, and PK models have been described for many of the antibiotics commonly used in the ICU. These can help to improve antibiotic administration by

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adapting the dose of the antibiotic, the method of administration or the interval between doses. Although it is evident that dosing based on PK models results in improved target attainment, and software packages are available to be used at the bedside, individualized antibiotic dosing has not been adopted in most ICUs [5, 6].

One of the strategies to increase target attainment for β-lactam antibiotics has been the use of continuous infusion. β-lactam antibiotics are time-dependent antibiotics, which means that keeping the concentration above a target concentration increases the efficacy of the drug. Continuous infusion of selected β-lactam antibiotics is used widely in some countries, with meropenem, piperacillin/tazobactam and ceftazidime most frequently administered as continuous infusions. Other antibiotics are also increasingly administered continuously, for example, vancomycin and linezolid [6–8].

This alternative administration method offers an opportunity for the application of target-controlled infusion (TCI) for antibiotic dosing. Primarily developed as a method for improved dosing of sedatives and analgesics in anesthesia, we hypothesize that TCI may also be used to individualize and optimize antibiotic dosing. In this chapter, we will provide an overview of the current status of TCI in critical care, highlight the importance for individualized antibiotic therapy in critically ill patients and discuss potential for TCI and antibiotic therapy to optimize antibiotic exposure and maximize effectiveness.

38.2 Target-Controlled Infusion History and Current Applications

38.2.1 What is a TCI-System?

TCI is a technique of continuously infusing intravenous drugs and is mainly known in the field of anesthetics. TCI allows the clinician to target a predefined predicted concentration in a specific body compartment or tissue of interest. The computer then calculates the optimal infusion rate required to achieve this concentration as fast as possible without overshooting the target. An on-line coupled infusion pump then delivers this optimal infusion regimen to the patient. The TCI system calculates the optimal infusion rate considering several patient specific covariates (e.g., age, weight, estimated creatinine clearance and the predefined target plasma concentration). For so-called open-loop TCI systems, the infusion scheme is static, whereas in closed-loop TCI it considers feedback from (continuously) measured variables (e.g., somatosensory evoked potentials to assess the anesthetic depth, blood pressure, measured blood concentrations, exhaled drug concentrations). TCI infusion systems have been used clinically in anesthesia for over two decades with an estimated 2.6 million patients in Europe receiving drugs by TCI annually [9, 10].

38.2.2 History and Current Applications

TCI technology is based on more than 30 years of research and is commercially available for several drugs. In 1996, ‘Diprifusor’ was the first microprocessor target

controlled system to be commercially available. Since its commercialization in 1996, more than 60,000 first- and second-generation TCI pumps have been sold worldwide. Nowadays, TCI is mainly used to administer propofol and opioids. For this purpose, an accurate PK/PD model is required. For the first commercialization of the TCI-pump there was only one PK/PD model available, namely the PK/PD model of Marsh et al. [11]. Because this PK/PD model is not the most suitable model for all patient subpopulations, new or expansions of the existing Marsh model have since been developed (e.g., the Shnider and Eleveld model). Most of the commercially available open-TCI pumps now also include an integrated PK/PD model published by Schnider et al., which offers more detailed covariate selection, such as age, sex, weight and height [12–16]. For an exhaustive overview of the history and development of currently used TCI systems the reader is referred to publications by Struys et al. and Absalom et al. [10, 17].

Propofol is the most well-known anesthetic drug for which the TCI concept is applied. In addition to the use of propofol, TCI is also used for other hypnotics, such as dexmedetomidine, and other drug classes, such as opioid and neuromuscular nondepolarizing agents [18].

38.3 Target-Controlled Infusion in Critical Care Medicine

Only a limited number of articles have described the use of TCI in critically ill patients and, so far, the focus has been on its use with hypnotics or analgesics. Propofol TCI has been used for sedating patients with respiratory failure with low tolerance to non-invasive ventilation (NIV) [19]. Arterial blood gases improved significantly in 10 patients who received TCI propofol during 85 NIV sessions. TCI enabled NIV to be well tolerated by all patients. During almost 99% of the infusion time, the sedation level was at the desired level, and patients recovered promptly [19]. Propofol TCI has been compared to midazolam for the treatment of refractory status epilepticus, and found to be equally effective, and associated with shorter hospital stays [20].

TCI has also been studied for the administration of dexmedetomidine in ICU patients. In patients after abdominal aortic aneurysm surgery, dexmedetomidine TCI requirements were much higher after remifentanil anesthesia than after fentanyl [18].

Chalumeau-Lemoine et al. evaluated remifentanil TCI in patients requiring fiberoptic bronchoscopy in a mixed ICU population. Fourteen patients received remifentanil TCI without severe hemodynamic or respiratory complications, and patients reported low pain levels [21]. Rezaiguia-Delclaux et al. also reported on the use of remifentanil TCI to facilitate fiberoptic bronchoscopy after postoperative thoracic surgery in non-intubated patients who had failed bronchoscopy by topical anesthesia. Remifentanil TCI was effective and acceptably safe [22].

In postoperative cardiac surgery patients, patient-controlled hydromorphone TCI offered satisfactory postoperative pain therapy with moderate side effects [23].

In summary, TCI is used only sparsely in the ICU and, when this is the case, it is used for the administration of hypnotics and/or analgesic drugs. Patient numbers are

consistently small, and studies may be underpowered for many clinically relevant endpoints. Furthermore, studies are often non-comparative, and the advantage of TCI for critically ill patients has not been appropriately studied in the majority of them.

38.4 Target-Controlled Infusion for Antibiotic Therapy

38.4.1 Advantages of TCI for Antibiotics

In comparison to manually controlled infusions, TCI systems have several (theoretical) advantages. First, TCI systems achieve the target plasma concentration faster without a significant overshoot of the target. Whereas conventionally a loading dose followed by a maintenance dose are required to attain timely steady-state drug exposure, TCI systems automate this process by continuously adjusting the drug infusion rate to exactly match the disposition and elimination kinetics of the drug during treatment [24]. Second, treatment individualization is made easy via the use of population PK models and associated covariate models implemented in the TCI devices. In comparison to dosing nomograms, which are practicable for a limited number of patient characteristics only, there is no limit on the number of patient characteristics and the complexity of the covariate models used in population PK models. Moreover, dosage adjustments with TCI are continuous, unlike dosage adjustments described in nomograms, which are limited to discrete (practicable) changes in infusion rates, dose strengths, dosing intervals, etc.

TCI has the additional advantage of flexibility. Once adequately validated, it allows the selection of a patient-tailored target. This reduces the selection of an optimal dosing regimen for a specific patient to the selection of the appropriate target concentration for a specific patient, which is the true cornerstone of patient-tailored treatment. Moreover, the use of TCI guarantees that, once consensus has been reached on the optimal therapeutic target for a specific patient, the dosing regimen administered to reach this target will be identical across countries, hospitals, wards, etc.

Combined with the extensive experience in the field of anesthesia this offers, in our opinion, the opportunity to introduce model-informed personalized dosing of antibiotics via a dosing device that is already somewhat familiar to many practitioners. This familiarity might overcome some of the current resistance and could facilitate widespread implementation of model-informed precision dosing.

38.4.2 Available Data

Currently, data on the use of TCI in antibiotic therapy are scarce, and the aforementioned advantages of TCI over manually controlled infusions have been evaluated *in silico* by two groups of authors, in two pre-clinical studies and one clinical study. Below is an overview of available data on TCI in antibiotic therapy.

38.4.2.1 Piperacillin

Horton and Black simulated concentration time profiles following TCI, continuous infusions and intermittent bolus administrations (according to the drug label) for piperacillin. The simulations showed superior PK/pharmacodynamic (PK/PD) target attainment and a significant decrease (±30%) in total daily drug usage for the TCI group. Based on these results, the authors concluded that, for piperacillin, TCI appears to offer cost, efficacy and potential safety advantages over continuous infusions and intermittent bolus dosing [24].

38.4.2.2 Vancomycin

Colin et al. [25] conducted a clinical trial simulation based on published population PK models for vancomycin. Performance metrics, such as PK/PD target attainment and the attainment of potentially toxic concentrations, were compared between published (therapeutic drug monitoring [TDM]-based) dosing recommendations for continuous dosing and a virtual TCI system based on the Thomson model [26], with or without TDM-based Bayesian forecasting. The results showed superior performance of adaptive TCI (aTCI) (where TCI is combined with infrequent TDM sampling) over conventional dosing guidelines, most notably in the first 2 days of therapy. Moreover, the probability of attaining potentially toxic concentrations was negligible for aTCI compared to the second-best performing method (25% versus 65%). Finally, the authors found that the performance of aTCI, unlike conventional dosing strategies, was consistent across subgroups of patients within the population [25].

38.4.2.3 Amoxicillin and Fosfomycin

At present, practical experience with TCI for dosing antibiotics is very limited. In pre-clinical studies computer-controlled infusion has been used to achieve concentrations that approximate the concentration-time profile typically seen in humans following oral administration. Bugnon et al. [27] and Woodnutt and Berry [28] used this approach to deliver fosfomycin and amoxicillin in a rabbit endocarditis model and a respiratory tract infection model in rats. Although the intention in these experiments was not to target and maintain a user-defined plasma concentration target, they nicely demonstrate the versatility of computer-controlled continuous infusions and the steerability of antibiotic concentration time profiles when using TCI.

38.4.2.4 Cefepime

To the best of our knowledge, the only clinical study evaluating TCI performance with antibiotics was recently presented by Jonckheere et al. at the 2018 European Congress of Clinical Microbiology and Infectious Diseases (personal communication). Jonckheere et al. prospectively evaluated the performance of a TCI model for cefepime in a cohort of 21 ICU patients. In this study, a population PK model previously developed by the same authors, was used to target a cefepime plasma concentration of 16 mg/L for 1–5 days (median: 4.5 days). Three to fourteen (median: 10) blood samples were drawn per patient and performance metrics were characterized according to Varvel et al. [29]. The median absolute prediction error (MdAPE: a measure of accuracy) and the median prediction error (a measure of bias) were

28.7% and 20.3%, respectively. Except for the positive bias, which was caused by an overestimation of the central compartment (V1) in the tested TCI model, performance was acceptable (i.e., MdAPE <30%) and in line with the performance of current PK models used in TCI pumps in anesthesia.

38.4.3 Challenges for the Implementation of TCI for Antibiotic Therapy

At the moment, the use of TCI outside anesthesia is limited to a handful of specific applications. In our opinion, TCI is ideally suited for dosing of intravenous antibiotics (for reasons outlined earlier) and some evidence is available suggesting that patients might benefit from switching from manually controlled infusions to TCI. Nevertheless, we envision some specific challenges that should be addressed to expedite the use of TCI for antibiotic dosing.

38.4.3.1 PK Model Development

In anesthesia, data-sharing has led to the development of generic population PK models for propofol [16] and remifentanil [30]. These models have demonstrated superior predictive performance across patient subgroups compared to subgroup specific models. In the field of antibiotics, a plethora of subgroup- and context-specific population PK models derived from (very) small-sized patient cohorts exist. It was previously shown that when applied to external datasets, the performance of these PK models differs widely [31, 32]. Large scale data-sharing initiatives, such as the "Open TCI Initiative" (www.opentci.org) do not exist for antibiotics at the moment and we believe that data-sharing initiatives are necessary to develop robust and generically applicable population PK models to serve as input to antibiotic TCI systems.

38.4.3.2 Altered Pharmacokinetics in the Critically Ill Patient

An implicit assumption in current TCI systems for anesthetic drugs is that PK parameters within an individual are constant. In anesthesia, this assumption is reasonable as the length of TCI drug administration is usually restricted to (several) hours. However, appropriate antibiotic therapy often requires several days of drug dosing during which the (patho)physiological state of a patient (especially in the critically ill) might change dramatically. Hence, the assumption of constant within-individual PK parameters is likely inappropriate and TCI systems for antibiotics should therefore be able to account for dynamic (disease-related) changes during the course of treatment.

38.4.3.3 Use of Therapeutic Drug Monitoring to Enhance TCI Accuracy in the Individual Patient

In contrast to anesthetic agents where the effect of treatment is readily visible (sedation state) or easily monitored (electroencephalogram [EEG]-derived measures), no

surrogate/clinical endpoints are available to guide antibiotic dosing. As a consequence, treatment individualization depends (solely) on measuring (local) antibiotic concentrations, and feedback control systems to individualize the patient's PK parameters during the drug infusion are likely needed to achieve clinically acceptable precision in PK/PD target attainment.

38.5 Future Perspectives

Opportunities for the application of TCI for antibiotic therapy in critical care are multiple. For the optimization of antibiotic treatment, dosing recommendations based on PK models and dosing simulations to identify optimized regimens are used for patients experiencing PK alterations, such as augmented renal clearance or patients infected with high-minimum inhibitory concentration (MIC) bacteria. While this approach is considered a form of therapeutic drug adaptation to improve target attainment, it is not individualized when used in a population. TDM of antibiotics on the other hand, is commonly seen as a highly individual strategy to overcome the variability in drug exposure amongst critically ill patients. Dose-adaptations based on TDM are commonly predicted and decided by the clinician, for example by increasing the dose or the dose-frequency by 25–50%; alternatively, doses could be predicted from PK software. This TDM-guided treatment individualization has been shown to increase clinical efficacy for vancomycin [33] and reduce mortality rates during aminoglycoside therapy [34]. We suggest that the same concept of TDM can be applied in the TCI system resulting in a closed-loop, adaptive, TCI system to further refine therapy (Fig. 38.1). In the case of antimicrobial drugs, feedback would ideally rely on the

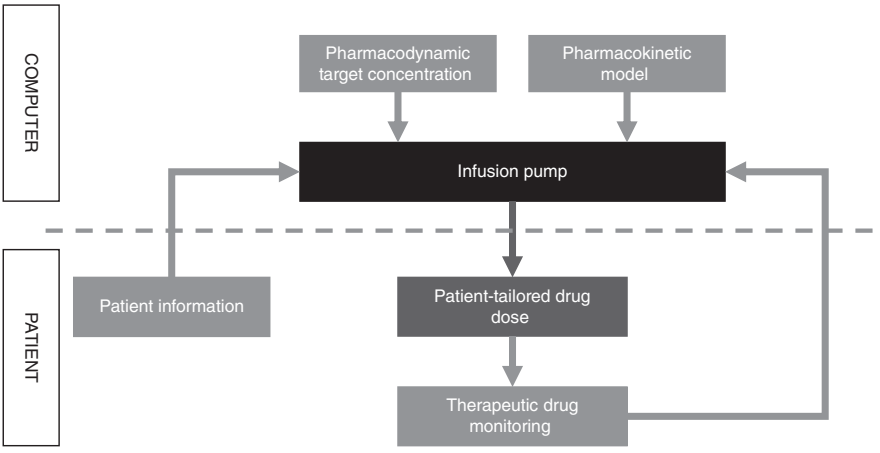

Fig. 38.1 Components of adaptive target controlled infusion of antibiotics

Table 38.1 Drugs of interest for adaptive target controlled infusion in critical care

Drug group	Drug name
Antibiotics	Piperacillin
	Ceftazidime
	Cefepime
	Meropenem
	Flucloxacillin
	Vancomycin
	Linezolid
Analgesics	Remifentanil
Hypnotics	Propofol
	Dexmedetomidine
	Pentobarbital
	Thiopental
	Ketamine
Anti-epileptics	Valproic acid
	Barbiturates

level of bacterial killing. However, in patients, it is not possible to continuously monitor the bacterial load. Therefore, we suggest that monitoring of plasma concentrations of antibiotics as a surrogate marker for (predicted) bacterial cell kill at the focus of infection can be used as feedback for the TCI pump. Closed-loop TCI has been explored mainly in the field of anesthetics, but for dose optimization of antimicrobial therapy this is a truly innovative and promising strategy to improve target attainment in critically ill patients.

The use of TCI in the ICU is not limited to the few antibiotics that have been studied so far. Apart from piperacillin, vancomycin and cefepime, the concept could also be applied to administer any drug that can be given as a continuous infusion (Table 38.1).

38.6 Conclusion

TCI has been adopted by many and is currently an established approach for administering anesthesia. In other specialties and for drugs other than those used in anesthesia, experience is very limited. As continuous infusion is also commonly used for many drugs in critical care, and as important PK variability is present for many of them, TCI can be considered an interesting concept for the ICU. More specifically, and although many challenges are present, TCI would offer a practical solution for improved administration of antibiotics. Research is needed to confirm that target attainment is better, and the role of TDM in an adaptive TCI approach also requires further investigation.

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