Title

Subcutaneous antibiotic therapy: the why, how, which drugs and when

Intended Category

Narrative Review

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Running title: Subcutaneous antibiotic therapy

Key words: Subcutaneous, subcutaneously administered, antibiotics, antimicrobials

Funding sources: This research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors.

Abstract length: 239 words

Article length: 2970 words, 1 table, 1 figure, 1 appendix.

Brief summary:

This study reports the rationale for subcutaneous (SC) administration of antibiotics and its limitations. Evidence suggests that the SC route could be an alternative to the IV route for time-dependent antibiotics in specific situations.

Abstract

Objectives: To describe the rationale for subcutaneous (SC) administration of antibiotics from available published data and to make propositions to help clinicians in daily practice.

Design: Narrative review

Setting and participants: Hospitalized patients, persons in long-term care facilities and ambulatory care.

Methods: We searched the MEDLINE/PubMed electronic database for evidence supporting SC administration of antibiotics, up to September 2019; the results of this primary search were supplemented by searching the references of the identified articles, as well as by searching in Google Scholar.

Results: Regarding tolerability, efficacy, and pharmacokinetic/pharmacodynamic (PK/PD) profiles, most studies suggest that the SC route could be an alternative to the IV route, particularly for time-dependent antibiotics and among certain patient populations, like patients with poor venous access, swallowing disorders or behavioural disturbance. However, clinical evidence of the benefits and risks of SC antibiotic administration is still scarce and of low level.

Conclusions and Implications: SC administration of antibiotics may be useful in various settings such as in hospitalized patients and among those in long-term care facilities or being cared for at home. However, further clinical studies are needed to assess the PK/PD properties, as well as the risks and benefits of SC administration of antibiotics. In this review, we highlight the potential benefits of SC administration of antibiotics and address practical recommendations for its use. This information will

enable improvement of treatment strategies and present the SC route as a potential option in specific situations.

Subcutaneous antibiotic therapy: Why, how, which drugs, and when

Introduction

Bacterial infections are one of the main causes of morbidity and mortality in the older population and pose many challenges to the clinician; one of the first challenges is selecting the route of antibiotic administration. The most frequently used routes for delivering antibiotics are intravenous (IV), oral, and intramuscular (IM), each one with benefits and drawbacks.[1]

In special populations like older adults, an IV access may become challenging because of a poor peripheral venous network or agitation. IM access can be associated with pain and is contraindicated in patients receiving anticoagulants. Moreover, drugs administered through IM route can inadvertently be delivered to the subcutaneous (SC) space.[2, 3, 4, 5] Oral administration may be compromised by swallowing disorders, altered mental state, or by limited treatment options. In addition, the oral bioavailability of certain antibiotics may be reduced by food-drug, drug-drug interactions, and gastrointestinal disorders. [2, 3, 4]

SC administration may help to circumvent those limitations frequently found in long-term care facilities, geriatric departments, palliative, and ambulatory care, which could partially explain why this route is mainly used in those settings.[6] Nevertheless, SC administration of antibiotics is still off-label for many of them. An up-to-date review on this issue is needed as a growing body of evidence could further support the use of the SC route.[7, 8, 9, 10] The main objectives of this review were to analyse the rationale for SC administration of antibiotics, and make practical propositions to help clinicians in daily practice, as well as the development of future clinical trials.

Methods

We conducted a MEDLINE/PubMed database research up to September 2019, the results of this primary search were supplemented by reviewing the references of the identified articles, and by searching Google Scholar. The initial PubMed search terms were: subcutaneous[All Fields] AND ("anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields] OR "antibiotic"[All Fields])) AND "humans"[MeSH Terms]. The initial search provided close to 500 articles. Any abstract that described SC administration of antibiotics in humans was considered eligible for inclusion. Abstracts that did not described SC administration of antibiotics, and animal-based studies were excluded. Posters and conference presentations were included if they described original research. The articles considered for inclusion were limited to those written in French, English, or Spanish. Finally, 37 articles, and 3 poster presentations were included.

Discussion

Why subcutaneous administration?

- **The subcutaneous route**

Drugs administered by SC route are delivered into the interstitial space, a fibro-collagenous network beneath the dermis.[11] Following their delivery, one of the first things that influences absorption is molecular weight. Small-molecules are absorbed into the interstitial vasculature by passive diffusion and endothelial permeability. Whereas high-molecular-weight agents are absorbed in the lymphatic system, which delays the time to achieve their maximum concentration.[12, 13] Other factors that influence the rate and extent of drugs absorption are: electric charge, hydrophilicity, degradation profile, and formulation (*e.g.*, concentration, volume, viscosity, and excipient profile).[14] In clinical practice, the SC route is routinely used to administer

vaccines, insulin, heparin, biological agents, and high-molecular-weight medications (*e.g.*, immunoglobulins).[15, 16]

- **Advantages of subcutaneous administration**

The SC route may usefully combine some advantages of both the oral and other parenteral routes,.[17, 18] SC administration of drugs is described as easy to perform (less demanding for nursing staff), it enables continuous administration of fluids (hypodermoclysis), or bolus administration of pharmacological agents in diverse settings.[19, 20, 21, 22] Also, compared to the IV route, the risks of thrombosis and catheter infections in SC route are less frequent or less severe, however strong evidence from comparative studies is lacking.[9, 23] Unlike IM route, SC administration is not contraindicated by anticoagulant therapy, which is common in older adults. In addition, the SC route has little impact on patient's mobility, which is a central component for the prevention of functional decline and rehabilitation.[24]

Taking into account the mentioned profile, SC administration of antibiotics could find a place in-hospital care, prolonged outpatient therapy, as well as in long-term care facilities.[25, 26]

- **Limitations of subcutaneous administration**

Adverse events (AEs) caused by SC administration of drugs may include pain, oedema, and inflammation at the injection site (details for AEs are described in **Appendix**). Also, solutions with high osmolality and/or very low or high pH cannot be administered through SC route due to the risk of cutaneous necrosis.[19] Reduced bioavailability (due to partial absorption) and potential underdosing are other relevant issues that should be considered when using the SC route.

- **Subcutaneous administration of antibiotics**

In some European countries, SC administration of antibiotics, although off-label, appears to be commonly considered by infectious diseases (ID) specialists and geriatricians.[6, 27, 28, 29] In a survey of 382 French practitioners, 96% of participants reported SC administration of antibiotics at some point, and more than a third of the geriatricians surveyed reported administering SC antibiotics at least weekly. Concerning the type of antibiotic, ID specialists and geriatricians reported previous use of SC route for ceftriaxone (100%), ertapenem (33%), teicoplanin (39%), aminoglycosides (35%), and amoxicillin (15%).[6] However, routine SC administration of antibiotics worldwide is infrequent.[28, 29]

How is the subcutaneous route being used for the administration of antibiotics?

Results from a prospective observational multicentric study that included 219 patients treated with SC antibiotics, showed that SC antibiotics are most frequently diluted in 0.9% NaCl (72.3%), administered by slow injection; *i.e.*, > 5 min (61.3%), and using a flexible catheter (67.9%). The preferred injection sites were the thighs (51.7%) and flanks (25.1%). AEs were reported in 50 patients (22.8%), and included local pain (13.2%), induration (7.8%), hematoma (7.3%), and erythema (2.7%).[27] AEs were usually transient, and mainly reported with teicoplanin (70%). Administration of teicoplanin, and rapid injection (< 5 min), were both predictors of AEs. Antiplatelet or anticoagulant agents were not associated with AEs. [27] However, the principal limits of this survey were the sample size, participation on voluntary basis, and uncontrolled design.

Based on our daily experience and available evidence, clinical recommendations include checking the injection site daily to identify any local AEs. Regarding an optimal dilution, there is no strong evidence or consensus, and we currently use the same dilution as for the IV route. Administration of antibiotics diluted in 50–100 mL of

solvent (NaCl 0.9% or glucose 5%) by slow injection (by gravity; 30–60 min) and the use of a flexible catheter seems to decrease the risk of local AEs. Flexible catheters may be either removed between infusions, considering a change of injection site at each administration or kept patent for 3–4 days. While thighs and flanks are the preferred sites of injection, the back may be considered to prevent catheter removal by an agitated patient. Surveillance of spillage and catheter misplacement are also important.[30]

Which antibiotics?

- Importance of pharmacokinetic/pharmacodynamic properties for SC antibiotic administration

The main PK/PD indices of antibiotics are: the minimum inhibitory concentration (MIC; minimum concentration of the antibiotic that inhibits bacterial growth), the minimal plasma or trough concentration (C_{min}), the peak concentration (C_{max}), time to reach C_{max} (T_{max}), the length of time during which the concentration of the drug is greater than the MIC (T>MIC), peak concentration divided by MIC (C_{max}/MIC), and the ratio of the 24 h area under the time-concentration curve divided by the MIC (AUC/MIC).[32, 33, 34]

Normally, the progressive diffusion of a molecule from the SC space to the intravascular compartment is associated with a decrease in the peak plasma concentration (reduced C_{max}) and a longer time to achieve it (increased T_{max}), compared with intermittent IV administration. However, the area under the time-concentration curve may be similar to that obtained with the IV route if the dose is entirely absorbed, *i.e.*, if the SC bioavailability is close to 100% (**Figure 1**). Hence, the SC route may be associated with prolongation of the action of a drug, even though its terminal half-life is unchanged compared to IV route. The next sections of the article will focus on the available evidence that supports how the SC route may optimize the PK/PD parameters

149 of time-dependent antibiotics, like certain β-lactams. By contrast, SC administration is
150 unlikely to optimize the PK/PD of concentration-dependent agents—e.g.
151 aminoglycosides and fluoroquinolones—as their C_{max} would be decreased.[35] Findings of
152 reports on SC administration of antibiotics are listed in **Appendix**, and summarised
153 along with practical recommendations in **Table 1**. These recommendations are mainly
154 based on PK/PD and safety data. An important consideration is the heterogeneity among
155 studies in terms of design, objectives, populations, reports of AE, clinical, and PK data.

156 **Ceftriaxone**

157 Ceftriaxone is frequently administered SC in some European countries, possibly due to
158 its spectrum, half-life, and previous marketing approval for SC route use until 2015.
159 However, this route has been discouraged by the European Medicines Agency because
160 of insufficient clinical data, so SC use is currently off-label.[36] Still, SC ceftriaxone is
161 prescribed in settings such as hospitalization, ambulatory assistance and palliative
162 care.[27, 37, 38, 39, 40, 41, 42, 43] SC administration of ceftriaxone is associated with a lower
163 peak concentration compared to IV administration, but its bioavailability approaches
164 100%.[39] Other PK parameters such as the trough level, AUC, and T>MIC (which is
165 predictive of the efficacy of β-lactams), are adequate compared to the IV route.[37, 38, 41, 42]
166 Moreover, co-administration of ceftriaxone with recombinant hyaluronidase is
167 associated with a higher C_{max} and reduced T_{max}.[39] Ceftriaxone is generally well
168 tolerated; the most frequently reported AE is pain at the injection site, which may be
169 ameliorated by previous application of lidocaine or recombinant hyaluronidase. [27, 37]
170 Rapid injection of ceftriaxone should be avoided as it increases pain. [27, 38, 39] The
171 available evidence for the efficacy and tolerability of ceftriaxone by SC route could
172 support its use. [27, 38, 40, 42] (**Appendix**).

173 **Ertapenem**

Ertapenem is mainly used to treat infections caused by Gram-negative bacteria that produce extended-spectrum β-lactamases (ESBL-E). SC administration of ertapenem has been studied, but its clinical use is off label. Frasca *et al*. reported that SC administration resulted in a lower C_{max} compared to IV administration, but the AUCs over the dosing interval were similar, which suggests a bioavailability close to 100%.[44] Similar findings have been reported for high-dose ertapenem in bone and joint infections (BJI).[45, 46] Population PK/PD parameters and the results of simulations suggest that SC ertapenem has a comparable T>MIC index respect to IV route.[26] In a recent study of older persons (mean age, 86 years) with mainly urinary or respiratory tract infections, SC and IV ertapenem presented no significant differences in individual AUCs or the chosen PTA (probability of target attainment) of maintaining a *f*T>MIC at least 40% of the time.[30] Forestier *et al*. has also reported successful SC use of ertapenem for urinary tract infections caused by ESBL-E.[47]

Studies mainly report mild AEs with SC use of ertapenem, excepting one report of skin necrosis.[26, 30, 44, 46] Therefore, SC administration of ertapenem could be considered as an alternative to IV administration. (Appendix).

- **Teicoplanin**

Teicoplanin is a glycopeptide used as an alternative to vancomycin for the treatment of infections caused by some Gram-positive bacteria. It has a long elimination half-life, and several days are necessary to achieve a steady-state concentration, which normally requires the use of loading doses during the first days of therapy.[48, 49] Four studies have evaluated the tolerance and efficacy of SC teicoplanin. The first assessed the efficacy, tolerance, and PK of teicoplanin delivered by SC and IV routes; PK results showed that the C_{min} did not differ between IV and SC routes during the first 14 days of treatment.[50] In the second study, the SC route was used after an initial IV loading. Wherein IV route

resulted in a higher peak concentration, the C_{min} was higher at 48 h after SC administration.[25] The third study, mainly comprised by older patients with BJI, showed that 85% of participants achieved the target C_{min} irrespective of the route of administration (IM, IV, or SC).[51] In addition, Cazaubon *et al*. showed that SC administration of teicoplanin was associated with a lower C_{min} and plasma concentration (AUC) after a 2-day loading phase, but these differences were absent after 14 days due to drug accumulation.[52, 53] SC teicoplanin has also been used to treat infective endocarditis, however this has only been anecdotal.[54]

The incidence of AEs after SC administration of teicoplanin ranges from 10% to 30% (mainly local pain). However, in the multicentric survey of Roubaud-Baudron *et al.*, SC teicoplanin was independently associated with AEs.[27] Similarly, El Samad *et al*. found that the frequency of SC teicoplanin-associated AEs increased for doses > 600 mg per day, suggesting that concentration could influence tolerance.[25] (**Appendix**).

- **Aminoglycosides**

Studies of SC administration of amikacin and tobramycin showed a lower C_{max}, higher T_{max}, and comparable bioavailability respect to IV administration. However, these studies are outdated and have methodological limitations; hence, their relevance to current clinical practice is limited.[55, 56, 57, 58] C_{max} is an important PK parameter for these concentration-dependent antibiotics and SC route could decrease their efficacy. Amikacin, and gentamycin have poor local tolerability and a high rate of severe local AEs, including painful nodules, ulcers, and cutaneous necrosis.[59, 60, 61, 62, 63] Currently, aminoglycosides are rarely administered by SC route, and the available evidence does not support their use.[7, 8, 9, 27] (**Appendix**).

Other antibiotics

SC administration of ampicillin, cefepime, and temocillin present a similar PK profile to that of the other studied antibiotics, characterized by a delayed T_{max} but similar AUCs.[55, 64, 65] However, these studies were performed in healthy volunteers and with single-dose PK analysis.

Some antibiotics—vancomycin, oxacillin, and cefuroxime—induce endothelial toxicity when administered IV, and may not be well tolerated when administered SC as their absorption would take place on interstitial vasculature.[31]

When to perform SC administration?

Current evidence shows that IV route represents the best option to initiate antibiotic therapy in severe infections (sepsis, septic shock), as therapeutic concentrations are rapidly achieved. However, switching from IV to SC once the patient has been stabilized is feasible, particularly for time-dependent antibiotics, provided that the AUCs and T>MIC values are comparable. In non-urgent situations, particularly when oral access is limited, initiating antibiotics by SC route could be discussed as an alternative.

Indications for SC administration of antibiotics are not standardized. In the previously described survey by Roubaud-Baudron *et al.* , in almost half the cases SC route was used as a switch from IV or oral routes.[27] Frequent reasons for SC administration were: poor venous access, palliative care, patient agitation, contraindications for oral and IM administration, and non-availability of a suitable oral antibiotic. Also, SC administration has been used to facilitate hospital discharge or prevent hospitalization. [27, 29]

Infections requiring prolonged antibiotic administration, usually managed in hospital (*e.g.*, BJI or infective endocarditis), could benefit from SC route due to its safety, potential suitability for ambulatory care, easy supervision, and its PK and PD properties.

SC administration could be particularly useful for people with poor venous access, such as older adults and IV drug users. It could also be a resource to consider in persons with hyperactive delirium, and to prevent functional decline, as it poses less of a restraint to mobility than continuous IV lines. SC administration of antibiotics may also be considered in special conditions, including patients with an altered mental state, patients with swallowing disorders, and those receiving palliative care. It is not infrequent that in those patients, central venous catheters or peripherally inserted central catheters (PICC) are placed, being inappropriate as they are uncomfortable, and increase the risk of further complications like thrombosis or infection.

- **Future perspectives regarding SC administration**

The interest in SC administration of drugs is increasing in many specialties, and for diverse agents.[66] Therefore, multiple strategies for optimizing the efficacy and tolerance of SC administration are under development, such as the use of recombinant human hyaluronidase to decrease the diffusion barrier.[67, 68, 69, 70] Also, interestingly, simple tools like mentholated warm compresses, may improve the SC blood flow rate and absorption of antibiotics.[71]

SC route may be a useful resource in the treatment of ambulatory patients in developing countries, as well as vulnerable patients (including IV drug users), people in remote locations and could also find applications in military medicine.

The absence of studies with clinical efficacy endpoints, adequate controls, large sample sizes, and the lack of analysis of PK/PD parameters limit the use of SC administration for most antibiotics. Still, studies focusing on PK/PD parameters and safety analysis of new routes for previously approved antibiotics may be appropriate for supporting (or

not) the use SC without necessarily conducting full comparative studies, as pointed in FDA guidelines and other publications.[72, 73]

Future studies should be conducted taking in account special populations (obese, older, and malnourished patients), antibiotics administered more than once daily, or in continuous infusion. They should also have an adequate modelling to limit the number of biologic samples taken from the population, and with parallel-group or crossover designs. Some current initiatives are already trying to address the main limitations.[74]

The potential advantages of SC administration of antibiotics must not override compliance with good clinical practices; particularly, avoidance of over-prescription and switching to a reduced-spectrum antibiotic once the results of drug susceptibility tests are available. Finally, daily inspection of the injection site is needed, as in all medical procedures that involve drug delivery.

Conclusion and implications

SC administration of antibiotics may be useful, reliable, economical, and easy to apply in various settings such as in-hospital care, long-term care facilities or ambulatory care. In some cases, the SC route for antibiotics may also be considered to facilitate hospital discharge in well selected patients. SC administration can optimize time above MIC but decreases C_{max}, hence "time dependent" antibiotics are probably the best candidates for this route. Further clinical studies are needed to assess the risks and benefits of SC administration in time-dependent antibiotics. Finally, SC administration should be considered during the development of new antimicrobial agents.

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74. Pharmacokinetics and Safety of Antimicrobial Agents Administered by Subcutaneous Route in Patients Aged Over 65 years (PhASAge) In. ClinicalTrials.gov ID: NCT03583749

512 **Table 1. Summary of evidence and practical recommendations**

Drug Categories	Summary of Evidence	Recommendations for clinicians
• **General considerations**	- SC use of antibiotics is associated with (*versus* IV): o ↓ C_{max} o ↑ T_{max} o *S*imilar AUCs (considering total absorption of antibiotic dose) o Similar T>MIC.[25-26, 30, 37-39, 41-42,44-45, 50, 52-53, 55-58] - T>MIC is critical for "time-dependant" antibiotics - C_{max}/MIC is critical for "concentration-dependant" antibiotics	• SC route for time-dependent antibiotics like beta-lactams might be considered given their PK/PD properties. * • SC route for concentration-dependent antibiotics like aminoglycosides should not be used given their PK/PD properties and a poor safety profile. * • SC route might be considered after an initial IV loading phase, as IV remains the route for emergency. * • SC route is reasonable as an initial option in patients with non-severe infections or patients in which other routes are not feasible / desirable. # • The use of a flexible catheter, slow injection (> 5 minutes), and daily surveillance of the device may decrease the risk of local AEs. † • Antibiotic dilution for SC or IV are the same †
• **Cephalosporins** • **Time-dependent antibiotics** Ceftriaxone++ Cefepime[64] Ceftazidime[71]	o Most of the available evidence comes from SC ceftriaxone. o Bioavailability ≈100%. Trough level, AUC, and T>MIC are non-inferior to IV route.[37-39, 41-42] o Evidence from clinical use in hospitalization, ambulatory care, and palliative-care (including older population).[6, 27, 29, 40, 42-43] o Described as well tolerated, pain may be reduced by previous injection of lidocaine.[37-40, 42, 43] o Co-administration of SC antibiotics (ceftriaxone) with	• SC use of ceftriaxone might be considered (similar bioavailability compared to the IV route with a good safety profile) * • Other cephalosporins may be considered too but evidence is scarce. *

	recombinant hyaluronidase has been described to ↑ C_{max} and ↓ T_{max}.[39] ◦ Approximate number of individuals having received SC cephalosporins within the revised studies: 438	
• **Carbapenems** • **Time-dependent antibiotics** Ertapenem	○ Ertapenem is the main carbapenem studied for SC use. ○ Similar AUC, T>MIC and PTA *versus* IV route.[26, 30, 44-45] ○ Clinical studies in hospitalized and ambulatory patients with ESBL-E infections (including older population).[6, 27, 29, 30, 44, 47] ○ Described as well tolerated, one reported case of skin necrosis.[30, 27, 44, 45, 47] ○ Approximate number of individuals having received SC Ertapenem within the revised studies: 174	○ SC use of ertapenem might be considered (similar bioavailability compared to the IV route with a good safety profile). *
• **Glycopeptides** • **Time-dependent antibiotics** Teicoplanin	○ ↑ or = C_{min} after loading phases.[25, 50, 52, 53] ○ Clinical evidence for hospitalized and ambulatory patients with BJI, and anecdotal use for endocarditis.[25, 27, 50, 52-54] ○ ↑ rate of AEs reported with teicoplanin in comparison with other SC antibiotics.[25, 27, 50, 53-54] ○ Approximate number of individuals having received SC Teicoplanin within the revised studies: 81 ○ Vancomycin is venotoxic	○ SC teicoplanin might be considered (similar bioavailability compared to the IV route with a good safety profile). * ○ Vancomycin should not be used by SC route. †
• **Aminoglycosides** • **Concentration dependent antibiotics** Tobramycin[55, 57] Amikacin[56] Netilmicin[58] Gentamycin[60-63]	○ ↓ C_{max} and ↑ T_{max}. Important caveat, as aminoglycosides are concentration-dependent antibiotics. ○ Comparable, or difficult to interpret bioavailability respect to the IV route.[55-58] ◦ Poor tolerability and diverse reports of cutaneous necrosis and painful ulcers.[29, 55, 59-63]	○ SC aminoglycosides should not be performed (poor safety profile and inappropriate PK/PD data) *

513 AE, adverse effects; AUC, area under the curve; BJI: bone-joint infection; C_{max}, peak concentration; C_{min}, minimal plasma concentration; ESBL,
514 extended spectrum beta-lactamase; *T*>MIC, time for plasma concentration above the minimal inhibitory concentration; IV, intravenous; LOE: Level of

evidence; LTCF, long-term care facility; PD, pharmacodynamics; PK, pharmacokinetics; PTA, probability of target attainment; SC, subcutaneous; T_{max}, time to peak concentration.

- * Data derived from prospective studies (randomized, cross over or parallel groups)
- # Only case studies
- † Consensus of expert opinion based on clinical practice surveys

522 **Legends to Figures**

523 **Figure 1:** illustration of plasma concentration profile of drugs administered by intravenous (IV) and
524 subcutaneous (SC) infusion. C_{max}, peak concentration; T_{max}, time to peak concentration; MIC,
525 minimal inhibitory concentration.

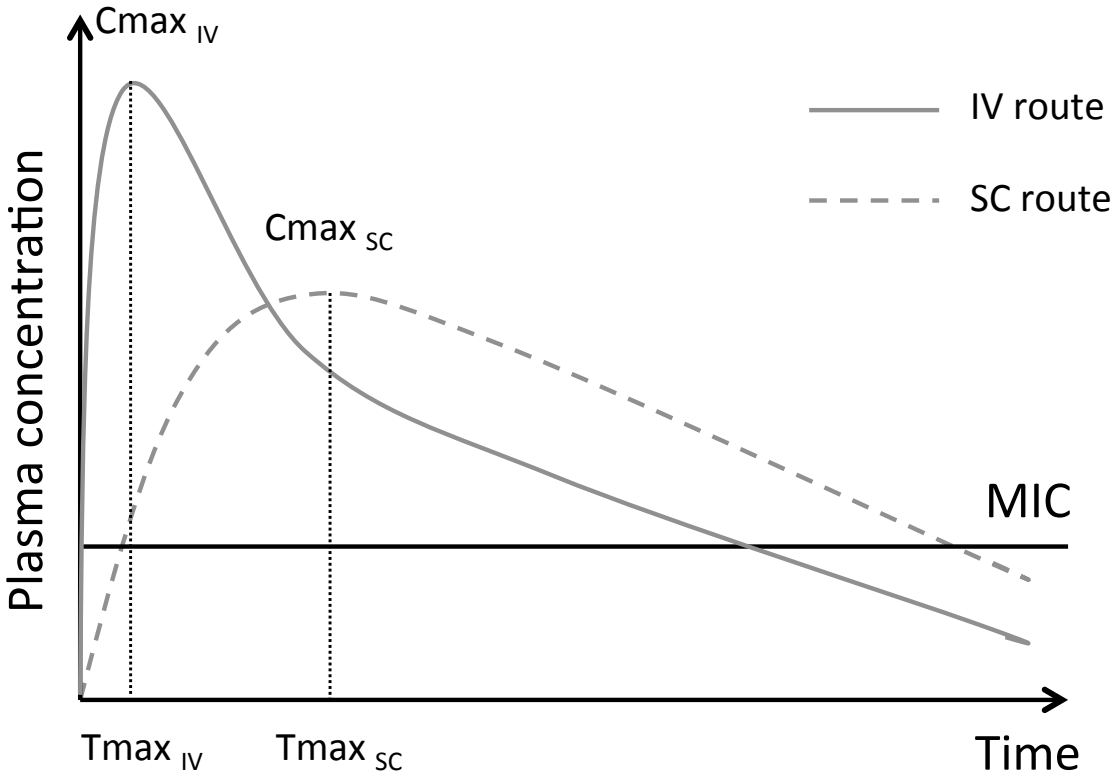
Cmax IV
Cmax SC
IV route
SC route
Plasma concentration
MIC
Tmax IV
Tmax SC
Time

Figure 1.