I.V. minocycline revisited for infections caused by multidrug-resistant organisms

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Purpose. The evidence supporting the potential use of i.v. minocycline for serious infections caused by multidrug-resistant organisms (MDROs) is summarized.

Summary. Minocycline achieves good tissue penetration and excellent oral absorption. Minocycline achieves serum concentrations comparable to other tetracyclines, with peak serum concentrations ranging from 3 to 8.75 mg/L following i.v. administration of 200 mg. Minocycline retains antimicrobial activity against methicillin-sensitive and methicillin-resistant Staphylococcus aureus as well as many gram-negative pathogens, such as Acinetobacter species, Citrobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Serratia marcescens, and Stenotrophomonas maltophilia. Minocycline has been used to treat respiratory infections caused by Acinetobacter baumannii and bloodstream infections. The majority of these gram-negative infections were treated with combination therapy, with results similar to those seen with first-line agents. The ability to switch from parenteral to oral therapy and its favorable tissue penetration make minocycline an attractive option for severe respiratory or skin and skin structure infections. For A. baumannii infections, minocycline is the second most active agent in vitro and may be the only therapeutic option in certain cases. The overall clinical experience with minocycline supports its use to treat A. baumannii infections alone or in combination with other agents. Minocycline could be used to treat other MDRO gram-negative infections but only as an agent of last resort due to the limited data available.

Conclusion. The available pharmacokinetic and clinical data support the use of i.v. minocycline for the treatment of MDRO infections, including infections due to S. aureus coagulase-negative and gram-negative pathogens.


Antibiotic resistance is estimated to contribute to 2 million illnesses and 23,000 deaths in the United States annually.1 Drug-resistant gram-positive bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci are prevalent in U.S. hospitals.2 Infections caused by gram-negative organisms with a high level of resistance to most antimicrobial agents are increasing in frequency and include extended-spectrum β-lactamase (ESBL)–resistant Escherichia coli, multidrug-resistant Acinetobacter species, and Klebsiella pneumoniae carbapenemase (KPC)–producing organisms.2 Practitioners are increasingly relying on older agents (e.g., minocycline, sulbactam) or unconventional therapeutic strategies (e.g., combination therapies with polymyxin-based regimens) to treat infections caused by these organisms.2,4

Given the lack of current therapeutic options for the treatment of multidrug-resistant organisms (MDROs), it is sensible to reconsider the use of older agents in the treatment of these
infections. Minocycline is one such agent. Minocycline was originally indicated for the treatment of staphylococcal and gram-negative infections, such as urinary tract infections resistant to tetracycline.\(^5\) Initial evaluations of i.v. minocycline were published in the early 1970s.\(^6\) Although i.v. minocycline was withdrawn in 2005 due to lack of use,\(^7\) it was reintroduced in 2009 to address the challenge of MDRO infections. Several publications have highlighted minocycline as a possible alternative therapy for MDRO infections.\(^7,8\) This article summarizes the evidence supporting the potential use of i.v. minocycline for serious infections caused by MDROs.

### Literature review

A relevant literature search included a Medline inquiry using the MESH term minocycline for articles published between 1966 and 2015. Scientific articles identified for review in this process were further searched for relevant citations. Conference abstracts were not included. The search was limited to English-language articles.

### Pharmacology of minocycline

Minocycline, a semisynthetic derivative of tetracycline, was first described in the 1960s.\(^9\) Minocycline maintains the hydronaphthacene nucleus and carboximide group at position C-2 that are essential for antibacterial activity but has an additional dimethylamino group at C-7 and no substituent at C-6.\(^9,10\) Compared with other tetracyclines, minocycline has a greater partition coefficient at a neutral pH, resulting in enhanced lipophilicity.\(^11\) These alterations result in a compound with a longer half-life, better oral absorption, and enhanced tissue penetration compared with other tetracyclines as well as being unaffected by many resistance mechanisms.\(^7\)

Similar to other tetracyclines, minocycline inhibits bacterial protein synthesis. Tetracyclines exhibit their antibacterial effect by reversibly binding to a single, high-affinity binding site of the ribosomal 30S subunit.\(^12\) This binding results in conformational changes in the 16S ribosomal RNA, preventing the association of aminoacyl transfer RNA to the ribosomal acceptor site.\(^13\) Due in part to the reversibility of this interaction, minocycline exhibits a bacteriostatic antibacterial effect.\(^14\)

### Spectrum of antimicrobial activity

Minocycline’s minimum inhibitory concentration (MIC) values of ≤4.0 μg/mL for Enterobacteriaceae, Acinetobacter species, and S. aureus are considered susceptible.\(^15\) Minocycline retains MIC\(_{50}\) values of ≤4.0 μg/mL (50% of tested isolates have an MIC equal to or less than this value) against many gram-positive pathogens, such as methicillin-sensitive S. aureus, MRSA, vancomycin-intermediate S. aureus, vancomycin-resistant S. aureus, and coagulase-negative staphylococci.\(^16,17\) Minocycline does not have consistent activity against enterococci. Minocycline retains MIC\(_{50}\) values of ≤4.0 μg/mL against many gram-negative pathogens, such as Acinetobacter species including carbapenem-resistant isolates, Citrobacter species, E. coli, Enterobacter species, K. pneumoniae, Stenotrophomonas maltophilia, and Serratia marcescens.\(^10,16,18\) Minocycline does not have any notable activity against Pseudomonas aeruginosa. A recent survey found that minocycline was the second most active agent against Acinetobacter baumannii from 2007 through 2011, with an MIC\(_{50}\) of 1 μg/mL; however, tigecycline values were not reported in this study.\(^19\) Recently, Qureshi et al.\(^19\) reported that 20 patients developed colistin-resistant A. baumannii infections while receiving colistin therapy. The authors reported that 50% of these isolates were susceptible to minocycline.

When comparing minocycline with other tetracyclines against 5478 clinical isolates of A. baumannii, minocycline was noted to be more active than doxycycline (79.1% versus 59.6% susceptible, respectively) and tetracycline (79.1% versus 30.2% susceptible, respectively).\(^10\) In addition, minocycline potency for Burkholderia cepacia and S. maltophilia was twofold and fourfold greater (MIC\(_{50}\); 2 and 0.5 μg/mL, respectively) than doxycycline and at least eightfold greater than tetracycline. Due to the increased potency of minocycline when treating B. cepacia and S. maltophilia infections, the Clinical and Laboratory Standards Institute (CLSI) recommends testing and reporting results for minocycline only for these two infectious agents.\(^20\) Due to the difference in activity between tetracycline and minocycline, laboratories are advised not to use tetracycline as a surrogate drug for reporting minocycline susceptibility results.

### Mechanisms of resistance

The bacterial tetracycline resistance gene tet(A) confers resistance generally to tetracycline alone, while tet(B) confers resistance to tetracycline and minocycline;\(^21\) therefore, if an organism has an elevated MIC to tetracycline, the gene does not necessarily confer resistance to minocycline. In addition, in a review of drug-resistant Acinetobacter species, Esterly et al.\(^22\) noted that there is conflicting evidence about whether tigecycline or minocycline is more active against A. baumannii isolates. This is partly due to the
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Pharmacokinetics and pharmacodynamics

The earliest studies of i.v. minocycline pharmacokinetics were conducted in the 1970s and found that the drug achieves serum concentrations comparable to those of other tetracyclines, with peak serum concentrations of 3–8.75 µg/mL and trough concentrations of 0.6–1.9 µg/mL after a 200-mg i.v. dose.13,26–30 Similarly, studies conducted by the manufacturer found peak concentrations of 2.52–6.63 µg/mL (mean, 4.2 µg/mL) and trough concentrations of 0.8–2.6 µg/mL (mean, 1.4 µg/mL) after the administration of a single 200-mg dose.13,26 Serum minocycline concentrations throughout the dosing interval are substantially higher for minocycline than for tigecycline. The pharmacokinetic parameters of i.v. minocycline are summarized in Table 1.

Minocycline is primarily eliminated via nonrenal routes, with only 5–12% of a dose being recovered in the urine.31 The remainder is metabolized by the liver or excreted through hepatobiliary circulation.26,32,33 The elimination half-life of minocycline (15–23 hours) is much longer than that of tetracycline but similar to that of doxycycline.14 Minocycline is 76% protein bound,26 less than that of doxycycline but similar to that of tetracycline.

Minocycline’s volume of distribution ranges from 67.5 to 115 L.26,32 Minocycline’s tissue penetration is better than that of tetracycline and doxycycline due to its enhanced lipophilicity. Macdonald et al.26 demonstrated tissue:serum concentration ratios of >1.00 in the liver, gallbladder and bile fluids, prostate, and genitourinary organs. In the lung, minocycline achieves a tissue:serum ratio of 3.80.26 Cerebrospinal fluid minocycline concentrations were found to be less than 50% of serum concentrations in human and animal studies but to exceed those of the other tetracyclines.13,26

The steady-state area under the concentration–time curve (AUC) for minocycline 200 mg i.v. administered every 24 hours was 69.8 µg·hr/mL.29 Compared with other antibacterials, such as the β-lactams, only minimal data regarding the pharmacodynamics of minocycline have been published. There has been some discussion that based on the clinically attainable drug exposures of the tetracyclines, they can be classified as AUC-driven agents.34 Limited data exist regarding the pharmacokinetics and pharmacodynamics for minocycline. However, evaluation of the available data seems to indicate that, for the tetracyclines, the ratio of the AUC of free drug over the MIC (AUC/MIC) is associated with an antibacterial effect in an in vitro model.31,35 Specifically, the target AUC/MIC ratios required to achieve 24-hour static and 1-log reductions against MRSA were 33.9 and 75.9, respectively.35 Therefore, when considering the reported AUCs

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### Table 1. Reported Pharmacokinetic Parameters of Intravenous Minocycline

| Ref. | Dosing | C_{max} (µg/mL) | C_{min} (µg/mL) | V_{e} (L) | t_{1/2} (hr) | CL (mL/min) | V (L) | AUC (mg·hr/L) | CL_{cr} (mL/min) | % Protein Binding | % Dose Excreted in Urine | % Tissue Protein Binding | % Tissue Excretion of Drug | % Tissue Excretion of Drug | % Tissue Excretion of Drug |
|------|--------|----------------|-----------------|---------|------------|------------|------|------------|-------------|-----------------|----------------|------------------|------------------|------------------|------------------|------------------|
| 15   | 10     | 4.2            | 1.4             | 1.9     | 15–23      | 3.5         | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 16   | 26     | 6.1            | 3.0             | 3.0     | 9–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 17   | 27     | 3.0            | 1.9             | 3.0     | 9–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 28   | 28     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 29   | 29     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 30   | 30     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 31   | 31     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 32   | 32     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 33   | 33     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 34   | 34     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               |
| 35   | 35     | 6.1            | 3.0             | 6.1     | 7–15       | ND          | ND   | ND         | ND          | ND              | ND              | ND               | ND               | ND               | ND               | ND               |

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a. AUC = area under the concentration–time curve, t_{1/2} = half-life, CL = total clearance, CL_{cr} = renal clearance, AUC = area under the concentration–time curve, ND = not determined.
from pharmacokinetic studies, current dosing regimens suggest that a desirable antibacterial effect would be attainable for organisms with minocycline MICs of <0.2 µg/mL. Currently, no specific fAUIC/MIC targets have been suggested for any of the tetracyclines.

**Clinical evaluations**

Clinical evaluations testing minocycline against gram-positive and gram-negative pathogens in a variety of infections have been conducted. The majority of evidence presented here are from limited case series or observational data. The available data contain varying or unspecified definitions for diagnoses and clinical cure and were obtained from small samples. Although large clinical trials to compare the safety and efficacy of minocycline with those of other agents are not available, the limited data available still provide valuable insight into the role of i.v. minocycline in treating infections. To determine the appropriateness of minocycline’s use in a patient, the severity of illness, risk for adverse events, lack of alternative agents, and strength of clinical evidence for the specific infection should all be weighed.

**Gram-positive infections. S. aureus.** In 1977, Rogers et al. reported the use of minocycline monotherapy for the treatment of three cases of *S. aureus* pneumonia and two cases of *S. aureus* skin and soft tissue infections as part of a larger clinical evaluation of i.v. minocycline use. Since the methicillin-resistance phenotype was unknown, only the minocycline susceptibilities of each isolate were documented. The one patient with a minocycline-resistant isolate did not experience a favorable clinical response.

**MRSA.** In 1984, Clumeck et al. published the results of a prospective, quasi-experimental study examining the combination of minocycline plus rifampin for a variety of MRSA infections. The infections treated varied from simple skin and soft tissue infections (n = 4) to more-difficult-to-treat infections such as pneumonia (n = 9), osteomyelitis (n = 4), septic thrombophlebitis (n = 3), septic urinary tract infection (n = 1), infective endocarditis (n = 1), and others (n = 3). Overall, 19 (76%) of 25 infections were successfully treated with the combination therapy. Of the 6 patients who did not respond to therapy, 2 had infections resistant to rifampin and 1 patient’s infection was resistant to both minocycline and rifampin.

Recently, a retrospective cohort study examined i.v. minocycline monotherapy for the treatment of MRSA and resistant gram-negative infections (n = 13), including skin and soft tissue infections (n = 5), pneumonia (n = 3), bacteremia (n = 3), infective endocarditis (n = 1), and osteomyelitis (n = 1). Despite including patients with deep-seated infections like infective endocarditis and osteomyelitis, the authors reported a 100% clinical success rate for all infections treated.

The most common staphylococcal infections for which i.v. minocycline therapy has been reported are skin and soft tissue infections (n = 11) and respiratory tract infections (n = 15). Approximately half of the isolates reported were methicillin resistant. Similar to data published for the treatment of *A. baumannii* infections, most available data are for i.v. minocycline used in combination therapy (58%). The most common combination agent used was rifampin. An overall high clinical cure rate of 83.7% was reported with i.v. minocycline use, including pneumonia (100%), and the successful treatment of several cases of deep-seated infections such as osteomyelitis (80%) and septic thrombophlebitis (66.7%) and offer a promising option for the treatment of staphylococcal infections.

**Gram-negative infections. A. baumannii.** Minocycline has maintained moderate activity against many *A. baumannii* isolates, including multidrug-resistant and tigecycline-resistant isolates. Clinical data describing minocycline’s utility in the treatment of infections caused by multidrug-resistant *A. baumannii* are sparse. The majority of data regarding minocycline’s use for the treatment of multidrug-resistant *A. baumannii* infections are limited to case series and retrospective cohorts totaling 106 patients.

Wood et al. in 2003, reported a case series of four patients with ventilator-associated pneumonia and reported clinical success in all four patients. In 2012, Jankowski et al. published a case series of i.v. minocycline for the treatment of multidrug-resistant *A. baumannii*. When treating respiratory, wound, urinary tract, and bacteremia infections with combination therapy including minocycline, the authors documented a clinical cure at discharge in four of five patients. Pogue et al. described a case series of patients who received minocycline for the treatment of carbapenem-resistant *A. baumannii* as part of an antimicrobial stewardship intervention to add i.v. minocycline. In this report, three patients with bloodstream infections, two with pneumonia, and one mixed surgical site and pneumonia infection were treated with minocycline. Clinical cure was achieved in four of the six patients.

As part of a retrospective cohort study examining antimicrobial therapy for the treatment of carbapenem-resistant *A. baumannii* ventilator-associated pneumonia, Chan et al. examined 36 patients treated with minocycline or doxycycline as monotherapy (n = 11) and combination therapy (n = 25). They documented a clinical cure in 9 (82%) of 11 patients treated with minocycline monotherapy and 20 (80%) of 25 treated with minocycline combination therapy. The authors did not clarify the number of patients treated with minocycline versus doxycycline. Bishburg et al. published a retrospective cohort study of patients treated with i.v. minocycline at a tertiary care hospital. Among the cohort were 6 patients with *A. baumannii infections*. All 6 patients were treated with minocycline monotherapy and survived to discharge.

Goff et al. recently conducted a retrospective cohort study of patients (n = 55) who received minocycline as
part of their treatment for multidrug-resistant *A. baumannii* infections, the majority of whom had respiratory infections (*n* = 32) and bloodstream infections (*n* = 10). Clinical success was documented in 40 patients (73%), with an infection-related mortality rate of 25%. Of the 14 patients who did not respond to therapy and died, 12 had pneumonia and 2 had bacteremia and pneumonia. The median age of these patients was 68 years (range, 27–85 years), and the median APACHE II score was 31 (range, 17–41).

Regarding *A. baumannii* infections, minocycline has been used predominantly to treat respiratory infections (*n* = 75) (including ventilator-associated pneumonia), followed by bloodstream (*n* = 13), bone (*n* = 10), and mixed (*n* = 17) infections. The majority of infections were treated with combination therapy, including regimens containing one or two additional antimicrobials. The additional agents were dependent on isolate susceptibility and commonly included colistin or ampicillin–sulbactam. Of the 17 patients who received minocycline monotherapy, 15 were treated for ventilator-associated pneumonia. Clinical cure rates appear comparable to those of other antimicrobials used to treat *A. baumannii* infections, but the majority of the data include minocycline as part of combination therapy.

*Enterobacteriaceae*. Limited clinical experience has been documented with minocycline for the treatment of both ESBL-producing and KPC-producing organisms. A retrospective cohort study of patients treated with i.v. minocycline published by Bishburg et al. described six infections caused by KPC-producing organisms and ESBL-producing organisms and two infections caused by ESBL-producing *E. coli*. All were treated with minocycline monotherapy, and only one patient (KPC bacteremia) did not survive to discharge. Pogue and colleagues included three patients with bacteremias caused by KPC-producing organisms in their case series, all of which were treated with minocycline as combination therapy. Two of the three patients experienced resolution of the signs and symptoms of their infections.

### Clinical application of current evidence

Limited data are available to support the use of i.v. minocycline for a variety of MDRO infections in ambulatory care and critically ill populations. Most of the published data on i.v. minocycline describe its use in the treatment of pneumonia, bloodstream infections, and skin and skin structure infections. The ability to switch from parenteral to oral therapy and its favorable tissue penetration make minocycline an attractive option for severe respiratory or skin and skin structure infections. Minocycline is a reliable alternative to standard therapy for both methicillin-resistant and methicillin-susceptible staphylococcal infections. For *A. baumannii* infections, minocycline is the second most active agent in vitro and may be the only therapeutic option in certain cases. The overall clinical experience with minocycline supports its use to treat *A. baumannii* infections alone or in combination with other agents. Minocycline could potentially be used to treat other MDRO gram-negative infections but only as an agent of last resort due to the limited data available.

### Cautions regarding the use of minocycline

Although the results of the clinical evaluations conducted are encouraging, several considerations should be made when deciding on the use of i.v. minocycline. Minocycline, like the other tetracyclines, may cause congenital defects. Animal studies have found evidence of teratogenicity and embryonic toxicity. Minocycline is not recommended for pregnant women or children age eight years or younger because it may cause permanent discoloration of the teeth and impair bone growth. The drug should only be used in these cases if no alternative is available and patients or parents have been advised of the risks.

Pharmacokinetic data for minocycline outside of healthy populations are very limited. The product labeling for i.v. minocycline does not provide renal dosage recommendations except not to exceed 200 mg in 24 hours in patients with renal impairment (creatinine clearance [CrCl] of <80 mL/min), and some controversy exists regarding the need for any adjustment at all. Bernard et al. reported a prolonged half-life (mean, 30 hours) in eight renally impaired patients (CrCl of <17 mL/min) who received 200 mg orally. Welling et al. evaluated a single i.v. infusion and five-day oral regimen of minocycline in renally impaired individuals (CrCl of <75 mL/min) and found no substantial differences in renal clearance in these patients. Sklenar et al. found that renal clearance decreased by 9–19% in anuric patients. Specific dose-related toxicities due to decreased renal elimination are unknown. No adjustment is needed in the case of hepatic dysfunction.

Minocycline is generally well tolerated, with some common adverse effects including nausea, diarrhea, and dizziness or lightheadedness. Although rare, dangerous reactions can occur. Patients should be monitored during therapy for new-onset rash, as drug rash with eosinophilia and systemic symptoms may occur. Pseudotumor cerebri is a potential complication and should be considered if patients develop a new headache or blurred vision.

### Future research

The package insert for i.v. minocycline does not recommend exceeding 400 mg in 24 hours, with the typical dose being 100 mg every 12 hours. Research suggests that an AUC:MIC of 75.9 is necessary to achieve a 1-log reduction in colony-forming units per milliliter for MRSA isolates. However, with pathogen MICs of ≥2 μg/mL, the recommended dosing strategy may lead to AUC:MIC ratios smaller than the target of 75.9. Interestingly, stroke neuroprotection trials have evaluated i.v. minocycline doses of ≤10 mg/kg/
day given for up to three days, without observing significant toxicity. In some cases, Pogue et al. administered 200 mg every 12 hours to achieve higher serum drug concentrations. Therefore, future research should confirm the optimal AUC:MIC target for a variety of pathogens and the safety and efficacy of minocycline doses exceeding 400 mg per 24 hours.

Lastly, the manufacturer just released a reformulated i.v. minocycline product (previously RPX-602) that incorporates magnesium sulfate, allowing the administration of minocycline in smaller volumes of fluid, which may improve the local tolerability of the i.v. infusions.

Conclusion

The available pharmacokinetic and clinical data support the use of i.v. minocycline for the treatment of MDRO infections, including infections due to S. aureus coagulase-negative and gram-negative pathogens.

Disclosures

Dr. Danziger is a consultant with the Medicines Company, Actavis Pharmaceuticals, and Theravance Biopharma. The authors have declared no other potential conflicts of interests.

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