

Clinical Communications

Doxycycline desensitization for a suspected case of ehrlichiosis

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Clinical Implications

- Desensitization can be achieved by administering doubling doses of medications to individuals with a history of acute onset adverse reactions that may be mediated by IgE, IgG, or other mechanisms.
- No previously published protocols for doxycycline desensitization exist.
- A stepwise protocol for rapid doxycycline desensitization was designed and implemented.

TO THE EDITOR:

Drug desensitization can achieve a temporary state of tolerance in individuals with histories of acute onset adverse reactions to specific medications.¹ Desensitization can be effective for individuals with IgE-, IgG-, or other acute mechanism-mediated reactions. Tetracyclines have never been shown to induce antigen-specific IgE. Administration of doubling doses of the target medication during the desensitization process may cause mast cells and basophils involved in the allergic response to become hyporesponsive, thus inducing a state of temporary immune tolerance to the medication.^{1,2} Desensitization to

a medication should be considered in 2 situations: first, when the desired medication is unique and no viable alternative exists and, second, when treatment alternatives exist but are not as effective as the drug of choice.³ Severe allergic reactions to antibiotics present significant challenges to clinicians treating infectious diseases in affected patients. Treatment of tick-borne illness in the setting of a history of an acute onset adverse reaction associated with previous doxycycline use is particularly difficult because the other treatment alternatives are less efficacious.^{4,5} When a critically ill patient with a history of a severe acute onset adverse reaction associated with previous doxycycline use presented to the intensive care unit, our multidisciplinary team quickly designed and implemented a protocol for doxycycline desensitization that we describe here.

A 41-year-old woman with a history of severe acute onset adverse reaction associated with previous doxycycline use was admitted to the medical intensive care unit of a tertiary-care hospital with altered mental status, fever, scleral icterus, hyponatremia, elevated liver function tests, leukopenia, and thrombocytopenia. Her only other medical history included asthma and hypertension. Medications included omeprazole and enalapril; the last dose of enalapril was 4 days before admission. The clinicians were concerned that tick-borne illness was the etiology of her symptoms and wanted to initiate prompt treatment for possible ehrlichiosis.

Doxycycline is the treatment of choice for ehrlichiosis and is superior to other antibiotics. Appropriate treatment should be initiated immediately in the absence of microbiologic confirmation because delay in therapy is known to increase the life-threatening risk from severe disease.⁶⁻⁸ The patient reported an adverse reaction to doxycycline 3 years earlier when prescribed

TABLE I. Doxycycline preparation specifications

Bag no.	Doxycycline concentration (mg/mL)	Total drug (mg)	Total saline solution (mL)	Total amount of saline solution infused (mL)	Total amount of saline solution wasted (mL)
1	0.1	5	50	38.75	11.25
2	1.0	100	100	97	3

TABLE II. Doxycycline desensitization protocol time

Dose	Bag no.	Start to end time (h)*	Rate (mL/h)	Infusion duration (min)	Monitoring duration (min)	Volume infused (mL)	Dose given (mg)	Cumulative dose given (mg)
1	1	0:00	15	5	10	1.25	0.125	0.125
2	1	0:15	30	5	10	2.5	0.25	0.375
3	1	0:30	60	5	10	5	0.5	0.875
4	1	0:45	120	5	10	10	1	1.875
5	1	1:00	240	5	10	20	2	3.875
6	2	1:15	38	5	10	3.2	3.2	7.07
7	2	1:30	75	5	10	6.3	6.3	13.3
8	2	1:45	150	5	10	12.5	12.5	25.8
9	2	2:00	100	15	10	25	25	50.8
10	2	2:25	100	30	30	50	50	100.8

Note. If the patient successfully tolerates desensitization, then begin maintenance dosing with doxycycline 100 mg intravenous or by mouth every 12 h. (Desensitization is temporary. If future scheduled doses are missed, then the patient will require repeated desensitization.)

*Total time: 3 hours and 25 minutes.

for treatment of a dental abscess. Approximately 1 hour after ingestion of the initial dose, the patient developed diffuse urticaria associated with facial and lip swelling as well as difficulty breathing. She had no vomiting or diarrhea. Her only other medication use at the time was a daily proton pump inhibitor. She required emergency evaluation and was treated with antihistamines, bronchodilators, and systemic corticosteroids. She was unsure if epinephrine was administered. After several hours of observation, her symptoms resolved, and she was discharged with instructions to avoid future doxycycline due to the severity of her reaction. The patient also recalled a remote history of a delayed papular rash without associated symptoms of anaphylaxis in response to sulfa-containing antibiotics and penicillin. Due to the patient's critical illness and history of suspected IgE-, IgG-, or other acute mechanism-mediated reaction to doxycycline, the division of allergy and immunology and department of pharmaceutical services were consulted for immediate desensitization to doxycycline.

Our group created a 10-step protocol for doxycycline desensitization (Tables I and II) based on previously published acute desensitization protocols.¹ The risks, benefits, and alternatives were discussed in detail with the patient, and she gave verbal consent to proceed with doxycycline desensitization. The target dose of doxycycline was 100 mg administered every 12 hours. The initial dose selected was 0.125 mg (1/10,000 of the target dose), which is consistent with current recommendations to choose a starting dose that is 1/1,000,000 to 1/100 of the target therapeutic dose, depending on the severity of the reported medication allergy and route of desensitization.^{3,9} Each subsequent dose was double the prior dose. Ten incremental dosage increases were administered, which is the minimum number suggested by current guidelines to reduce the risk of adverse effects.^{3,9}

Two different concentrations of doxycycline were prepared for intravenous administration. Bag 1 contained a 50-mL solution with a doxycycline concentration of 0.1 mg/mL, and bag 2 contained a 100-mL solution with a concentration of 1 mg/mL. These solutions were loaded into an infusion pump, and each dose administration was programmed individually. A flush bag of normal saline solution was infused simultaneously given the small volume of some of the doses. Use of a medication pump and formulation of only 2 solution bags allowed for easy dose adjustment and precise dosage delivery to reduce the risk of an error in doxycycline administration.

The desensitization procedure was performed in the intensive care unit to allow for continuous monitoring of the patient for potential adverse reactions, including anaphylaxis. Clinical assessments and vital signs checks were ordered before each dosage increase. The protocol instructed the nurse to contact the provider and hold subsequent doses until further orders if any adverse reactions occurred. The provider would then determine the subsequent course of action, depending on the reaction severity. Mild reactions that involved a single organ system, such as wheezing or urticaria alone, may be symptomatically treated with bronchodilators or antihistamines along with repeating the previously tolerated dose. More severe reactions, such as anaphylaxis or patient instability, would prompt discontinuation of the protocol and treatment with epinephrine 0.3 mg intramuscularly, which was available at the bedside. Doses 1 through 8 were infused over a 5-minute intervals, followed by a 10-minute monitoring

period between each dose. The ninth dose was infused over 15 minutes followed by a 10-minute monitoring period. The tenth dose was infused over 30 minutes, and the patient was subsequently monitored and her vital signs were recorded for an additional 30 minutes. The entire desensitization process lasted 3 hours and 25 minutes. The patient successfully completed desensitization without any adverse reactions. She was continued on doxycycline at a dose of 100 mg every 12 hours for 14 days and fully recovered from her illness.

To our knowledge, this is the first description of a protocol for rapid desensitization to doxycycline. The critical components of this desensitization were the short duration of the desensitization process, appropriate monitoring for severe reactions, streamlined preparation of 2 infusion solutions rather than multiple individual syringes, and programmed infusion pump for simple dosing to minimize delivery errors. A similar approach could be used to develop additional desensitization protocols in the future.

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