A Tale of Unequal Substitution: Minocycline and Acute Autoimmune Hepatitis

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Abstract

Objective: In this case report, we describe the development of an acute autoimmune hepatitis associated with a short course of minocycline prescribed for a skin infection. Due to a drug shortage, minocycline was substituted for doxycycline. **Conclusions:** It is imperative that practitioners be aware of the different risks that accompany switching between drugs in the tetracycline class, particularly the risk of autoimmune conditions including hepatitis.

Keywords

doxycycline, minocycline, autoimmune hepatitis, drug shortage

Introduction and Objective

Minocycline is an oral tetracycline antibiotic used primarily in dermatology for its anti-inflammatory effects. However, it is also useful in treating bacterial infections susceptible to tetracycline antibiotics. Recently, minocycline has seen increased usage due to drug shortages affecting the availability of doxycycline, the oral tetracycline typically chosen for most anti-infective treatment outside of acne.

Although similar in bacterial spectrum to doxycycline, minocycline carries with it several risks that have been infrequently reported with doxycycline. Among these risks is the possibility of autoimmune-mediated conditions including lupus and hepatitis.¹ While doxycycline, minocycline, and other tetracyclines have been associated with direct liver injury and hepatitis (including the potential for fulminate hepatic failure), the etiology of their role in drug-induced autoimmune hepatitis is not completely clear.² The hepatitis that develops is pathophysiologically distinct, and this can be noted clinically through elevations in antinuclear antibodies, anti-smooth muscle antibodies, and immunoglobulins in addition to the hepatic cellular changes and liver enzyme elevations.²

To investigate the association between minocycline and autoimmune hepatitis, we performed a MEDLINE database search of the English-language literature (1966-June 2013) using various combinations of the following terms: minocycline, hepatitis, autoimmune, liver injury, and toxicity. A TOXNET search was also performed, using the aforementioned terms. The results of this investigation revealed that minocycline has been associated with cases of both direct liver damage and, although uncommon, a number of cases of an autoimmune-based hepatitis condition.¹⁻¹³ The cases

of autoimmune hepatitis were seen in patients typically after long-term treatment with the drug for acne. These cases indicated that the hepatitis may have developed over several weeks to months, in contrast with the case reported here where hepatitis developed after a much shorter drug exposure.^{1,7,8}

In this case report, we demonstrate a relationship between the use of minocycline for a short-term infectious process and the rapid development of a life-threatening hepatitis, and we emphasize that this phenomenon may be a potential drawback to the increased utilization of minocycline for short-term infectious indications.

Description of the Case

The patient was a 54-year-old white male (weight 95 kg, height 70 in., body mass index 30.2 kg/m²). He presented to the hospital following an episode of vague chest and back pain that radiated throughout the chest. He also reported experiencing sweats and a low-grade temperature. The patient reported no significant alcohol consumption or history of pancreatitis. However, the patient reported several different levels of alcohol consumption to different providers during the admission process, although it was determined that his drinking was minimal to moderate at most. He also

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denied skin rashes, arthralgias, insect bites, or toxin exposures. He reported that as recently as the previous week he was performing his normal activities without limitation. His home medications were gathered from several different sources and included atorvastatin 20 mg, omeprazole 20 mg, ASA 81 mg, fish oil supplements, and vitamin D supplementation. The patient was admitted to the hospital for work up of his chest pain, and his home medications were held.

During his first day of hospitalization, the patient's clinical condition worsened significantly. Initial laboratory data noted that the patient had significant abnormalities: troponin 0.58 ng/mL (normal range <0.04 ng/mL), creatinine 1.3 mg/dL (no baseline level available), white blood cells = 12.09, aspartate aminotransferase (AST) = 278 U/L (normal range 0-37 U/L), alanine aminotransferase (ALT) = 244 U/L (normal range 0-40 U/L), carbon dioxide = 19 mEq/L (normal range 22-29 mEq/L), and an anion gap of 19.3 mEq/L (normal range = 7-16 mEq/L). The patient's bilirubin level was normal. Not long after his admission, the patient developed labored breathing, mottling, a distended abdomen, an elevated pulse rate (137 bpm), and low blood pressure (90/60 mm Hg). At this time the patient was questioned as to his recent medical history and home medications, supplements, and alcohol consumption. The patient was transferred to the intensive care unit (ICU) due to hemodynamic instability. The patient was given intravenous fluids and oxygen on admission to the ICU and taken for immediate imaging of the abdomen and chest. Ampicillin-sulbactam was empirically initiated in suspicion a septic process in the abdomen.

After the patient was stabilized in the ICU, a computed tomography scan revealed no aortic dissection. The radiologist noted nonspecific peri-portal edema and thickening of the gallbladder wall that were suggestive of acute hepatitis. The following day the patient's liver enzymes had dramatically increased with an AST of 1077 U/L and ALT of 727 U/L, although his vital signs and other laboratory values were improved. An ultrasound of the abdomen and gallbladder was conducted on the second day of hospitalization, which revealed no evidence of cholecystitis or stones in the gallbladder or ducts, leading to the increased probability of hepatitis as the diagnosis.

The patient and his family denied excessive alcohol consumption and the consumption of over-the-counter drugs or supplements. However, during this repeat questioning, the patient's wife stated that she had failed to mention that the patient had very recently finished a 10-day course of minocycline for a sebaceous cyst. Due to the timing of the recently discovered exposure to minocycline, it was suspected that the patient was experiencing either a drug-induced liver injury or an immune-mediated hepatitis associated with drug exposure. To differentiate between these possibilities, an antinuclear antibody (ANA) level was ordered. This test revealed that the patient's ANA level

was reported as positive (1:40 titer). Assays for hepatitis A, immunoglobulin G, and immunoglobulin M were negative, as were tests for acetaminophen and salicylates in the serum.

Over the next several days, the patient improved clinically with supportive care, and his aminotransferase levels dropped rapidly until he was discharged on day 6 with his AST normalized and with slightly elevated ALT (129 U/L). The patient's chest and back pain also resolved rapidly. The patient was restarted on his original home medications and discharged, although his atorvastatin was held until his follow-up visit with his primary care physician and the complete resolution of his elevated liver enzymes.

Discussion

Minocycline is a synthetic tetracycline antibiotic that has a relatively broad antimicrobial spectrum that includes methicillin-resistant *Staphylococcus aureus* (MRSA) as well as other *Staphylococcus* and *Streptococcus* species. These characteristics make it a reasonable choice for substitution in instances where doxycycline would be chosen, including treatment of community-acquired MRSA infection, such as might be found in an infected sebaceous cyst. Doxycycline, which is usually widely available and affordable, has been periodically affected by drug shortages. Many therapeutic agents have recently become scarce due to manufacturing problems, declining supplies, and often other, unknown reasons. These drug shortages have had a major impact on the therapeutic options available to practitioners, who may choose a closely related drug as a substitute, not recognizing the subtle differences between related agents. This case highlights the risk that there may be small, but often critical, differences between drugs in the same class, notably the risk of adverse events.

Drug-induced autoimmune hepatitis is an unusual complication of drug therapy. It has primarily been reported with nitrofurantoin and minocycline, although there are several other classes of drugs that have been implicated (eg, statins and the biological agents infliximab and adalimumab, among others).² Most of the cases of autoimmune hepatitis related to minocycline have been reported in patients using the drug for acne, where it is used for anti-infective as well as anti-inflammatory properties.^{1,9-11} A case series of minocycline-related autoimmune hepatitis notes 4 cases of adolescents developing hepatitis after 1 year to 18 months of exposure, and notes previous reports occurring after at least 1 month of treatment.⁸ Many of these case reports note the presence of symptoms such as fever and lymphadenopathy that started weeks or months prior to the diagnosis of hepatitis.⁸ Although the package insert for minocycline notes that hepatotoxicity is a potential side effect, no specific monitoring of hepatic function is recommended by the FDA-approved package insert.

Although the Naranjo Nomogram is the flagship method to assess the potential for a drug-induced cause of an adverse event or drug reaction, there exist several different scoring systems that may more precisely elucidate the relationship between a drug and a specific effect. The Roussel-Uclaf Causality Assessment method (RUCAM) scale and the Maria and Victorina (M&V) system of causality in drug-induced liver injury were both developed to specifically assess the likelihood of a causal relationship between a drug and liver injury (including autoimmune hepatitis). While these 2 scales have similarities, they are also complementary in that the M&V scale includes points for the extra-hepatic manifestations of drug-induced liver injury not noted in the RUCAM system. We used these rating scales to assess our patient with resultant scores of +10 for the RUCAM scale (range -9 to +14) and a +10 for the M&V scale (range -6 to +20), with higher scores indicating a stronger relationship for both scales. Our patient's score for the RUCAM scale is interpreted as "highly probable," and his score for the M&V scale is interpreted as "probable." This strongly suggests that minocycline was the causative agent of this patient's autoimmune hepatitis. A major component of the score for both scales is the temporal relationship between the minocycline and the rapid development and resolution of the hepatitis. If our patient had received a drug rechallenge and his reaction could have been observed, it may have allowed us to classify minocycline as the definitive cause of his condition. However, this was neither necessary for his treatment nor wise, as he improved so rapidly after the drug was withdrawn. The patient also did not need treatment with corticosteroids as he improved definitively with supportive care; however, prednisone 60 mg daily or equivalent would be the treatment of choice if he had not shown significant improvement.²

The exact cause of drug-induced autoimmune hepatitis is not precisely defined in every case. It is possible that a rapid onset of the disease can represent worsening of a pre-existing chronic hepatitis, the interaction of more than one hepatotoxic agent, or the development of new disease.² Our patient did possess a questionable history of alcohol consumption and had been taking atorvastatin, which has also been implicated in autoimmune hepatitis. However, he did not present with any previous diagnosis of liver injury from alcohol consumption or signs of long-standing hepatic toxicity. The patient had also been maintained on atorvastatin chronically without symptoms or liver enzyme elevation, which substantially reduces the likelihood that it was the causative agent in this case. If the RUCAM and M&V scoring systems are performed looking at atorvastatin as the potential causative agent, both scores indicate that it may be a possible cause of the hepatitis; however, it does not display the same strong temporal relationship to the event that minocycline does. It is possible that the interplay of factors between atorvastatin and minocycline contributed to this adverse event. This case would also emphasize the potential

hazards of using minocycline as it may have interactions with chronic medications that doxycycline may not have.

Conclusion

This case report demonstrates a rare but serious complication of anti-infective therapy with minocycline. Of primary importance in this observation is the development of autoimmune hepatitis immediately after a short course of minocycline for a skin infection, where minocycline was substituted for doxycycline. Providers should be aware that changes to their therapeutic choices precipitated by drug shortages and substitutions may result in different and potentially serious adverse events in their patients. Consultation with a clinical pharmacist and careful monitoring of patients for unusual signs or symptoms of toxicity is of utmost importance when substituting similar drugs by necessity or choice.

Declaration of Conflicting Interests

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