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Tetracyclines

Updated: April 10, 2019.

OVERVIEW

The tetracyclines are broad-spectrum, bacteriostatic antibiotics that are active against many pathogens including gram positive and gram negative bacteria, spirochetes, chlamydia, leptospira, mycoplasma and rickettsia. They are widely used in medical practice, but currently have restricted usefulness. Tetracyclines act by binding to bacterial ribosomes inhibiting protein synthesis. Bacterial resistance is common and is usually caused by plasmids that decrease the bacterial cell wall permeability.

At least eight different tetracyclines are currently available in the United States: tetracycline, doxycycline, minocycline, tigecycline, sarecycline, omadacycline, eravacycline and demeclocycline. Several others tetracyclines have been used in the past in the United States or Europe, but have been withdrawn (chlortetracycline, aureomycin, triacetyloleandomycin, rolitetracycline, oxytetracycline). While all tetracyclines are capable of causing a distinctive form of acute fatty liver disease when given intravenously in high doses, liver injury from oral forms tetracyclines vary greatly in frequency and clinical features. Minocycline is the most commonly implicated tetracycline in causing liver injury and generally ranks within the 10 most common causes of drug induced liver injury in developed nations. Minocycline hepatotoxicity generally presents with a long latency, hepatocellular enzyme elevations, prominent autoimmune features, apparent response to corticosteroid therapy and relatively bengn course. Doxycycline, in contrast, usually presents with a short latency (within 60 days), a cholestatic course, mild immunoallergic or autoimmune features and sometimes prolonged, but ultimately benign course. The other tetracyclines have had limited clinical use and are generally suspected but unproven potential causes of liver injury.

- Demeclocycline
- Doxycycline
- Eravacycline
- Minocycline
- Omadacycline
- Sarecycline
- Tetracycline
- Tigecycline

ANNOTATED BIBLIOGRAPHY

References updated: 10 April 2019

Zimmerman HJ. Tetracyclines. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999. p. 599-602.

(Expert review of tetracycline and liver injury published in 1999; the tetracyclines cause two forms of drug induced liver injury, microvesicular fat and liver failure occurring after 4-10 days with high does of parenteral tetracyclines and an idiosyncratic liver injury that occurs with the oral agents, doxycycline causing a cholestatic and minocycline a hepatocellular injury which may be associated with autoimmune features).

Moseley RH. Tetracyclines. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 468.

(Expert review of tetracycline induced liver injury mentions that the hepatotoxicity of intravenous tetracycline is of historic interest only as it is no longer given parenterally; both doxycycline and minocycline have been associated with idiosyncratic liver injury).

MacDougall C. Protein synthesis inhibitors and miscellaneous antibacterial agents. In, Brunton LL, Hilal-Dandan R, Knollman KC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1049-65.

(Textbook of pharmacology and therapeutics).

Schultz JC, Adamson JS Jr, Workman WW, Norman TD. Fatal liver disease after intravenous administration of tetracycline in high dosage. N Engl J Med 1963; 269: 999-1004. PubMed PMID: 14059734.

(Initial dramatic report of acute fatty liver due to iv tetracycline; a rapidly fatal multisystem disease appeared in 6 pregnant women in their last trimester or early postpartum period after 3 to 5 days of relatively high doses of iv tetracycline; all developed jaundice [bilirubin 4.9-12.5 mg/dL] with mild AST [72-170 U/L] and Alk P [9-17 King Armstrong U/L] elevations, prolongation of protime, acidosis and renal dysfunction. Autopsy showed foamy hepatocytes, fat by oil red O stain and minimal hepatocyte necrosis).

Tetracyclines and the liver in pregnancy. Lancet 1966; 1: 357-8. PubMed PMID: 4159865.

(Editorial on the history of acute fatty liver of pregnancy, first described by Sheehan in 1940 and later linked to high dose iv tetracycline in pregnancy, but also in nonpregnant women and in men).

Peters RL, Edmondson HA, Mikkelsen WP, Tatter D. Tetracycline-induced fatty liver in nonpregnant patients. A report of six cases. Am J Surg 1967; 113: 622-32. PubMed PMID: 6021433.

(Classical description of clinical and histologic features of tetracycline induced acute fatty liver in nonpregnant patients; 6 nonpregnant women, ages 18-62, given iv tetracycline for 3-13 days [9-26 g] presenting with jaundice and lethargy; peak AST 52-960 U/L; bilirubin 2.7-7.4 mg/dL, often with complex and critical course, pancreatitis and renal failure, acidosis; fatty liver on autopsy).

Combes B, Whalley PJ, Adams RH. Tetracycline and the liver. Prog Liver Dis 1972; 4: 589-96. PubMed PMID: 4569011.

(Review of hepatotoxicity of tetracycline, including studies of pathogenesis).

Adams LE, Hess EV. Drug-related lupus. Incidence, mechanisms and clinical implications. Drug Saf 1991; 6: 431-49. PubMed PMID: 1793523.

(Review of drug related lupus-like syndrome, linked to more than 60 agents including isoniazid, hydralazine, chlorpromazine, methyldopa and procainamide. Usually presents with arthralgias and fever and ANA positivity, usually occurring with long term use of the medication).

Carson JL, Strom BL, Duff A, et al. Acute liver disease associated with erythromycins, sulfonamides, and tetracyclines. Ann Intern Med 1993; 119 (7 Pt 1): 576-83. PubMed PMID: 8363168.

(Case control study using Medicaid billing results between 1980-87 found 107 cases of hospitalization for unexplained hepatitis, odds ratios for erythromycin 5.2; sulfonamides 11.4; tetracyclines 5.2; total of 5 cases exposed to tetracycline, doxycycline or minocycline).

Hunt CM, Washington K. Tetracycline-induced bile duct paucity and prolonged cholestasis. Gastroenterology 1994; 107: 1844-7. PubMed PMID: 7958700.

(Two cases of severe and prolonged cholestatic hepatitis and bile duct paucity after oral tetracyclines; 37 year old woman developed jaundice 2 days after 3 day course of doxycycline with prolonged cholestasis [peak bilirubin 30 mg/dL], but ultimate recovery; 63 year old woman developed jaundice 6 weeks after a 2 week course of tetracycline [bilirubin 11.8 mg/dL, ALT 245 U/L], with prolonged jaundice [peak bilirubin 29.5 mg/dL) and persistence of enzyme elevations for >3 years [Alk P 631 U/L, ALT 97 U/L]).

Friis H, Andreasen PB. Drug-induced hepatic injury: an analysis of 1100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. J Intern Med 1992; 232: 133-8. PubMed PMID: 1506809.

(Adverse drug reaction reports between 1978 and 1987 in Denmark; no tetracycline is mentioned as a cause).

Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years' experience. N Z Med J 1996; 109: 315-9. PubMed PMID: 8816722.

(Adverse drug reaction reports identified 943 liver injuries over 21 years in New Zealand; triacetyloleandomycin accounted for 21 cases [2.1%] and minocycline for at least 4).

Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. Report of 13 patients and review of the literature. Arch Dermatol 1996; 132: 934-9. PubMed PMID: 8712844.

(15 cases with adverse reactions to minocycline; one with Stevens-Johnson syndrome and acute liver failure arising within 29 days of starting minocycline, necessitating liver transplantation).

Björnsson E, Lindberg J, Olsson R. Liver reactions to oral low-dose tetracyclines. Scand J Gastroenterol 1997; 32: 390-5. Review. PubMed PMID: 9140164.

(32 year old man developed abdominal pain, dark urine and rash within 24 hours of starting doxycycline which he had received in the past [bilirubin 4.3- 8.1 mg/dL, ALT 3.5 times ULN, Alk P 1.1 times ULN], resolving within 3 months of stopping; thorough review of all published and SADRAC reported cases of oral tetracycline associated liver injury found 15 cases, only 6 rated as likely, none with tetracycline, 5 doxycycline, 1 lymecycline).

Shapiro LE, Knowles SR, Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. Arch Dermatol 1997; 133: 1224-30. PubMed PMID: 9382560.

(Review of toxicity of tetracyclines from literature and a Canadian database; minocycline had the highest rates of adverse events, but all were relatively safe: no lupus-like syndrome associated with doxycycline or tetracycline).

Elkayam O, Yaron M, Caspi D. Minocycline-induced autoimmune syndromes: an overview. Semin Arthritis Rheum 1999; 28: 392-7. PubMed PMID: 10406406.

(Systematic review of literature on autoimmune syndromes from minocycline, 4 patterns: serum sickness, lupus-like syndrome, autoimmune hepatitis and vasculitis; usually presenting after 1-20 years, ANA common but so is pANCA, features may overlap, hepatitis most common: 66 cases reported).

Goldstein NS, Bayati N, Silverman AL, Gordon SC. Minocycline as a cause of drug-induced autoimmune hepatitis. Report of four cases and comparison with autoimmune hepatitis. Am J Clin Pathol 2000; 114: 591-8. PubMed PMID: 11026106.

(Four cases of minocycline hepatitis and comparison to 10 spontaneous autoimmune hepatitis cases showed no distinguishing features except resolution with stopping drug; 16-52 year old women developed liver injury 4 months to 12 years after starting minocycline [bilirubin 0.4, 1.2, 6.5 and 7.3 mg/dL, ALT 137, 343, 700, and 1288 U/L, Alk P 49, 83, 138 and 253 U/L, all ANA positive], histology showed fibrosis in 2, all responded to prednisone with resolution persisting after stopping corticosteroids).

Goh KP. Management of hyponatremia. Am Fam Physician 2004; 69: 2387-94. PubMed PMID: 15168958.

(Review of the causes, diagnosis and management of hyponatremia and inappropriate antidiuretic hormone syndrome, with discussion of use of demeclocycline).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the US between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, none of which were attributed to minocycline, doxycycline or tetracycline).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-1101. PubMed PMID: 16165719.

(Among 103 cases of fulminant drug induced liver injury reported to a Swedish registry between 1966 and 2002, one case was attributed to doxycycline, but no other tetracycline mentioned).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, Garcia-Ruiz E, Garcia-Munoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish Registry over a 10-year period. Gastroenterology 2005; 129: 512-21. PubMed PMID: 16083708.

(Reports to a Spanish network found 461 cases of drug induced liver disease; no tetracycline was listed among the top 20 agents implicated [at least 5 cases]).

Rubinstein E, Vaughan D. Tigecycline: a novel glycylcycline. Drugs 2005; 65: 1317-36. PubMed PMID: 15977966.

(Review article on tigecycline reporting low rates of ALT and AST elevations [<2%] in phase III randomized controlled trials).

Heaton PC, Fenwick SR, Brewer DE. Association between tetracycline or doxycycline and hepatotoxicity: a population based case-control study. J Clin Pharm Ther 2007; 32: 483-7. PubMed PMID: 17875115.

(Analysis of 2 years of Medicaid claims in California found 3377 cases of "hepatotoxicity"; 20 had received tetracycline <45 days before onset; only 4 controls had: adjusted odds ratio 3.7; not elevated for doxycycline; this despite safety record of oral tetracyclines and known hepatotoxicity of doxycycline).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, minocycline accounted for 3 cases, doxycycline for 3 cases and tetracycline was listed as a secondary possible cause for one).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database containing 9036 hepatic adverse drug reactions in children includes 117 cases attributed to minocycline, but no other tetracycline listed in the top 40 causes).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; none were due to tetracyclines).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury and 25 to antituberculosis agents, including 15 to isoniazid alone [ranking first], 6 to isoniazid combined with other agents, 3 to rifampin and pyrazinamide, and 1 to dapsone).

Leitner JM, Graninger W, Thalhammer F. Hepatotoxicity of antibacterials: Pathomechanisms and clinical. Infection 2010; 38: 3-11. PubMed PMID: 20107858.

(Review of hepatotoxicity of antibiotics; mentions that hepatotoxicity from oral tetracycline is rare ~1.5 cases per million prescriptions, whereas minocycline has been associated with either an immediate reaction with eosinophilia, dermatitis and enzyme elevations or a delayed autoimmune hepatitis-like syndrome).

Kadoyama K, Sakaeda T, Tamon A, Okuno Y. Adverse event profile of tigecycline: data mining of the public version of the U.S. Food and Drug Administration adverse event reporting system. Biol Pharm Bul. 2012; 35: 967-70. PubMed PMID: 22687540.

(Analysis of adverse event reports on tigecycline compared to other agents, suggested increased rates of nausea, vomiting, pancreatitis, liver failure, ALT and Alk P elevations).

Noel GJ, Draper MP, Hait H, Tanaka SK, Arbeit RD. A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother 2012; 56: 5650-4. PubMed PMID: 22908151.

(Among 219 adults with complicated skin and skin structure infections treated with omadacycline vs linezolid, clinical response rates were similar [97% vs 93%] as were adverse event rates, ALT elevations occurring in 3% of both groups).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to doxycycline or other tetracyclines).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, 37 of which were attributed to an antibiotic, but none to a tetracycline).

Douros A, Bronder E, Andersohn F, Klimpel A, Thomae M, Sarganas G, Kreutz R, et al. Drug-induced liver injury: results from the hospital-based Berlin Case-Control Surveillance Study. Br J Clin Pharmacol 2015; 79: 988-99. PubMed PMID: 25444550.

(Among 76 inpatients with hepatitis of uniknown cause enrolled in a prospective case-cohort surveillance study between 2002 and 2011, one was attributed to doxycycline, but no other tetracycline was implicated).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 323 [36%] were attributed to antibiotics including 28 [3%] to minocycline and 4 [0.4%] to doxycycline).

Zhanel GG, Cheung D, Adam H, Zelenitsky S, Golden A, Schweizer F, Gorityala B, et al. Review of eravacycline, a novel fluorocycline antibacterial agent. Drugs 2016; 76: 567-88. PubMed PMID: 26863149.

(Review of the structure, antibacterial spectrum of activity, pharmacology, clinical efficacy and safety of eravacycline; mentions that the most common adverse event is nausea and vomiting, but that other event rates are similar to those in comparator arm subjects; no discussion of ALT elevations or hepatotoxicity).

Solomkin J, Evans D, Slepavicius A, Lee P, Marsh A, Tsai L, Sutcliffe JA, et al. Assessing the efficacy and safety of eravacycline vs ertapenem in complicated intra-abdominal infections in the investigating gram-negative infections treated with eravacycline (IGNITE 1) trial: a randomized clinical trial. JAMA Surg 2017; 152: 224-32. PubMed PMID: 27851857.

(Among 541 patients with complicated intraabdominal infections treated with eravacycline [1 mg/kg every 12 hours] or ertapenem [1 gm every 24 hours] for 4-14 days, rates of clinical cure were similar [87% vs 88%] while adverse events were more frequent with eravacycline [42% vs 28%], although severe adverse event rates were similar [6% vs 5.6%]; no mention of ALT elevations or hepatotoxicity).

Urban TJ, Nicoletti P, Chalasani N, Serrano J, Stolz A, Daly AK, Aithal GP, et al; Drug-Induced Liver Injury Network (DILIN); Pharmacogenetics of Drug-Induced Liver Injury group (DILIGEN); International Serious Adverse Events Consortium (iSAEC). Minocycline hepatotoxicity: clinical characterization and identification of HLA-B*35:02 as a risk factor. J Hepatol 2017; 67: 137-44. PubMed PMID: 28323125.

*(The uncommon HLA allele B*35:02 was found in 4 of 25 [16%] of patients with minocycline hepatotoxicity vs 0.6% in a population control group; those with and without this allele did not different in clinical features or outcome).*

Leyden JJ, Sniukiene V, Berk DR, Kaoukhov A. Efficacy and safety of sarecycline, a novel, once-daily, narrow spectrum antibiotic for the treatment of moderate to severe facial acne vulgaris: results of a phase 2, dose-ranging study. J Drugs Dermatol 2018; 17: 333-8. PubMed PMID: 29537451.

(Among 285 patients, ages 12 to 45 years, with severe facial acne vulgaris treated with 3 doses of sarecycline or placebo once daily for 12 weeks, inflammatory lesions were improved with higher doses of sarecycline vs placebo while adverse event rates were comparable and there were no serious adverse events; no mention of ALT elevations or hepatotoxicity).

Markham A, Keam SJ. Omadacycline: first global approval. Drugs 2018; 78: 1931-7. PubMed PMID: 30471003.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and safety of omadacycline shortly after its first approval for use in the US; mentions that ALT or AST elevations arose in 3-4% of patients treated with omadacycline but that similar rates were reported in patients on comparator antibiotic regimens).

Deeks ED. Sarecycline: first global approval. Drugs. 2019; 79: 325-9. PubMed PMID: 30659422.

(Review of the mechanism of action, pharmacology, clinical efficacy and safety of sarecycline from clinical trials on which its FDA approval was based; mentions that adverse events were uncommon but included nausea, vomiting, abdominal pain, sunburn, vulvovaginal candidiasis and mycotic infections; no mention of ALT elevations or hepatotoxicity).