Clindamycin: An overview

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INTRODUCTION

Clindamycin is a lincosamide antibiotic that has been approved by the US Food and Drug Administration for the treatment of anaerobic, streptococcal, and staphylococcal infections. Its major disadvantage is its propensity to cause antibiotic-associated diarrhea, including *Clostridioides* (formerly *Clostridium*) *difficile* colitis. (See "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology".)

There has been increased interest in the use of clindamycin because it achieves high intracellular levels in phagocytic cells, high levels in bone, and appears to be able to reduce toxin production in toxin-elaborating strains of streptococci and staphylococci. (See "Invasive group A streptococcal infection and toxic shock syndrome: Epidemiology, clinical manifestations, and diagnosis".)

The spectrum of activity, pharmacology, and adverse effects of clindamycin will be reviewed here. The clinical use of clindamycin is discussed separately in the appropriate topic reviews on specific infections. (See "Anaerobic bacterial infections" and "Complications, diagnosis, and treatment of odontogenic infections" and "Deep neck space infections in adults" and "Submandibular space infections (Ludwig's angina)" and "Peritonsillar cellulitis and abscess" and "Lung abscess in adults" and "Methicillin-resistant Staphylococcus aureus (MRSA) in adults: Treatment of skin and soft tissue infections" and "Staphylococcus aureus in children: Overview of treatment of invasive infections".)

MECHANISM OF ACTION

Clindamycin works primarily by binding to the 50s ribosomal subunit of bacteria. This agent disrupts protein synthesis by interfering with the transpeptidation reaction, which thereby inhibits early chain elongation. Chloramphenicol and macrolides such as erythromycin, clarithromycin, and azithromycin also act at the 50s ribosomal subunit and may compete for binding at this site. Clindamycin and the related drug lincomycin are often discussed along with the macrolides but are not chemically related. (See "Azithromycin and clarithromycin", section on 'Mechanism of action and chemical structure'.)

Clindamycin may potentiate the opsonization and phagocytosis of bacteria even at subinhibitory concentrations [1,2]. By disrupting bacterial protein synthesis, clindamycin causes changes in the cell wall surface, which decreases adherence of bacteria to host cells and increases intracellular killing of organisms. The drug also exerts an extended postantibiotic effect against some strains of bacteria, which may be attributed to persistence of the drug at the ribosomal binding site.

Clindamycin is considered a bacteriostatic antibiotic but is bactericidal against some strains of staphylococci, streptococci, and anaerobes such as *Bacteroides fragilis*. However, killing activity may vary with drug concentration, bacterial species, and inoculum. Bactericidal activity against *B. fragilis* is inconsistent [3]. Penicillins are more rapidly bactericidal versus *Staphylococcus aureus* than is clindamycin [4]. However, clindamycin does inhibit production of staphylococcal toxin associated with the toxic shock syndrome [5]. Clindamycin has also been shown to almost completely inhibit alpha toxin expression in *S. aureus* in contrast with beta-lactams, which strongly induce, and fluoroquinolones, which partially induce, expression [6].

SPECTRUM OF ACTIVITY

Clindamycin generally has in vitro activity against staphylococci, viridans group streptococci, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. It also demonstrates potent activity against anaerobes such as *B. fragilis*, *Clostridium perfringens*, *Fusobacterium* spp, *Prevotella melaninogenicus*, and *Peptostreptococcus* spp. However, increasing rates of resistance among *B. fragilis* have limited its utility against these organisms. (See 'Resistance' below.)

Clindamycin is not typically active against *Haemophilus influenzae*, enterococci, or *Neisseria meningitidis*. *Mycoplasma pneumoniae* and aerobic gram-negative bacilli are usually resistant.

Clindamycin is active in vitro against *Toxoplasma gondii*, *Actinomyces israelii*, *Nocardia asteroides*, and *Babesia* spp. Clindamycin also has some activity against *Plasmodium falciparum* and *Plasmodium vivax* (both chloroquine-susceptible and -resistant strains). Combination therapy

with quinine or chloroquine has been tried [7]; clindamycin should **not** be used alone for the treatment or prevention of malaria. (See "Treatment of uncomplicated falciparum malaria in nonpregnant adults and children", section on 'Chloroquine-resistant malaria'.)

RESISTANCE

There are several mechanisms of bacterial resistance to clindamycin, including modification of the target, inactivation of the drug, or efflux of the drug. Resistance has been conferred by both plasmid- and chromosomally mediated mechanisms, including:

- Plasmid-mediated resistance in *S. aureus* and *B. fragilis*, conferred by enzymes that methylate specific adenine residues in the ribosomal-binding site in the 23s ribosomal RNA of the 50s ribosomal subunit [8]. In gram-positive cocci, this mechanism also confers resistance to macrolides. (See "Azithromycin and clarithromycin", section on 'Resistance'.)

- Alteration of a single 50s ribosomal protein of the receptor site, which also confers resistance to macrolides.

- Adenylation conferred by a plasmid-mediated 3-lincomycin 4-clindamycin 0-nucleotidyltransferase that catalyzes the nucleotidylation of the hydroxyl group of position 4 of clindamycin [9]. This mechanism of resistance is most frequently found in staphylococcal isolates, including *S. aureus*, and impairs bactericidal activity and reduces activity at high inoculum levels. Although adenylation confers high-level resistance to lincomycin, clindamycin resistance may not be detected by routine testing methods. This type of resistance is uncommon and probably not of great clinical importance.

- Gram-negative organisms such as *Pseudomonas* spp, Enterobacteriaceae, and *Acinetobacter* spp are intrinsically resistant to clindamycin due to poor permeability of the cellular outer envelope to the drug [10].

Cross-resistance of *S. aureus* to lincomycin and clindamycin is complete. In addition, bacteria that are erythromycin-resistant may quickly develop resistance when exposed to clindamycin. Strains of *S. aureus* have also developed resistance to clindamycin during treatment. Other bacteria such as *S. pneumoniae*, group A *Streptococcus*, *Corynebacterium diphtheriae*, *B. fragilis*, *Peptostreptococcus* spp, and *Cutibacterium* (formerly *Propionibacterium*) *acnes* have also developed resistance to clindamycin.

Increasing resistance among group B streptococci has also been reported [11-14]. In a report of group B streptococcal isolates obtained as part of routine prenatal screening in Louisiana,

clindamycin resistance was present in 33 percent of 544 isolates [15]. In 30 percent of strains, clindamycin resistance was constitutively expressed, and in 70 percent it was inducible. Rates of inducible clindamycin resistance in other studies of group B *Streptococcus* have been substantially lower [14].

A resistance phenotype identified in erythromycin-susceptible, clindamycin-resistant strains of *Streptococcus agalactiae* had high minimum inhibitory concentrations (MICs) to clindamycin and lincomycin plus high MICs to dalfopristin, a streptogramin-A antibacterial agent [16]. By contrast, the strains were susceptible to macrolides and quinupristin, a streptogramin B-type antibiotic.

Rates of resistance of the *B. fragilis* group to clindamycin have increased over time in the United States and Europe. In the United States, the frequency of clindamycin resistance in *B. fragilis* increased from 3 percent in 1987 to 26 percent from 1997 to 2004 [17,18]. Some centers have reported clindamycin resistance rates of *B. fragilis* to be as high as 44 percent [19]. (See "Anaerobic bacterial infections", section on 'Antimicrobial resistance'.)

Since rates of antibiotic resistance within *Bacteroides* may vary with geographic area and local antibiotic use, local susceptibility patterns should be considered in the selection of empiric therapy. Susceptibility testing for anaerobic bacteria is not routinely performed in the clinical laboratory setting, since the techniques are cumbersome and not well-standardized. However, testing may be indicated in certain clinical situations, including brain abscess, endocarditis, osteomyelitis, arthritis, prosthetic device or vascular graft infection, and refractory or recurrent bacteremia [20]. Testing may be particularly useful in the setting of serious infection, persistent infections, potentially resistant pathogens that will be treated medically rather than surgically, or when prolonged therapy is anticipated.

The primary benefit of susceptibility testing is not documentation of susceptibility but rather demonstration of unexpected resistance to an antimicrobial that is normally useful. The clinical relevance of documented bacterial resistance in the setting of mixed anaerobic infections remains unclear. An alternative approach to requesting susceptibility testing upon isolation of a *Bacteroides* spp is to reserve such testing for a clinical treatment failure or recurrent infection and to send an isolate to a reference laboratory at that time.

C. difficile is often resistant to clindamycin but susceptible to metronidazole and vancomycin. *C. perfringens* is usually uniformly susceptible, but other clostridial species may be resistant in 15 to 30 percent of cases.

PHARMACOKINETICS

Clindamycin is well absorbed after oral administration and is approximately 90 percent bioavailable. The drug generally distributes well into body tissues but does not achieve significant levels in the cerebrospinal fluid, even during episodes of meningitis. It does penetrate well into bone. Since the drug is actively transported into polymorphonuclear leukocytes and macrophages, it may also achieve excellent penetration into abscesses.

Clindamycin is metabolized in the liver to active and inactive metabolites. One active metabolite, N-demethyl clindamycin, is more active than the parent compound. Clindamycin is excreted in urine and, to a lesser extent, in the bile as metabolites. The half-life in patients with normal renal function is 2.4 hours, but it is extended to approximately six hours in those with renal insufficiency. The half-life of the drug is also extended in patients with hepatic failure. The drug is not appreciably removed by peritoneal dialysis or hemodialysis.

TOXICITY

The most common adverse effects associated with clindamycin are diarrhea and allergic reactions.

Gastrointestinal — Diarrhea has been reported in 2 to 20 percent of those receiving clindamycin. Typically, the diarrhea is mild and self-limited in nature and resolves upon discontinuation of the drug. Clindamycin has been frequently implicated in antibiotic-associated diarrhea due to *C. difficile* [21,22]. Pseudomembranous colitis caused by overgrowth of *C. difficile* has been reported in 0.1 to 10 percent of patients receiving clindamycin and can be severe or life threatening. Although this condition has been documented with almost all antibiotics, clindamycin, ampicillin, amoxicillin, and the cephalosporins are most frequently implicated, the last three based upon the frequency of use. In a comparison of clindamycin and ampicillin, pseudomembranes were documented by endoscopy in 2 percent of patients receiving clindamycin and 0.3 percent of patients receiving ampicillin [21]. (See "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology".)

Antibiotic-associated diarrhea can occur during antibiotic therapy or even several weeks after the cessation of therapy. Topical and vaginal preparations of clindamycin have also been implicated in causing this disease, which may be attributable to systemic absorption of the drug [23,24]. Clindamycin should be used with caution among patients with inflammatory bowel disease, since antibiotic-associated diarrhea in this patient population may be particularly intolerable.

Other gastrointestinal side effects have been reported with clindamycin. These include nausea, vomiting, flatulence, metallic taste, anorexia, and esophagitis. Following administration of clindamycin, it is advisable to sit upright for 30 minutes to minimize risk of gastrointestinal discomfort.

Allergic reactions — Maculopapular skin rash has been noted in up to 10 percent of patients receiving clindamycin. Other reactions such as drug fever, eosinophilia, erythema multiforme, drug rash with eosinophilia and systemic symptoms [25], Sweet syndrome, and urticaria have also been reported. Some cases have resembled Stevens-Johnson syndrome. Although rare, cardiopulmonary arrest and hypotension have been reported with rapid intravenous infusions of clindamycin. Delayed-type hypersensitivity reactions including maculopapular exanthema and pruritus have also been reported following skin prick or intradermal testing for clindamycin in some patients [26].

Local reactions — Injection-site pain and swelling have been reported with the use of intravenous and intramuscular clindamycin. Thrombophlebitis may occur with infusions of intravenous clindamycin. Induration and sterile abscess have been reported with intramuscular administration of the drug. Contact dermatitis may be associated with topical forms of clindamycin. In addition, symptomatic vaginitis and vulvar irritation have been reported with intravaginal clindamycin.

Other — Less common adverse reactions reported with the use of clindamycin include elevation of liver transaminases, jaundice, and polyarthritis. Hematopoietic effects such as neutropenia, leukopenia, agranulocytosis, and thrombocytopenic purpura have also been reported. Renal dysfunction associated with the use of clindamycin is rare but may be characterized by oliguria, azotemia, and proteinuria.

DRUG INTERACTIONS

Clindamycin undergoes hepatic metabolism by CYP3A4. Potent inducers of CYP3A4 metabolism (eg, rifampin) can significantly decrease clindamycin serum concentrations [27-29]. Although in one study, a reduction in the rate of clinical cure was not observed when clindamycin was administered with rifampin for the treatment of gram-positive bone and joint infections [29], decreased clindamycin effect is possible if it is combined with strong CYP3A4 inducers (table 1).

Since clindamycin has neuromuscular-blocking properties, it should be used with caution in patients receiving neuromuscular-blocking agents. Since clindamycin, macrolides, and

chloramphenicol target the same ribosomal site, these drugs should not be used in combination.

Details about specific interactions may be obtained by using the Lexicomp drug interactions tool included within UpToDate.

DOSING AND ADMINISTRATION

Clindamycin is available for oral, parenteral, and topical administration. (See "Clindamycin (systemic): Drug information" and "Clindamycin (topical): Drug information" and "Clindamycin (systemic): Pediatric drug information" and "Clindamycin (topical): Pediatric drug information".)

SPECIAL POPULATIONS

Pregnancy — No reports linking clindamycin with congenital defects have been published to date, and animal studies have failed to demonstrate fetal risk with clindamycin therapy. However, a lack of controlled studies in pregnant women warrants a US Food and Drug Administration pregnancy risk category of B (table 2). Clindamycin does cross the placenta with levels approximating 50 percent of maternal serum levels.

A study evaluating pharmacokinetics of clindamycin in pregnant women reported lower clindamycin concentrations in umbilical cord blood than maternal blood and suggested that maternal concentrations may not exceed the area under the curve to minimum inhibitory concentration target for effective group B *Streptococcus* prevention for neonates during delivery [30].

In a study of pregnant women with bacterial vaginosis at 15.6 weeks gestation (mean), use of clindamycin (300 mg by mouth twice daily for five days) was associated with fewer miscarriages or preterm deliveries when compared with placebo [31]. In contrast, since intravaginal clindamycin has been associated with an increased risk of preterm birth, clindamycin intravaginal cream should **not** be used in pregnant women.

Nursing — Clindamycin is excreted in the breast milk, but the American Academy of Pediatrics considers clindamycin administration compatible with breastfeeding. However, some practitioners may still elect to avoid clindamycin therapy in women who are nursing.

Neonates — Clindamycin should generally be avoided in neonates since each milliliter of intravenous clindamycin contains 9.45 mg of benzyl alcohol. Organ system functions should be

carefully monitored in infants receiving clindamycin intravenously.

Dialysis — Clindamycin does not appear to be significantly removed by hemodialysis or peritoneal dialysis. Thus, no dosing adjustments are necessary in patients undergoing dialysis. Patients undergoing hemofiltration also do not appear to require clindamycin dose adjustments.

Renal and hepatic dysfunction — No specific dose adjustments are recommended for patients with renal or hepatic dysfunction receiving clindamycin. However, as noted above, the half-life of the drug is prolonged in such patients, which could increase the potential for adverse events. Such patients should be monitored closely, and dose adjustments should be considered if toxicity is suspected.

MONITORING DURING THERAPY

Patients receiving clindamycin should be monitored for hepatic or renal dysfunction and for the occurrence of potential side effects. If diarrhea occurs, the drug should be stopped. Patients experiencing diarrhea during or after receiving antibiotic therapy should be evaluated for the presence of *C. difficile* and treated accordingly.

SUMMARY

- Clindamycin is a lincosamide antibiotic that has been approved by the US Food and Drug Administration for the treatment of anaerobic, streptococcal, and staphylococcal infections. Its major disadvantage is its propensity to cause antibiotic-associated diarrhea. (See 'Introduction' above.)

- Clindamycin works primarily by binding to the 50s ribosomal subunit of bacteria. This agent disrupts protein synthesis by interfering with the transpeptidation reaction, which thereby inhibits early chain elongation. (See 'Mechanism of action' above.)

- Clindamycin is considered a bacteriostatic antibiotic but is bactericidal against some strains of staphylococci, streptococci, and anaerobes such as *Bacteroides fragilis*. However, killing activity may vary with drug concentration, bacterial species, and inoculum. Bactericidal activity against *B. fragilis* is inconsistent. Penicillins are more rapidly bactericidal versus *Staphylococcus aureus* than is clindamycin. However, clindamycin does inhibit production of staphylococcal toxin associated with the toxic shock syndrome. Clindamycin has also been

shown to almost completely inhibit alpha toxin expression in *S. aureus*. (See 'Mechanism of action' above.)

- Clindamycin generally has in vitro activity against staphylococci, viridans group streptococci, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. It also demonstrates potent activity against anaerobes such as *B. fragilis*, *Clostridium perfringens*, *Fusobacterium* spp, *Prevotella melaninogenicus*, and *Peptostreptococcus* spp. (See 'Spectrum of activity' above.)

- There are several mechanisms of bacterial resistance to clindamycin, including modification of the target, inactivation of the drug, or efflux of the drug. Resistance has been conferred by both plasmid- and chromosomally mediated mechanisms. Rates of resistance of the *B. fragilis* group to clindamycin have increased over time in the United States and Europe. (See 'Resistance' above.)

- Clindamycin is well absorbed after oral administration and is approximately 90 percent bioavailable. The drug generally distributes well into body tissues but does not achieve significant levels in the cerebrospinal fluid, even during episodes of meningitis. It does penetrate well into bone. Since the drug is actively transported into polymorphonuclear leukocytes and macrophages, it may also achieve excellent penetration into abscesses. (See 'Pharmacokinetics' above.)

- Since clindamycin has neuromuscular-blocking properties, it should be used with caution in patients receiving neuromuscular-blocking agents. Since clindamycin, macrolides, and chloramphenicol target the same ribosomal site, these drugs should not be used in combination. (See 'Drug interactions' above.)

- The most common adverse effects associated with clindamycin are diarrhea, including *Clostridioides* (formerly *Clostridium*) *difficile* colitis, and allergic reactions. (See 'Toxicity' above.)

- No specific dose adjustments are recommended for patients with renal or hepatic dysfunction receiving clindamycin. However, the half-life of the drug is prolonged in such patients, which could increase the potential for adverse events. Such patients should be monitored closely, and dose adjustments should be considered if toxicity is suspected. (See 'Renal and hepatic dysfunction' above.)

REFERENCES

1. Veringa EM, Lambe DW Jr, Ferguson DA Jr, Verhoef J. Enhancement of opsonophagocytosis of Bacteroides spp. by clindamycin in subinhibitory concentrations. J Antimicrob Chemother 1989; 23:577.
2. Veringa EM, Verhoef J. Influence of subinhibitory concentrations of clindamycin on opsonophagocytosis of Staphylococcus aureus, a protein-A-dependent process. Antimicrob Agents Chemother 1986; 30:796.
3. Nastro LJ, Finegold SM. Bactericidal activity of five antimicrobial agents against Bacteroides fragilis. J Infect Dis 1972; 126:104.
4. Sande MA, Johnson ML. Antimicrobial therapy of experimental endocarditis caused by Staphylococcus aureus. J Infect Dis 1975; 131:367.
5. Schlievert PM, Kelly JA. Clindamycin-induced suppression of toxic-shock syndrome--associated exotoxin production. J Infect Dis 1984; 149:471.
6. Ohlsen K, Ziebuhr W, Koller KP, et al. Effects of subinhibitory concentrations of antibiotics on alpha-toxin (hla) gene expression of methicillin-sensitive and methicillin-resistant Staphylococcus aureus isolates. Antimicrob Agents Chemother 1998; 42:2817.
7. Kremsner PG, Radloff P, Metzger W, et al. Quinine plus clindamycin improves chemotherapy of severe malaria in children. Antimicrob Agents Chemother 1995; 39:1603.
8. Leclercq R, Courvalin P. Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. Antimicrob Agents Chemother 1991; 35:1267.
9. Brisson-Noël A, Delrieu P, Samain D, Courvalin P. Inactivation of lincosaminide antibiotics in Staphylococcus. Identification of lincosaminide O-nucleotidyltransferases and comparison of the corresponding resistance genes. J Biol Chem 1988; 263:15880.
10. Leclercq R, Courvalin P. Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. Antimicrob Agents Chemother 1991; 35:1273.
11. Castor ML, Whitney CG, Como-Sabetti K, et al. Antibiotic resistance patterns in invasive group B streptococcal isolates. Infect Dis Obstet Gynecol 2008; 2008:727505.
12. DiPersio LP, DiPersio JR. High rates of erythromycin and clindamycin resistance among OBGYN isolates of group B Streptococcus. Diagn Microbiol Infect Dis 2006; 54:79.
13. Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. JAMA 2008; 299:2056.
14. Back EE, O'Grady EJ, Back JD. High rates of perinatal group B Streptococcus clindamycin and erythromycin resistance in an upstate New York hospital. Antimicrob Agents Chemother 2012; 56:739.

15. Capraro GA, Rambin ED, Vanchiere JA, et al. High rates of inducible clindamycin resistance among prenatal group B streptococcal isolates in one northwest Louisiana academic medical center. J Clin Microbiol 2013; 51:2469.
16. Malbruny B, Werno AM, Anderson TP, et al. A new phenotype of resistance to lincosamide and streptogramin A-type antibiotics in Streptococcus agalactiae in New Zealand. J Antimicrob Chemother 2004; 54:1040.
17. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of Bacteroides fragilis group: report and analysis of trends in the United States from 1997 to 2004. Antimicrob Agents Chemother 2007; 51:1649.
18. Snydman DR, Jacobus NV, McDermott LA, et al. National survey on the susceptibility of Bacteroides Fragilis Group: report and analysis of trends for 1997-2000. Clin Infect Dis 2002; 35:S126.
19. Hecht DW. Prevalence of antibiotic resistance in anaerobic bacteria: worrisome developments. Clin Infect Dis 2004; 39:92.
20. NCCLS. Methods for antimicrobial susceptibility testing of anaerobic bacteria; approved sta ndard- fourth edition. NCCLS document M11-A4. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 1997.
21. Gurwith MJ, Rabin HR, Love K. Diarrhea associated with clindamycin and ampicillin therapy: preliminary results of a cooperative study. J Infect Dis 1977; 135 Suppl:S104.
22. Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis. A prospective study. Ann Intern Med 1974; 81:429.
23. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 1986; 122:583.
24. Meadowcroft AM, Diaz PR, Latham GS. Clostridium difficile toxin-induced colitis after use of clindamycin phosphate vaginal cream. Ann Pharmacother 1998; 32:309.
25. Tian D, Mohan RJ, Stallings G. Drug rash with eosinophilia and systemic symptoms syndrome associated with clindamycin. Am J Med 2010; 123:e7.
26. Papakonstantinou E, Müller S, Röhrbein JH, et al. Generalized reactions during skin testing with clindamycin in drug hypersensitivity: a report of 3 cases and review of the literature. Contact Dermatitis 2018; 78:274.
27. Curis E, Pestre V, Jullien V, et al. Pharmacokinetic variability of clindamycin and influence of rifampicin on clindamycin concentration in patients with bone and joint infections. Infection 2015; 43:473.

28. Bernard A, Kermarrec G, Parize P, et al. Dramatic reduction of clindamycin serum concentration in staphylococcal osteoarticular infection patients treated with the oral clindamycin-rifampicin combination. J Infect 2015; 71:200.
29. Zeller V, Dzeing-Ella A, Kitzis MD, et al. Continuous clindamycin infusion, an innovative approach to treating bone and joint infections. Antimicrob Agents Chemother 2010; 54:88.
30. Muller AE, Mouton JW, Oostvogel PM, et al. Pharmacokinetics of clindamycin in pregnant women in the peripartum period. Antimicrob Agents Chemother 2010; 54:2175.
31. Ugwumadu A, Manyonda I, Reid F, Hay P. Effect of early oral clindamycin on late miscarriage and preterm delivery in asymptomatic women with abnormal vaginal flora and bacterial vaginosis: a randomised controlled trial. Lancet 2003; 361:983.

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GRAPHICS

Cytochrome P450 3A (including 3A4) inhibitors and inducers

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate inducers
Atazanavir	Amiodarone*	Apalutamide	Bexarotene
Ceritinib	Aprepitant	Carbamazepine	Bosentan
Clarithromycin	Berotralstat	Enzalutamide	Cenobamate
Cobicistat and cobicistat-containing coformulations	Cimetidine*	Fosphenytoin	Dabrafenib
Darunavir	Conivaptan	Lumacaftor	Dexamethasone¶
Idelalisib	Crizotinib	Lumacaftor-ivacaftor	Dipyrone
Indinavir	Cyclosporine*	Mitotane	Efavirenz
Itraconazole	Diltiazem	Phenobarbital	Elagolix, estradiol, and norethindrone therapy pack$^{\Delta}$
Ketoconazole	Duvelisib	Phenytoin	Eslicarbazepine
Lonafarnib	Dronedarone	Primidone	Etravirine
Lopinavir	Erythromycin	Rifampin (rifampicin)	Lorlatinib
Mifepristone	Fedratinib		Modafinil
Nefazodone	Fluconazole		Nafcillin
Nelfinavir	Fosamprenavir		Pexidartinib
Ombitasvir-paritaprevir-ritonavir	Fosaprepitant*		Rifabutin
Ombitasvir-paritaprevir-ritonavir plus dasabuvir	Grapefruit juice		Rifapentine
Posaconazole	Imatinib		St. John's wort
Ritonavir and ritonavir-containing coformulations	Isavuconazole (isavuconazonium sulfate)		
Saquinavir	Lefamulin		
Telithromycin	Letermovir		
Tucatinib	Netupitant		
Voriconazole	Nilotinib		
	Ribociclib		
	Schisandra		
	Verapamil		

- For drug interaction purposes, the inhibitors and inducers of CYP3A metabolism listed above can alter serum concentrations of drugs that are dependent upon the CYP3A subfamily of liver enzymes, including CYP3A4, for elimination or activation.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- Data are for systemic drug forms. Degree of inhibition or induction may be altered by dose, method, and timing of administration.
- Weak inhibitors and inducers are not listed in this table with exception of a few examples. Clinically significant interactions can occasionally occur due to weak inhibitors and inducers (eg, target drug is highly dependent on CYP3A4 metabolism and has a narrow therapeutic index). Accordingly, specific interactions should be checked using a drug interaction program such as the Lexicomp drug interactions program included within UpToDate.
- Refer to UpToDate topics on specific agents and indications for further details.

* Classified as a weak inhibitor of CYP3A4 according to FDA system.[1]

¶ Classified as a weak inducer of CYP3A4 according to FDA system.[1]

Δ The fixed-dose combination therapy pack taken in the approved regimen has moderate CYP3A4 induction effects. When elagolix is used as a single agent, it is a weak CYP3A4 inducer. Norethindrone and estradiol are not CYP3A4 inducers.

References:

1. *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry (January 2020) available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions.*
2. *US Food & Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

Graphic 76992 Version 78.0

Drug ratings in pregnancy (US Food and Drug Administration)

Category	Interpretation
A	Controlled human studies show no risk
	Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	No evidence of risk in studies
	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.
C	Risk cannot be ruled out
	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	Positive evidence of risk
	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Contraindicated in pregnancy
	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

In 2015, the US Food and Drug Administration (FDA) began overseeing the phase-out of pregnancy risk categories (A, B, C, D, and X) from prescription drug labeling and began requiring information from available human and animal studies of (1) known or potential maternal or fetal adverse reactions and (2) dose adjustments needed during pregnancy and the postpartum period. Additional information is available at the FDA website: Pregnancy and Lactation Labeling Final Rule.

Graphic 50021 Version 31.0

Contributor Disclosures

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