Chapter 4

PHARMACOLOGICAL PROPERTIES OF HYDROXYCHLOROQUINE, AZITHROMYCIN, FAVIPIRAVIR AND LOPINAVIR/RITONAVIR USED IN THE COVID-19 TREATMENT

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INTRODUCTION

COVID-19, due to SARS-CoV-2, which was first reported from Wuhan, Hubei province of the Republic of China, and spreads all over the world, causing pandemics, has no effective treatment yet. Therefore, the use of certain drugs, such as hydroxychloroquine (HCQ), azithromycin, favipiravir and lopinavir/ritonavir, has been granted an emergency use authorization (EUA) by authorities(1,2). The EUA of HCQ in COVID-19 treatment was issued by the FDA in April 2020, but revoked in June 2020(3). However, its effectiveness in COVID-19 continues to be investigated by clinical studies(4). HCQ administration in COVID-19 prophylaxis and/or treatment is still recommended in Turkey(2).

Pharmacokinetics and pharmacodynamics of HCQ, azithromycin, favipiravir and lopinavir/ritonavir, effects on reproduction, pregnancy and breastfeeding, drug-drug interactions are detailed in subtitles.

HYDROXYCHLOROQUINE

HCQ is an antimalarial drug of the aminoquinoline group, that has been used since 1955(5). Besides malaria treatment, it is used in diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), chronic discoid lupus erythematosus, dermatomyositis (cutaneous disease), porphyria cutanea tarda, primary Sjögren syndrome (extraglandular involvements), Q fever (*Coxiella burnetii*), Sarcoidosis (arthropathy and cutaneous disease) etc(5,6). Pharmacokinetics and pharmacodynamics of HCQ are presented in Table 1.

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REFERENCES

1. https://www.covid19treatmentguidelines.nih.gov, entry date: 17.12.2020
2. https://covid19bilgi.saglik.gov.tr/tr/covid-19-rehberi.html, entry date: 17.12.2020
3. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and, entry date: 17.12.2020
4. https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Hydroxychloroquine&cntry=&state=&city=&dist=, entry date: 17.12.2020
5. FDA Approved Drug Products: Hydroxychloroquine Oral Tablets. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/009768Orig1s051lbl.pdf
6. Ben-Zvi I, Kivity S, Langevitz P, et al. Hydroxychloroquine: from malaria to autoimmunity. Clin Rev Allergy Immunol. 2012;42:145-153. doi:10.1007/s12016-010-8243-x.
7. Tett SE. Clinical pharmacokinetics of slow-acting antirheumatic drugs. Clin Pharmacokinet. 1993;25:392-407. doi:10.2165/00003088-199325050-00005.
8. McChesney EW, Conway WD, Banks Jr WF, et al. Studies of the metabolism of some compounds of the 4-amino-7-chloroquinolone series. J Pharmacol Exp Ther. 1966;151:482-493.
9. Furst DE. Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. Lupus. 1996;5 Suppl 1:S11-5.
10. Lim HS, Im JS, Cho JY, et al. Pharmacokinetics of hydroxychloroquine and its clinical mplications in chemoprophylaxis against malaria caused by Plasmodium vivax. Antimicrob Agents Chemother. 2009;53:1468-1475. doi:10.1128/AAC.00339-08.
11. Collins KP, Jackson KM, Gustafson DL. Hydroxychloroquine: A Physiologically-Based Pharmacokinetic Model in the Context of Cancer-Related Autophagy Modulation. J Pharmacol Exp Ther. 2018;365:447-459. doi:10.1124/jpet.117.245639.
12. Browning, David J. (2014). Hydroxychloroquine and chloroquine retinopathy. Springer. [ISBN:978-1-4939-0597-3].
13. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Semin Arthritis Rheum. 1993;23(2 Suppl 1):82-91.
14. Chou AC, Fitch CD. Heme polymerase: modulation by chloroquine treatment of a rodent malaria. Life Sci. 1992;51:2073-2078. doi: 10.1016/0024-3205(92)90158-l.
15. Chary MA, Barbuto AF, Izadmehr S, et al. COVID-19: Therapeutics and Their Toxicities. J Med Toxicol. 2020; 16:284–294. doi:10.1007/s13181-020-00777-5.
16. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69. doi:10.1186/1743-422X-2-69.
17. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71:732-739. doi:10.1093/cid/ciaa237.
18. https://chem.nlm.nih.gov/chemidplus/sid/0000118423
19. Petri M, Elkhalifa M, Li J, et al. Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. Arthritis Rheumatol. 2020;72:448-453. doi:10.1002/art.41121.
20. Mohammad S, Clowse MEB, Eudy AM, et al. Examination of hydroxychloroquine use and hemolytic anemia in G6PDH-deficient patients. Arthritis Care Res (Hoboken). 2018;70(3):481-485. doi:10.1002/acr.23296.
21. Cansu DU, Korkmaz C. Hypoglycaemia induced by hydroxychloroquine in a non-diabetic patient treated for RA. Rheumatology (Oxford). 2008; 47:378-379.
22. UpToDate, Inc. Lexi-Interact Online. www.uptodate.com/drug-interactions/?source=responsive_home#di-druglist, entry date: 17.12.2020
23. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol. 2020;72:529-556. doi:10.1002/art.41191.

24. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71:1771-1782.
25. Costedoat-Chalumeau N, Amoura Z, Aymard G, et al. Evidence of transplacental passage of hydroxychloroquine in humans. Arthritis Rheum. 2002;46:1123-1124.
26. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis. 2017;76:476-485. doi:10.1136/annrheumdis-2016-209770.
27. Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press. 2019. https://wwwnc.cdc.gov/travel/yellowbook/2020/table-of-contents
28. Talabi MB, Clowse MEB. Antirheumatic medications in pregnancy and breastfeeding. Curr Opin Rheumatol. 2020;32:238-246. doi:10.1097/BOR.0000000000000710.
29. Diav-Citrin O, Blyakhman S, Shechtman S, et al. Pregnancy outcome following in utero exposure to hydroxychloroquine: a prospective comparative observational study. Reprod Toxicol. 2013;39:58-62. doi:10.1016/j.reprotox.2013.04.005.
30. Paufique L, Magnard P. Retinal degeneration in 2 children following preventive antimalarial treatment of the mother during pregnancy. Bull Soc Ophthalmol Fr 1969;69:466-467.
31. Renault F, Flores-Guevara R, Renaud C, et al. Visual neurophysiological dysfunction in infants exposed to hydroxychloroquine in utero. Acta Paediatr. 2009;98:1500-1503. doi:10.1111/j.1651-2227.2009.01379.x.
32. Mulholland CP, Pollock TJ. The Peters anomaly following antenatal exposure to methotrexate and hydroxychloroquine. Can J Ophthalmol. 2011;46:289-290. doi:10.1016/j.jcjo.2011.05.001.
33. Cooper WO, Cheetham TC, Li DK, et al. Brief report: Risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. Arthritis Rheumatol. 2014;66:444-450. doi:10.1002/art.38262.
34. Gravani A, Gaitanis G, Zioga A, et al. Synthetic antimalarial drugs and the triggering of psoriasis - do we need disease-specific guidelines for the management of patients with psoriasis at risk of malaria? Int J Dermatol. 2014;53:327-330. doi: 10.1111/ijd.12231.
35. Levy RA, Vilela VS, Cataldo MJ, et al. Hydroxychloroquine (HCQ) in Lupus Pregnancy: double-blind and placebo-controlled study. Lupus, 2001;10:401-404.
36. Motta M, Tincani A, Faden D et al. Antimalarial agents in pregnancy. Lancet. 2002;359:524-525. doi:10.1016/S0140-6736(02)07643-2.
37. Klinger G, Morad Y, Westall CA, et al. Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. Lancet. 2001;358:813-814. doi:10.1016/S0140-6736(01)06004-4.
38. Osadchy A, Ratnapalan T, Koren G. Ocular toxicity in children exposed in utero to antimalarial drugs: review of the literature. J Rheumatol. 2011;38:2504-2508.
39. Kaplan YC, Ozarfati J, Nickel C, et al. Reproductive outcomes following hydroxychloroquine use for autoimmune diseases: a systematic review and meta-analysis. Br J Clin Pharmacol 2015;81:835-848. doi:10.1111/bcp.12872.
40. Plaquenil (hydroxychloroquine) [prescribing information]. St. Michael, Barbados: Concordia Pharmaceuticals Inc; September 2019.
41. Cissoko H, Rouger J, Zahr N, et al. Breast milk concentrations of hydroxychloroquine. Fundam Clin Pharmacol. 2010;24(suppl 1):420. Abstract. doi.org/10.1111/j.1472-8206.2010.00819.x.
42. Peng W, Liu R, Zhang L, et al. Breast milk concentration of hydroxychloroquine in Chinese lactating women with connective tissue diseases. Eur J Clin Pharmacol. 2019;75:1547-1553. doi:10.1007/s00228-019-02723-z.

43. Nation RL, Hackett LP, Dusci LJ, et al. Excretion of hydroxychloroquine in human milk. Br J Clin Pharmacol 1984;17:368-369. doi:10.1111/j.1365-2125.1984.tb02358.x.
44. Ostensen M, Brown ND, Chiang PK, et al. Hydroxychloroquine in human breast milk. Eur J Clin Pharmacol. 1985;28:357. doi:10.1007/BF00543338.
45. Anderson PO, Sauberan JB. Modeling drug passage into human milk. Clin Pharmacol Ther. 2016;100:42-52. doi:10.1002/cpt.377.
46. Ito S. Drug therapy for breast-feeding women. N Engl J Med. 2000;343:118-126. doi:10.1056/NEJM200007133430208.
47. Cimaz R, Brucato A, Meregalli E, et al. Electroretinograms of children born from mothers treated with hydroxychloroquine during pregnancy and breast-feeding. Lupus. 2004;13:755.
48. Tincani A, Faden D, Lojacono A et al. Hydroxychloroquine in pregnant patients with rheumatic disease. Arthritis Rheum. 2001;44 (Suppl 9):S397. Abstract 2065.
49. Kavanaugh A, Cush JJ, Ahmed MS, et al. Proceedings from the American College of Rheumatology Reproductive Health Summit: the management of fertility, pregnancy, and lactation in women with autoimmune and systemic inflammatory diseases. Arthritis Care Res (Hoboken). 2015;67:313–325. doi:10.1002/acr.22516.
50. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016;55:1693–1697. doi:10.1093/rheumatology/kev404.
51. Skorpen CG, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75:795–810.
52. Fohner AE, Sparreboom A, Altman RB, et al. PharmGKB summary: Macrolide antibiotic pathway, pharmacokinetics/pharmacodynamics. Pharmacogenet Genomics. 2017;27:164-167. doi:10.1097/FPC.0000000000000270.
53. https://s3-us-west-2.amazonaws.com/drugbank/cite_this/attachments/files/000/003/154/original/zithromax_fda.pdf?1548452062
54. https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Azithromycin&cntry=&state=&city=&dist=, entry date: 05.08.2020
55. McMullan BJ, Mostaghim M. Prescribing azithromycin. Aust Prescr. 2015;38:87-89. doi:10.18773/austprescr.2015.030.
56. Singlas E. Clinical pharmacokinetics of azithromycin. Pathol Biol (Paris). 1995;43:505-511.
57. https://hmdb.ca/metabolites/HMDB0014352
58. Champney WS, Miller M. Inhibition of 50S ribosomal subunit assembly in Haemophilus influenzae cells by azithromycin and erythromycin. Curr Microbiol. 2002;44:418-424. doi:10.1007/s00284-001-0016-6.
59. American Society of Health-System Pharmacists 2012; Drug Information 2012. Bethesda, MD. 2012, p. 238
60. https://chem.nlm.nih.gov/chemidplus/sid/0083905015
61. https://www.uptodate.com/contents/azithromycin-systemic-drug-information?-search=azitromisin&source=panel_search_result&selectedTitle=1~145&usage_type=panel&display_rank=1
62. Fresenius Kabi USA, LLC. 2019. Azithromycin product labeling. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b69917c0-95d5-4b29-b0e3-07054a4fd79f
63. Ramsey PS, Vaules MB, Vasdev GM, et al. Maternal and transplacental pharmacokinetics of azithromycin. Am J Obstet Gynecol. 2003;188:714-718. doi:10.1067/mob.2003.141.
64. American College of Obstetricians and Gynecologists (ACOG). Committee on practice bulletins-obstetrics. ACOG practice bulletin No. 199: use of prophylactic antibiotics in labor and delivery. Obstet Gynecol. 2018;132:e103-e119. doi:10.1097/AOG.0000000000002833.

65. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015 [published correction appears in MMWR Recomm Rep. 2015;64(33):924]. MMWR Recomm Rep. 2015;64(RR-03):1-137.
66. US Department of Health and Human Services (HHS) Panel on COVID-19 Treatment Guidelines. Coronavirus disease 2019 (COVID-19) treatment guidelines. https://covid19treatmentguidelines.nih.gov/. Updated April 21, 2020. Accessed April 22, 2020.
67. Savitcheva AM, Tchkhartishvili MG, Arzhanova ON et al: The course and outcome of pregnancy in women with chlamydial infection. J Perinat Med 2001;29(Suppl 1):372.
68. Cooper WO, Hernadez-Diaz S, Arbogast PG, Ray WA: Antibiotics potentially used in response to bioterrorism and major congenital malformations. Pharmacoepidemiol Drug Saf 2006;15(Suppl 1):S6-S7.
69. Salman S, Davis TM, Page-Sharp M, et al. Pharmacokinetics of transfer of azithromycin into the breast milk of African mothers. Antimicrob Agents Chemother. 2015;60:1592-1599. doi:10.1128/AAC.02668-15.
70. Kelsey JJ, Moser LR, Jennings JC, et al. Presence of azithromycin breast milk concentrations: a case report. Am J Obstet Gynecol. 1994;170(5, pt 1):1375-1376. doi:10.1016/s0002-9378(94)70161-x.
71. Sutton AL, Acosta EP, Larson KB, et al. Perinatal pharmacokinetics of azithromycin for cesarean prophylaxis. Am J Obstet Gynecol. 2015;212:812.e1-6. doi: 10.1016/j.ajog.2015.01.015.
72. Goldstein LH, Berlin M, Tsur L, et al. The safety of macrolides during lactation. Breastfeed Med. 2009;4:197-200. doi:10.1089/bfm.2008.0135.
73. Lund M, Pasternak B, Davidsen RB, et al. Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis: nationwide cohort study. BMJ. 2014;348:g1908. doi:10.1136/bmj.g1908.
74. Sorensen HT, Skriver MV, Pedersen L, et al. Risk of infantile hypertrophic pyloric stenosis after maternal postnatal use of macrolides. Scand J Infect Dis. 2003;35:104-106. doi:10.1080/0036554021000027010.
75. Almaramhy HH, Al-Zalabani AH. The association of prenatal and postnatal macrolide exposure with subsequent development of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis. Ital J Pediatr. 2019;45:20. doi:10.1186/s13052-019-0613-2.
76. Abdellatif M, Ghozy S, Kamel MG et al. Association between exposure to macrolides and the development of infantile hypertrophic pyloric stenosis: a systematic review and meta-analysis. Eur J Pediatr. 2019;178:301-314. doi:10.1007/s00431-018-3287-7.
77. World Health Organization (WHO). Breastfeeding and maternal medication, recommendations for drugs in the eleventh WHO model list of essential drugs. 2002. http://www.who.int/maternal_child_adolescent/documents/55732/en/
78. Hayden FG, Shindo N. Influenza virus polymerase inhibitors in clinical development. Curr Opin Infect Dis. 2019;32:176-186. doi:10.1097/QCO.0000000000000532.
79. https://clinicaltrials.gov/ct2/results?cond=Covid19&term=favipiravir&cntry=&state=&city=&dist=, entry date: 05.08.2020
80. Nguyen TH, Guedj J, Anglaret X, et al. Favipiravir pharmacokinetics in Ebola-Infected patients of the JIKI trial reveals concentrations lower than targeted. PLoS Negl Trop Dis. 2017;11:e0005389. doi:10.1371/journal.pntd.0005389.
81. Pharmaceuticals and Medical Devices Agency: Avigan (favipiravir) Review Report. Available from: https://www.pmda.go.jp/files/000210319.pdf
82. Madelain V, Nguyen TH, Olivo A, et al. Ebola Virus Infection: Review of the Pharmacokinetic and Pharmacodynamic Properties of Drugs Considered for Testing in Human Efficacy Trials. Clin Pharmacokinet. 2016;55:907-923. doi:10.1007/s40262-015-0364-1.
83. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93(7):449-463. doi:10.2183/pjab.93.027.

84. Venkataraman S, Prasad BVLS, Selvarajan R. RNA Dependent RNA Polymerases: insights from structure, function and evolution. Viruses. 2018;10:76. doi: 10.3390/v10020076.
85. https://www.uptodate.com/contents/favipiravir-united-states-not-commercially-available-refer-to-prescribing-and-access-restrictions-drug-information?search=favipiravir&source=panel_search_result&selectedTitle=1~7&usage_type=panel&kp_tab=drug_general&display_rank=1#F54379629
86. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Res. 2018;153:85-94. doi:10.1016/j.antiviral.2018.03.003.
87. FDA Approved Drug Products: Kaletra (lopinavir/ritonavir) for oral use: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021251s058,021906s053lbl.pdf
88. https://clinicaltrials.gov/ct2/results?cond=Covid19&term=lopinavir&cntry=&state=&city=&dist=, entry date: 05.08.2020
89. Health Canada Product Monograph: Kaletra (lopinavir/ritonavir) for oral use . Avilable from: https://pdf.hres.ca/dpd_pm/00053305.PDF
90. FDA Approved Drug Products: NORVIR (ritonavir) Capsules, Soft Gelatin for Oral use. Avialable from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020945s033lbl.pdf
91. Kumar GN, Jayanti V, Lee RD, et al. In vitro metabolism of the HIV-1 protease inhibitor ABT-378: species comparison and metabolite identification. Drug Metab Dispos. 1999;27:86-91.
92. Niu WJ, Sun T, Liu L, et al. Population pharmacokinetics and dosing regimen optimisation of lopinavir in Chinese adults infected with HIV. Basic Clin Pharmacol Toxicol. 2019;124:456-465. doi:10.1111/bcpt.13154.
93. Sundquist WI, Krausslich HG. HIV-1 assembly, budding, and maturation. Cold Spring Harb Perspect Med. 2012;2:a006924. doi:10.1101/cshperspect.a006924.
94. De Clercq E. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. Int J Antimicrob Agents. 2009;33:307-320. doi:10.1016/j.ijantimicag.2008.10.010.
95. https://www.uptodate.com/contents/lopinavir-and-ritonavir-drug-information?search=lopinavir % 20ritonavir&source=panel_search_result&selectedTitle=1~54&usage_type=panel&kp_tab=drug_general&display_rank=1#F189746
96. US Department of Health and Human Services (HHS) Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Updated December 24, 2019. Accessed January 2, 2020.