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Drugs for Hepatitis

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The plethora of new drugs to treat hepatitis presents a confusing array of options to treat the nursing mother. LactMed has recently undertaken an extensive review of these drugs to put them into a consistent context.

Hepatitis A

No drugs are available to treat hepatitis A, so LactMed information is limited to records on hepatitis A vaccine and immune globulin, neither of which is contraindicated during breastfeeding.

Hepatitis B

Reduction of the vertical transmission of hepatitis B virus (HBV) is important. No difference exists in infection rates between breast-fed and formula-fed infants born to hepatitis B-infected women, as long as the infant receives hepatitis B immune globulin and hepatitis B vaccine at birth. Recently, an expert review from the Society for Maternal-Fetal Medicine stated, ''We recommend that women with HBV infection be encouraged to breast feed as long as the infant receives immunoprophylaxis at birth (HBV vaccination and hepatitis B immunoglobulin).''[1] Although LactMed generally does not provide specific treatment information, the importance of infants' receiving these products and the negligible risk of vertical transmission if they are given are provided in the record for each drug used to treat hepatitis B.

Lamivudine and tenofovir are commonly used to treat hepatitis B. These drugs have not been studied in nursing mothers who are being treated solely for hepatitis B infection. However, they have both been studied fairly well in nursing mothers who are HIV+ with and without HBV infection. FDA-approved labeling for these drugs is somewhat confusing. The lamivudine (Epivir-HBV) label discusses excretion of lamivudine into milk at three to six times the dose used to treat hepatitis B (i.e., the dose used for HIV infection) and then states, ''Because of the potential for serious adverse reactions in nursing infants, a decision should be made to discontinue Epivir-HBV taking into consideration the importance of continued hepatitis B therapy to the mother and the known benefits of breastfeeding.'' The warning for tenofovir (Viread) is even stronger, although it confusingly intertwines HIV transmission with hepatitis B, stating, ''Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving Viread.''

A recent expert review concluded that there is currently no justification for contraindicating the use of lamivudine or tenofovir for hepatitis B during breastfeeding.[2] An accompanying editorial pointed out the inconsistencies between their use during pregnancy and during breastfeeding in both labeling and international guidelines. Labeling and guidelines both recommend using tenofovir and lamivudine during pregnancy (where fetal exposure is much greater than breastfeeding exposure) for both HIV and hepatitis B infections and recommend that the drugs be continued during breastfeeding in HIV+ mothers, but they recommend against breastfeeding in mothers who have only hepatitis B infections.[3] Another recent expert review from Australia, New Zealand, and the UK also states that breastfeeding should not be contraindicated for mothers with HBV infection taking tenofovir.[4]

The evidence

Tenofovir has the same dosage for both HIV and hepatitis B, 300 mg daily. Tenofovir has very poor oral bioavailability, so it is marketed as the more bioavailable tenofovir disoproxil fumarate. Once absorbed, tenofovir is metabolized intracellularly to the active metabolite tenofovir diphosphate. The bioavailabilities of tenofovir and tenofovir diphosphate from breastmilk in infants are not known, but presumed to be very low. Tenofovir has been measured in breastmilk of mothers undergoing HIV therapy and in their breast-fed infants. Tenofovir levels in breastmilk are very low after 300 mg doses, a median of 5 mcg/L in one study and peak concentrations of less than 15 mcg/L in another. The latter investigators estimated that an exclusively breast-fed infant would receive about 0.03% of the proposed infant dose for tenofovir. Measurement of infant plasma tenofovir concentrations bears out this low dose and poor oral absorption. Most of the 30 breast-fed infants who have been studied had low-to-undetectable plasma concentrations. In the largest study, 25 infants had a median morning infant plasma tenofovir concentration of 24 mcg/L at 6 months of age, which was less than one-third of maternal plasma levels. At 12 months of age, all infants had unquantifiable plasma concentrations of tenofovir.[5]

The lamivudine dosage of mothers with HIV infections, with or without concurrent hepatitis B infection, is 300 mg daily. For mothers with hepatitis B infection alone, the dosage

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is only 100 mg daily. Two studies with the 300 mg/day dosage compared infant plasma concentrations with those of their mother and found that median infant plasma concentrations were only 2–6% of the maternal plasma levels.[5]

Adefovir, entecavir, and telbivudine also have indications for treatment of hepatitis B and emtricitabine is used off-label. Neither adefovir, entecavir, nor telbivudine has any available information on its use during breastfeeding. Emtricitabine has been studied in only five HIV+ mothers in whom about 2% of the relative infant dosage was excreted into breastmilk. These drugs should be considered second-line alternative therapies in nursing mothers because of the lack of information during breastfeeding. In addition to these oral agents, interferon alfa-2b and peginterferon alfa-2a are approved for treating hepatitis B, but they are given by injection and less preferred. The amounts of these alfa-interferons were very low in the breastmilk of three mothers studied. Plasma levels in breast-fed infants have not been measured, but the infant would receive them orally, reducing the likelihood of their systemic absorption.

Hepatitis C

The first consideration is that hepatitis C is not transmitted through breastmilk[6,7] and breastmilk has even been shown to inactivate hepatitis C virus (HCV).[8,9] Although breastfeeding is not contraindicated, the Centers for Disease Control and Prevention recommends that mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding.[7] It is not clear whether this warning applies equally to mothers who are receiving drug treatment for hepatitis C. Current recommendations further state that infants born to mothers with HCV infection should be tested for HCV infection. Because maternal antibody is present for the first 18 months of life and before the infant mounts an immunologic response, nucleic acid testing is recommended.[6,7]

The remarkable efficacy of the new drugs for hepatitis C has inevitably led to questions about the safety of these drugs in the nursing mother. Unfortunately, none of these new drugs has any human information relative to their use in breastfeeding. The drugs available at the time of writing include boceprevir, daclatasvir, dasabuvir, elbasvir, grazoprevir, ledipasvir, ombitasvir, paritaprevir, peginterferons alfa-2a and 2b, ribavirin, simeprevir, sofosbuvir, and velpatasvir. A low dose of ritonavir is included in some combination regimens to inhibit CYP3A4 metabolism of a concomitant protease inhibitor to enhance its oral bioavailability.

The FDA-approved labeling of hepatitis C drugs is distinctly divided between drugs approved before and after the new FDA Pregnancy and Lactation Labeling Rule (PLLR) took effect on June 30, 2015. Drugs approved before PLLR include boceprevir, alfa interferons, ribavirin, and simeprevir. The labels of these drugs contain the familiar wording, ''It is not known whether drug x is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue drug x.'' Drugs approved *after* the PLLR have the much improved wording of, ''the development and health benefits of breastfeeding should be considered along with the mother's clinical need for drug x and any potential adverse effects on the breastfed child from drug x or from the underlying maternal condition.'' These differences in wording appear to be merely artifacts of the PLLR labeling changes and not related to any inherent difference in risk between the older and newer drugs.

Labeling that all hepatitis C drugs have in common is, ''if drug x is administered with ribavirin, the nursing mother's information for ribavirin also applies to this combination regimen. Refer to the ribavirin prescribing information for more information on use during lactation.'' Of course, ribavirin has the old labeling and admonition to stop breastfeeding if it is used. Ribavirin is teratogenic and embryocidal in animals, so its use during pregnancy is contraindicated, although human pregnancy data are limited and inconclusive. These pregnancy concerns are not relevant to nursing infants, and infants are often treated directly with ribavirin inhalation for respiratory syncytial virus with few nonpulmonary side effects.

The evidence

Authors from Italy have recently addressed the use of hepatitis C drugs during pregnancy and breastfeeding.[10] Because of the lack of human data, they approached the topics from the standpoints of the drugs' pharmacokinetics and animal studies. Unfortunately, the article often conflates pregnancy and lactation risks (which is not generally true), so its recommendations are occasionally puzzling. Nevertheless, the authors point out that the drugs have not caused any adverse effects in the pups of lactating animals and that the pharmacokinetic properties of these drugs are generally favorable.

Plasma protein binding of most of the hepatitis C drugs is quite extensive. With the exception of boceprevir (75%), ribavirin (0%), and sofosbuvir (60% drug, 0% metabolite), all of the other oral drugs for hepatitis C are more than 97% bound to maternal proteins and most of them are more than 99% bound. This means that less than 1–3% of these drugs in maternal plasma will pass into breastmilk. Extensive protein binding is a relatively good predictor of low infant plasma levels and safe drug use during breastfeeding.[11]

Given the favorable pharmacokinetics, generally low toxicity, and the relatively permissive product labeling of most drugs for hepatitis C, LactMed uses the standard language of, ''If drug x is required by the mother, it is not a reason to discontinue breastfeeding. Some sources recommend against breastfeeding when drug x is used with ribavirin.'' The information on the lack of transmissibility of hepatitis C through breastmilk except for the possible risk with cracked nipples and information on infant testing are also included in each LactMed record.

Disclosure Statement

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