The Difficulties in Antihypertensive Drug Prescription During Lactation: Is the Information Consistent?

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Abstract

Introduction: The lack of consistent official information on the use of medications during lactation is probably one of the main reasons leading to an excess of prudence, based on presumption of risk rather than on evidence. The objective of this study was to compare the level of agreement between different official sources available to doctors and women on the use of medications during lactation.

Materials and Methods: Sources of information included governmental regulatory agencies (RAs) and scientific sources (SS). The package leaflets (PLs) and summaries of product characteristics (SPCs) were retrieved from online databases of the European Union and U.S. RAs. Among the SS, the latest edition of the book *Medications and Mothers' Milk* by Hale and Rowe and the LactMed database were selected. Information about the use of 11 antihypertensive medications during breastfeeding was analyzed.

Results: The PLs and SPCs report a higher risk profile than the one expressed by SS, and they often suggest the interruption of lactation even for compatible medications.

Conclusions: Health professionals should be supported by official, accurate, comprehensive, and consistent information about maternally ingested medication and breastfeeding management to facilitate proper decision-making.

Introduction

ACCORDING TO THE AMERICAN ACADEMY of Pediatrics, “many mothers are inappropriately advised to discontinue breastfeeding or avoid taking essential medications because of fears of adverse effects on their infants.”^{1(p.e796)} This cautious approach may often be unnecessary, depending on the pharmacokinetics and pharmacodynamics of the drug, the level of its excretion in breastmilk, or its widespread use in pediatrics (on or off label). In other cases, an alternative medication may be available.^{1,2} As a consequence, mothers who do not intend to discontinue breastfeeding may decide not to take the medication or to switch to “natural” products or self-medication, exposing themselves and their children to the risk of using products whose safety in breastfeeding has not been demonstrated.³

In the European Union (EU) and in the United States, the main official sources of information on the use of medications during lactation are the summary of product characteristics (SPC) and the package leaflet (PL), provided by the regulatory agencies (RAs) to healthcare professionals and users, respectively. However, drug safety information given by national and international agencies and scientific societies is not uniform, and often the PLs of different brands of identical medications contain inconsistent or contradictory information.⁴ The decision-making process about the use of medications during lactation is a complex phenomenon.⁵ The choice of a drug in the postpartum period should be made on a case-by-case basis, based on various determinants, including the mother's needs, the child's age, the infant feeding practice, and consequently the pharmacokinetics and pharmacodynamics of the available drugs, giving precedence to medications with a low milk/

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The findings have been presented as an oral communication to the XXXIII National Congress for Midwives, held October 2–4, 2014, in Rome, Italy, and as a poster presentation to the European Conference “Safety of Medication Use in Pregnancy,” held February 2–4, 2015, in Poznan, Poland.

plasma ratio.⁶ The lack of reliable and consistent official information and the widespread presumption of availability of breastmilk substitute are probably among the main reasons for an excess of prudence by physicians, based on a presumption of risk rather than on evidence. This in turn causes confusion in mothers who try and understand the real implications of using a certain medication.

The aim of this study is to determine how the contents of the PLs and SPCs provided by the EU and U.S. drug RAs and the information retrieved from scientific sources (SS) regarding the safety of the use of several antihypertensive medications during breastfeeding are consistent or differ.

Materials and Methods

In April and May 2014, the contents of PLs and SPCs from the EU and U.S. RAs were consulted and compared with the contents of the main SS on the use of medications during lactation. This study was not subject to Institutional Review Board approval because no personal information was obtained from individuals for the presented results.

Sources of information on use of medications during lactation

Two main categories of information were selected: governmental RAs and SS.

RAs. There are two agencies in Europe included in the present work: the European Medicines Agency (EMA)⁷ for drugs that require a centralized European procedure and the Heads of Medicine Agencies (HMA) for medications registered by the National Competent Authorities in the European Economic Area.⁸ If the PLs and SPCs of an active ingredient were not available on the European databases, they were retrieved from the Italian Medicines Agency (AIFA) database.⁹ The AIFA database was chosen for convenience because the

authors work in Italy; however, all European countries have similar regulation systems. All selected drugs were registered in the HMA database except methyldopa, whose PL and SPC were found in the AIFA database. For the United States, the Food and Drug Administration (FDA) database was included.¹⁰ The evaluation of the PL and SPC ("label" for the FDA) was focused on the "Contraindications" and "Pregnancy and breastfeeding" sections. In addition, a free text search was performed in the full PL and SPC, using the key words "breastfeeding," "lactation," "milk," and "nursing."

SS. Among the SS of information, two were chosen because of their continuous updates: Hale and Rowe's *Medications and Mothers' Milk*⁶ and the LactMed database.¹¹ Other agencies, such as the World Health Organization,¹² the American Academy of Pediatrics,^{1,2} and the National Institute for Health and Clinical Excellence¹³ have published documents on this topic. However, they were excluded for various reasons: the World Health Organization document is outdated, the American Academy of Pediatrics refers the reader to the LactMed database, and the National Institute for Health and Clinical Excellence guidelines are specific for pregnancy but lacking for breastfeeding. Hale and Rowe's *Medications and Mothers' Milk*⁶ is a collection of evidence-based monographs on drugs, in which the authors propose a classification into five categories (L1–L5), based on the risk for the infant or for lactation (Table 1). LactMed¹¹ is an online drug and lactation database provided by the U.S. National Library of Medicine's TOXNET system. All fields of the LactMed database were consulted, with a special focus on the summary of use.

Choice of antihypertensive drugs

Antihypertensive medications were chosen because hypertension is one of the most common disorders in pregnancy.¹⁴

TABLE 1. LACTATION RISK CATEGORIES OF HALE AND ROWE⁶

<i>Classification</i>	<i>Description</i>
L1 (compatible)	Drug that has been taken by a large number of breastfeeding mothers without any observed increase adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote, or the product is not orally bioavailable in an infant.
L2 (probably compatible)	Drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant and/or the evidence of a demonstrated risk that is likely to follow use of the medication in a breastfeeding woman is remote.
L3 (probably compatible)	There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal nonthreatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant. (New medications that have absolutely no published data are automatically categorized in this category, regardless of how safe they may be.)
L4 (possibly hazardous)	There is positive evidence of risk to a breastfed infant or to breastmilk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g., 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).
L5 (hazardous)	Studies in breastfeeding mothers have demonstrated that there is a significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using of the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

Using the literature,^{15–19} the most common therapeutic categories of antihypertensive medications were included: angiotensin converting enzyme inhibitors, calcium channel blockers, beta-blockers with high maternal protein binding, methyldopa, diuretics, and angiotensin receptor blockers. For each category, we selected the two “oldest” active ingredients, still currently available, according to the year the drug was first registered in Italy. This criterion is based on the fact that the drugs registered a longer time ago have a wider range of scientific evidence and a more defined safety profile than more recent molecules.^{6,19} Only active ingredients that were available in databases of both RAs were considered. If they were not available, the first active ingredient next registered was included (which is the case for furosemide and indapamide).

Applying these criteria, captopril and enalapril (angiotensin converting enzyme inhibitors), nifedipine and verapamil (calcium channel blockers), atenolol and propranolol (beta-blockers), methyldopa, and losartan and valsartan (angiotensin receptor blockers) were included. In the diuretics category, the first two registered drugs were hydrochlorothiazide and spironolactone (in 1959 and 1962, respectively). However, they were excluded because they were present in the FDA database only in association with other active ingredients, not as a single molecule. Therefore, furosemide and indapamide, registered in 1965 and 1979, respectively, were included.

Branded drugs were chosen, rather than generic formulations. Except in special cases, generic producers are exonerated from presenting studies of efficacy and safety because the molecule is already known.²⁰ It follows therefore that the contents of the PL and SPC of generics do not contain additional or different information about their safety use during lactation from branded drugs. When more branded drugs with the same active ingredient were present in the databases of RAs, after it was verified that the PL and SPC contents relevant for our purpose were comparable, the choice of the medication was made randomly. While retrieving data from the selected sources, only information regarding healthy, full-term, and normal weight newborns was considered. The contents of PLs, SPCs, Hale and Rowe's book,⁶ and the LactMed database¹¹ were categorized using NVivo version 10 software (QSR International Pty Ltd., Melbourne, Australia) for the content analysis.

Results

Table 2 summarizes the results, according to a color code consisting of five options: dark gray for drugs compatible with breastfeeding, light gray for probably compatible medications, hatched for not recommended drugs, black for contraindicated medications, and white in case of contradictory PL and SPC contents. The legend shows more details on this classification. The color code was assigned by two researchers. When the researchers did not agree on how to classify the drug, a team of pharmacoepidemiologists was consulted. The main contents extracted from the selected sources of information are reported below.

Complete findings are given in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/bfm).

Captopril

According to HMA's PLs and SPCs, captopril should be used if the treatment is deemed necessary, but the infant should be observed for any adverse effects. As for the FDA, the SPC reports that the medication is found in the milk at 1% of the maternal blood level, and the choice of whether to discontinue breastfeeding or the drug use should be evaluated taking into account the importance of the treatment for the mother and the potential adverse reaction in the infant. Captopril is classified as L2 by Hale and Rowe.⁶ According to LactMed,¹¹ it is compatible with breastfeeding with the observation of the child's well-being.

Enalapril

HMA reports that enalapril can be detected in breastmilk, and therefore its use in the first weeks after delivery is not recommended because of the hypothetical risk of cardiovascular and renal effects. In the case of an older infant, the use of enalapril may be taken into consideration if necessary for the mother and if the baby is observed for any adverse effects. The EU SPC contains a large amount of information about pharmacokinetics. The FDA adopts a more cautious approach, stating that “because of the potential adverse reactions in infants, a decision should be made whether to discontinue nursing or to discontinue enalapril.”¹⁰ Hale and Rowe⁶ classify enalapril as L2. According to LactMed,¹¹ amounts ingested by the infant are small and would not be expected to cause adverse effects.

Nifedipine

According to the information provided by HMA, nifedipine should not be administered to breastfeeding women. The U.S. label reports that nifedipine is excreted in human milk; therefore nursing mothers should not to breastfeed their children when taking the medication. Hale and Rowe⁶ classify nifedipine as L2. LactMed¹¹ reports that the amount of the drug in breastmilk is minimal, and no adverse effects in exposed infants have been reported.

Verapamil

The information retrieved from the HMA and FDA databases is similar: the drug is excreted in human milk, and breastfeeding should be discontinued because of the possible side effects in exposed infants. According to the HMA, verapamil is not recommended because there are no available data on its use during lactation, and alternative treatments with a better safety profile are preferred. The PL and SPC provided by the FDA¹⁰ recommend discontinuing breastfeeding because of the potential adverse reactions in exposed infants. According to Hale and Rowe,⁶ verapamil is an L2 drug because the amount transferred to the infant is relatively small. Similarly, LactMed¹¹ reports that the drug levels in breastmilk are low and are not expected to cause adverse effects, especially in infants older than 2 months.

Atenolol

Both the PLs and SPCs in the EU and the United States state that adverse effects in the children exposed to the drug in breastmilk are possible. The EU SPC specifies that, in spite of

TABLE 2. COMPARISON OF THE CONTENT OF OFFICIAL INFORMATION AND OTHER SCIENTIFIC SOURCES

Therapeutic category, drug	Regulatory agencies		Scientific sources	
	HMA/EMA	FDA ¹⁰	Hale class ⁶	LactMed ¹¹
ACE inhibitors				
Captopril	○	◐	●	●
Enalapril	○	◐	●	●
Calcium channel blockers				
Nifedipine	◐	◐	●	●
Verapamil	◐	◐	●	●
Beta-blockers				
Atenolol	○	◐	◐	◐
Propranolol	◐	◐	●	●
Alpha-adrenergic agonist				
Methyldopa	◐	◐	●	●
Diuretics				
Furosemide	●	◐	◐	◐
Indapamide	◐	◐	◐	◐
Angiotensin II receptor antagonists				
Losartan	◐	◐	◐	◐
Valsartan	◐	◐	◐	◐

For regulatory agencies, dark gray symbols indicate breastfeeding or breastfeeding *and* observation for any adverse effect on infants; for scientific sources, they indicate compatible drug or probably compatible drug. For regulatory agencies, light gray symbols indicate exercise caution; not in newborns, postponed use; alternative treatments *or* taking drug if necessary, with observation for any adverse effect on infants; or the drug may decrease breastmilk production. For scientific sources, they indicate probably compatible (limited data); the drug may decrease breastmilk production. For regulatory agencies, hatched symbols indicate not recommended; discontinue breastfeeding; discontinue the drug; discontinue breastfeeding or the drug; or the drug is not intended to be prescribed. For scientific sources, they indicate possibly hazardous drug. For regulatory agencies, black symbols indicate contraindicated; for scientific sources, they indicate hazardous drug. For regulatory agencies, open symbols indicate the package leaflet is contradictory to the summary of product characteristics, the package leaflet is contradictory in different sections of the same package leaflet, or the summary of product characteristics is contradictory in different sections of the same summary of product characteristics.

ACE, angiotensin converting enzyme; FDA, Food and Drug Administration; HMA/EMA, Heads of Medicine Agencies/European Medicines Agency.

the fact that milk levels are high compared with plasma levels, only minimal levels of the drug are found in the child but that long-term risks cannot be ruled out. Resuming breastfeeding 6 hours after taking atenolol and feeding the baby with infant formula in the meantime are therefore recommended. The U.S. label recommends caution when the drug is taken by nursing mothers because it is excreted in the milk. Hale and Rowe⁶ classify atenolol as an L3 drug and affirm that data on the secretion into breastmilk conflict. LactMed¹¹ suggests avoiding this drug during lactation and using alternative agents because of the relatively extensive excretion into breastmilk.

Propranolol

The EU and U.S. PLs and SPCs report that propranolol is not recommended during lactation because it is excreted in breastmilk. Propranolol is classified as an L2 drug by Hale and Rowe.⁶ LactMed¹¹ reports that because of the low levels of propranolol in breastmilk, amounts ingested by the infant are small and would not be expected to cause any adverse effects in full-term infants.

Methyldopa

The EU PL and SPC recommend assessing risks and benefits. The FDA¹⁰ states that caution should be exercised because the drug is excreted into breastmilk. Methyldopa is

classified as L2 by Hale and Rowe.⁶ LactMed¹¹ reports that the amounts ingested by the infant are small because of the low levels in breastmilk and would not be expected to cause any adverse effects in breastfed infants.

Furosemide

The EU PL and SPC categorize this drug as contraindicated, and in the lactation section, the facts that it is excreted in breastmilk and could inhibit lactation are reported as reasons supporting this recommendation. The FDA reports that because the drug is excreted in breastmilk, caution should be exercised. According to Hale and Rowe,⁶ furosemide is an L3 drug: the medication has been found in breastmilk, although levels are unreported, but pediatric use is common. They report that the concern that diuretics could potentially reduce milk production by decreasing blood volume is largely theoretical. LactMed¹¹ advises that alternate drugs might be preferred due to the lack of information and to the concern that an increased diuresis could decrease lactation.

Indapamide

The EU PL and SPC do not recommend breastfeeding because indapamide is excreted in human milk, and effects on the child are likely. The FDA¹⁰ reports that it is not known whether this drug is excreted in human milk, but in case of its

use, the mother should stop breastfeeding because most drugs are excreted in human milk. Hale and Rowe⁶ classify indapamide as L3. According to LactMed,¹¹ if the mother needs to take indapamide, this would not be a reason to discontinue breastfeeding. However, intense diuresis with large doses may decrease breastmilk production.

Losartan and valsartan

The available information on angiotensin receptor blockers is the same, so losartan and valsartan are presented together in this section. The EU PLs and SPCs do not recommend their use during breastfeeding due to the lack of information and advise using alternate drugs, especially when nursing a newborn. The FDA¹⁰ recommends that a decision should be made about whether to discontinue nursing or discontinue angiotensin receptor blockers, taking into account the importance of the therapy to the mother as well as the potential adverse effects on the infant. Hale and Rowe⁶ classify these drugs as L3, and LactMed¹¹ openly advises using alternate drugs as no data are available on their use during breastfeeding.

Discussion

The SPC and PL are official legal documents that describe the main characteristics of the drugs.²¹ The SPC is the basis of information for healthcare professionals about how to use the medication safely and effectively, and the PL, which is aimed at users, indicates how the drug must be administered in accordance with the SPC.

As for the contents, the guidelines given to companies for the drafting of the SPC by the EMA suggests mentioning pregnancy and lactation in the “Contraindications” section only if the drug is actually contraindicated.²¹ As such, the content of the “Pregnancy and lactation” section should consider all available evidence from clinical and nonclinical studies, studies on the pharmacological activity, and post-marketing surveillance studies, in order to allow for a more accurate recommendation. In particular, data derived from clinical pharmacokinetic studies in nursing infants exposed to the drug and adverse reactions information should be mentioned, if available. Recommendations about suspension or continuation of breastfeeding and/or about the interruption or continuation of pharmacological treatment should be evidence based.²¹ The FDA’s current requirements for content to be included in the lactation section of the PLs and SPCs are quite similar to the EMA’s. The FDA additionally recommends referring to ways to minimize infant exposure to the medication, such as the amount of time to let elapse before the next feeding or milk expression, the dosage to be followed, the potential effects of the drug on the infant, and recommendations to monitor or respond to these effects.²² Of note, however, is that none of the PLs and SPCs of the selected antihypertensive medications reviewed in this study provides this comprehensive and detailed information.

Pharmaceutical companies should follow the recommendations of the FDA and the EMA when writing PLs and SPCs more closely to enable doctors and families to have a more complete picture. In this regard, the FDA is amending the rule on labeling requirements about “Pregnancy and lactation” section. According to this new regulation (effective June 30, 2015), the labeling should include more relevant information to support the prescriber in the decision-making process.²³

This study confirmed two major problems: the contradictory nature of the information and recommendations given by different, authoritative sources, as well as a substantial lack of comprehensive information from RAs to support the prescriber and the mother in the choice of the best treatment. Important discrepancies emerge about medication use during breastfeeding from the comparison of the content of official information and SS (Table 2). Furosemide is defined as “contraindicated” by the official sources with no reference to evidence or pharmacokinetics data. In the “Lactation” section, discontinuing either breastfeeding or the use of the medication is often recommended, with no evidence justifying the suspension or any suggestions about the possibility of using alternative medications.

In contrast, the SS suggest a better safety profile and more often give evidence or pharmacokinetics data to support their recommendation. For none of the medications reviewed is the recommendation on the use of the drug consistent among all the information sources. In no case do the SPCs give adequate reasons, based on clinical studies or on pharmacokinetics, for the discontinuation of breastfeeding, whereas the SS do so. In some cases, such as for captopril, enalapril, nifedipine, verapamil, and propranolol, discrepancies in recommendations may vary from “recommended” to “nonrecommended” drug. Some PLs and SPCs provide contradictory information in different sections of the same document. This kind of generic and sometimes contradictory indication may be confusing and lead to a presumption of risk when there is no scientific evidence for it. Finally, the language of some PLs and SPCs is inadequate, as instead of the expression “medication not recommended during breastfeeding” they sometimes state “breastfeeding not recommended.” Breastfeeding is the biological norm, and breastmilk is the feeding option providing the optimal health outcomes for infants, so the scientific language should be coherent with this principle.²⁴

In general, information on breastfeeding management strategies is not provided (except in one case [atenolol, EU documentation]). One of the key points that should be included is information for mothers about the possibility of using alternative and safer drugs, or, when alternatives are not available, of the option of timing the breastfeeding so as to avoid the peak plasma concentration of the drug. When suspension is necessary, the mother should be informed about the possibility of maintaining milk production by pumping during the interruption or to relactate after the treatment. Discontinuation of breastfeeding should be suggested only if no safe alternative drug exists.

One last consideration is that, as for any pharmacological treatment in adults or in children, the mother and the breastfed infant should be monitored, and any suspected adverse drug reactions should be reported to the pharmacovigilance system.

One limitation of this study is that it was conducted on only some of the antihypertensive medications available. Further studies are needed to assess whether the heterogeneity of the contents and recommendations also affects other drugs or not.

Conclusions

The inconsistency noted between different sources of information and the presence in the PLs and SPCs of indications that discourage breastfeeding, although not supported

by scientific evidence, reinforce the already widespread view among women and healthcare professionals that it is necessary to discontinue breastfeeding in case of maternal pharmacotherapy. This situation can lead to improper interruption of breastfeeding. Health professionals and mothers should be supported by official, accurate, comprehensive information about medications, breastfeeding management, and pharmacovigilance to aid their decision-making process.

Disclosure Statement

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