Management of Hypertension During Lactation

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SUMMARY There has been a dramatic increase in the number of women breast-feeding during the last decade. Since little is known about the excretion of antihypertensive drugs into human breast milk, the management of hypertension during lactation can be problematical. To enable the clinician to better advise the hypertensive, lactating mother, the published literature on the excretion of antihypertensive agents into human milk has been reviewed and is presented in this report.
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KEY WORDS hypertension lactation antihypertensives human breast milk

RECENT reports from surveys during the 1970s suggest a substantial increase in the incidence of breast-feeding in the United States and Canada. By the late 1970s, more than half of American mothers were breast-feeding at the time of discharge from the hospital, and the majority of them continued until their infants were 4 months old. The increasing number of women delaying pregnancy until their fourth decade may be associated with an increase in the number of women with chronic hypertension (exclusive of pregnancy-induced hypertension or pre-eclampsia) requiring management throughout pregnancy and during the period of lactation. While little is known about the effects of most antihypertensive agents on the developing fetus, even less information has been reported on the consequences of breast-feeding an infant while the mother takes antihypertensive drugs.

Most medical problems in the pregnant patient are followed by the obstetrician, but the management of hypertension postpartum is often referred to the internist who has less general knowledge about lactation and less exposure to breast-feeding patients. It becomes difficult to advise the mother to nurse her infant while taking an antihypertensive agent because of the lack of data on excretion of the various agents into human breast milk. This review updates the information of antihypertensive drug excretion into human milk and hopefully will be a useful guide to the clinician treating hypertensive, lactating mothers.

No long-term, controlled trials investigating the effects of any antihypertensive drugs on breast-feeding infants have been reported. Most information published on the various agents has been in the form of case reports or based on studies in small groups of lactating women. In addition, few studies have been undertaken with the pharmacokinetic behavior of the drug in mind, so that random milk levels without regard to the drug's elimination time or peak in plasma levels often are the only available data. Finally, the recent use of high performance liquid chromatography (HPLC) and electrochemical detection has greatly improved the sensitivity in chemical analysis of body fluids, so that earlier studies that have reported "undetectable" levels of a drug in milk may be incorrect.

General Factors Affecting Drug Excretion into Breast Milk

The unionized portion of a drug passes from plasma to milk through a semipermeable lipid membrane so that an equilibrium is established between the portion in the aqueous phase of milk (milk ultrafiltrate) and plasma at a given plasma concentration of the drug. Excluded from the milk ultrafiltrate are the portions of the drug bound to plasma or milk proteins, whereas lipid-soluble agents dissolve in milk fat.

The extent and affinity of drug binding to plasma and milk proteins are a determinant of drug concentration in whole milk. Highly plasma protein-bound drugs generally do not pass readily into milk and are associated with a milk to plasma (M/P) concentration ratio of less than 1. Lipid-soluble drugs can partition into milk fat and achieve a higher concentration in milk than in plasma, yet this oil/water partition coefficient appears to have a limited effect on the total drug concentration in milk.

Ionization of a drug may play a significant role in the drug's transfer from plasma to milk. Since the pH of human milk (approximately 7.0) is less than that of plasma (7.40), the concentration that a drug attains in milk is dependent on its pKa value. Wilson and colleagues have published the formulas below to estimate the ratio of total drug in an ultrafiltrate of milk compared with plasma (M/P ratio) based on rearrangements of the Henderson-Hasselbach equation:

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Acidic drug M/P ratio = \( \frac{1 + 10^{(\text{pH}_m - \text{pK}_a)}}{1 + 10^{(\text{pH}_b - \text{pK}_a)}} \)  

Basic drug M/P ratio = \( \frac{1 + 10^{(\text{pK}_a - \text{pH}_m)}}{1 + 10^{(\text{pK}_a - \text{pH}_b)}} \)

where \( \text{pH}_m = \) pH of milk; \( \text{pH}_b = \) pH of blood; and \( \text{pK}_a = \) drug pK\(_a\). In general, the ultrafiltrate M/P concentration ratio for weak acids is less than 1 and for weak bases is greater than 1.

The rate of passage of drugs into milk is a dynamic, reversible process determined largely by the physiochemical properties of the drug and mammary blood flow. Lipid-soluble drugs pass more rapidly into milk than do more water-soluble drugs. Agents existing primarily in the ionized form at a physiological pH diffuse more slowly into milk. It is not unusual for the peak concentration in milk to lag behind the peak concentration in plasma because of slow transfer into milk and for levels in milk to persist longer than in plasma because of slow back-diffusion into plasma.

An estimate of drug intake in an infant can be made if levels in the breast milk and maternal dose are known. Certain factors such as immature neonatal excretory mechanisms, maternal drug absorption, and variations in breast milk pH may alter the estimated levels. Newborn infants take in an average of 165 ml/kg/day of milk. Therefore, the formula used to calculate the estimated maximal dose to the infant is: peak concentration in milk (ng/ml or \( \mu g/ml \)) × 165 ml/kg/day = the daily dose (ng or \( \mu g/kg/day \)). As is noted throughout the remainder of this review, infant plasma specimens have rarely been measured in studies evaluating antihypertensive drug excretion in human milk.

Antihypertensive Drugs in Lactation

The specific concentrations of the various agents in breast milk are summarized in Table 1.

Diuretics

Thiazide diuretics have been reported to decrease the production of milk and have even been used to suppress lactation. After single-dose kinetic studies, chlorothiazide and hydrochlorothiazide were found to be excreted in minimal levels in breast milk, and in the latter study, the level of hydrochlorothiazide was undetectable in the breast-fed infant. Chlorothalidone also demonstrated a very low M/P concentration ratio. Canrenone, a weak, active metabolite of spironolactone, was excreted in low amounts into maternal milk, and it is doubtful that significant amounts were ingested. No data have been reported on the excretion of furosemide into breast milk, but it is likely that a reduction in milk production would occur with this potent diuretic.

Beta-Adrenergic Blocking Agents

The \( \beta \)-blocking drugs are weak bases as a group, with an average pK\(_a\) of 9.2 to 9.5. Human breast milk has an acidic pH relative to plasma. Therefore, these agents are often “trapped” in milk as a result of ionization. The M/P concentration ratio is over 3 for atenolol, metoprolol, metoprolol, and nadolol, yet accumulated amounts of atenolol and metoprolol have not amounted to enough to cause adverse effects or detectable transfer in the breast-fed infant. Mepindolol, a potent analog of pindolol, has been reported as having an M/P ratio of 0.6 after a single 20 mg dose. Numerous investigators have studied the excretion of various doses of propranolol in human breast milk (see Table 1). These reports demonstrated that the M/P concentration ratio of propranolol was less than 1, that the excretion was dose-dependent, and that no adverse effects have been observed in the infants studied. No studies reporting the excretion of timolol or pindolol into human breast milk have been located.

Central and Peripheral Alpha-Adrenergic Agents

Although methyldopa has been widely used to treat the hypertension of pregnancy, no follow-up studies examining the excretion of this agent into human breast milk have been reported. Preliminary studies by Jones and Cummings showed low, random levels of free methyldopa in the milk at time of delivery in four mothers. In a single mother-infant study, methyldopa was excreted in the milk in amounts high enough to obtain measurable, low plasma levels in the breast-fed infant (White WB, unpublished data).

It has been reported that clonidine is excreted in very small amounts into milk, with a M/P concentration ratio of 1.5. No reports regarding the use of prazosin or guanabenz during lactation have been published.

Miscellaneous Agents

Hydralazine is commonly used during severe elevations of blood pressure during the last trimester and during labor, but it is rarely continued postpartum. One report has been published demonstrating a calculated dose of 0.013 mg of hydralazine per feeding when the maternal dose was 150 mg per day in three divided doses.

Reserpine, a less commonly used antihypertensive agent, has been reported to appear in breast milk, with a possible adverse effect in the breast-fed infant of nasal congestion and increased respiratory secretions. Guanethidine and guanadrel are not used in the management of hypertension in pregnancy and would not generally have a place in a postpartum antihypertensive regimen. In a review by Tayki, guanethidine was reported to be excreted in human milk in minute quantities.

A thorough investigation of captopril in human plasma and breast milk demonstrated delayed excretion of captopril in the milk, with levels in the range of 0.6% of maternal plasma levels. This study suggested selective restriction of the passage of captopril from blood into milk and "safe" levels for breast-feeding even with a relatively large daily dosage (300 mg per day).
Conclusions and Recommendations

Scientific support for breast-feeding has emerged from a variety of disciplines because breast milk is known to possess nutritional and immunologic properties superior to those found in infant formulas. Women of child-bearing age with chronic diseases including hypertension may wish to breast-feed their infants despite the need for antihypertensive drug therapy during lactation. Both the physician and the breast-feeding mother have to weigh the risk/benefit ratio when maternal medication is prescribed. Based on the data reported in this review, there are differences between the various antihypertensive agents in their ability to pass into breast milk. Since most antihypertensive agents are excreted via human breast milk, the obvious general recommendation would be to prescribe those agents found in minimal concentrations in the milk. Then at the time the mother discontinues breast-feeding, a change could be made to another agent that is more effective and perhaps better tolerated.

Use of diuretics as an antihypertensive therapy should probably be avoided during lactation. Although excessive amounts have not been reported in breast milk, a substantial decrease in milk volume may occur. Except for propranolol all the β-blocking agents are found in larger concentrations in milk than in maternal plasma. It would, therefore, probably be most appropriate to use propranolol if a β-blocking agent was indicated. However, in the accumulated experience with 37 patients on the other β-blocking agents superior to those found in infant formulas. An extensive review of the available information on the excretion of antihypertensive agents into human breast milk is presented, which may be of considerable value to the physicians and patients who are considering the use of these agents during lactation.

### Table 1. Excretion of Antihypertensive Drugs into Human Breast Milk

<table>
<thead>
<tr>
<th>Drug (ref)</th>
<th>No. of patients</th>
<th>Dose</th>
<th>Concentrations, peak</th>
<th>M/P ratio</th>
<th>Effect on infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serum or plasma</td>
<td>Milk</td>
<td></td>
</tr>
<tr>
<td>Alpha-Methyldopa (26, UD)*</td>
<td>3</td>
<td>500 mg</td>
<td>4.3 µg/ml</td>
<td>1.14 µg/ml</td>
<td>0.26</td>
</tr>
<tr>
<td>Atenolol (14, 15)</td>
<td>8</td>
<td>50 mg</td>
<td>0.36 µg/ml</td>
<td>1 µg/ml</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg</td>
<td>0.62 µg/ml</td>
<td>1.8 µg/ml</td>
<td>2.9</td>
</tr>
<tr>
<td>Captopril (31)</td>
<td>11</td>
<td>100 mg t.i.d.</td>
<td>713 ng/ml</td>
<td>4.7 ng/ml</td>
<td>0.01</td>
</tr>
<tr>
<td>Clonidine (27)</td>
<td>?</td>
<td>0.15 mg</td>
<td>1.0 ng/ml</td>
<td>1.5 ng/ml</td>
<td>1.5</td>
</tr>
<tr>
<td>Guanethidine (29)</td>
<td>1</td>
<td>no levels reported</td>
<td>no levels reported</td>
<td>no levels reported</td>
<td>0.49</td>
</tr>
<tr>
<td>Hydralazine (28)</td>
<td>1</td>
<td>50 mg t.i.d.</td>
<td>1.53 µg/ml</td>
<td>0.76 µg/ml</td>
<td>0.49</td>
</tr>
<tr>
<td>Mepindolol (18)</td>
<td>5</td>
<td>20 mg</td>
<td>54 ng/ml</td>
<td>33 ng/ml</td>
<td>0.61</td>
</tr>
<tr>
<td>Metoprolol (15, 16)</td>
<td>12</td>
<td>100 mg</td>
<td>0.43 µg/ml</td>
<td>1.56 µg/ml</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
<td>0.36 µg/ml</td>
<td>1.69 µg/ml</td>
<td>3.0</td>
</tr>
<tr>
<td>Nadolol (17)</td>
<td>12</td>
<td>80 mg</td>
<td>77 ng/ml</td>
<td>357 ng/ml</td>
<td>4.6</td>
</tr>
<tr>
<td>Propranolol (19-24)</td>
<td>9</td>
<td>20 mg b.i.d.</td>
<td>17 ng/ml</td>
<td>4 ng/ml</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg t.i.d.</td>
<td>38 ng/ml</td>
<td>2 mg/ml</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg once</td>
<td>60 ng/ml</td>
<td>10 ng/ml</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 mg once</td>
<td>75 ng/ml</td>
<td>60 ng/ml</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>160 mg once</td>
<td>210 ng/ml</td>
<td>160 ng/ml</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg q.i.d.</td>
<td>65 ng/ml</td>
<td>42 ng/ml</td>
<td>0.64</td>
</tr>
<tr>
<td>Reserpin (29)</td>
<td>1</td>
<td>no levels reported</td>
<td>no levels reported</td>
<td>no infants studied</td>
<td></td>
</tr>
<tr>
<td>Spironolactone (canrenone) (13)</td>
<td>1</td>
<td>25 mg q.i.d.</td>
<td>144 ng/ml</td>
<td>104 ng/ml</td>
<td>0.72</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone (12)</td>
<td>7</td>
<td>50 mg</td>
<td>6.48 µg/ml</td>
<td>0.36 µg/ml</td>
<td>0.05</td>
</tr>
<tr>
<td>Hydrochlorothiazide (11)</td>
<td>1</td>
<td>50 mg</td>
<td>280 ng/ml</td>
<td>120 ng/ml</td>
<td>0.43</td>
</tr>
<tr>
<td>Chlorothiazide (10)</td>
<td>2</td>
<td>500 mg</td>
<td>&lt; 1 µg/ml</td>
<td>&lt; 1 µg/ml</td>
<td>—</td>
</tr>
</tbody>
</table>

*UD = unpublished data; White WB, Andreoli JW, Cohn RD.

Abbreviations: M/P = milk-to-plasma concentration ratio; b.i.d. = twice daily, t.i.d. = three times/day; q.i.d. = four times/day.
drugs,\(^{14-18}\) no adverse effects of any nature on the suckling infant have been reported, and standard maternal doses yielded very low β-blocker concentrations in the milk. Other sympathetic inhibitors and vasodilators may be safe for use during lactation, but the data are so sparse that general recommendations regarding these antihypertensive agents are not possible at this time. Finally, in lactating patients with severe or accelerated hypertension, captopril seems to be an agent that may be safely administered in the usual therapeutic doses.

**Addendum**

Since the submission of this manuscript, Fidler and colleagues\(^ {22}\) have reported on the excretion of oxprenolol and timolol in breast milk. Single breast milk and plasma samples were collected approximately 2 hours after a fasting dose and showed the following: the average excretion of timolol (15 mg/day) into breast milk was 15.9 ± 16 ng/ml with an M/P ratio of 0.8 ± 0.21. The average excretion of oxprenolol (160 mg/day) into breast milk was 128 ± 118 ng/ml with an M/P ratio of 0.29 ± 0.14. The calculated dose of timolol that a 3 kg infant might receive was 0.0024 mg/kg/day, and the dose estimated for oxprenolol was 0.019 mg/kg/day.

**References**

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