St. John's Wort (*Hypericum perforatum*) and Breastfeeding: Plasma and Breast Milk Concentrations of Hyperforin for 5 Mothers and 2 Infants

Claudia M. Klier, M.D.; Brigitte Schmid-Siegel, M.D., M.D.; Miriam R. Schäfer, M.D.; Gerhard Lenz, M.D.; Alois Saria, Ph.D.; Amy Lee, M.Sc.; and Gerald Zernig, M.D.

Background: Herbal preparations for depression, such as St. John's wort, are often preferred over pharmaceutical preparations by mothers and midwives after childbirth because these preparations are available to patients as over-the-counter "natural" treatments and are popularly assumed to be safe. The only existing report on St. John's wort excretion into human milk showed that only 1 active component (hyperforin) was detectable in breast milk, but was not detectable in the infants' plasma. Another report found more cases of minor problems in infants breast-fed by women taking St. John's wort. However, significance was reached only in comparison with disease-matched women ($p < .01$), not healthy controls ($p = .20$).

Method: Five mothers who were taking 300 mg of St. John's wort 3 times daily (LI 160 [Jarsin], Lichtwer Pharma GmbH; Berlin, Germany) and their breastfed infants were assessed. Thirty-six breast milk samples (foremilk and hindmilk collected during an 18-hour period) and 5 mothers' and 2 infants' plasma samples were analyzed for hyperforin levels by tandem mass spectrometry (LC/MS/MS; limit of quantification = 0.1 ng/mL). Data were gathered from January 2001 to February 2002.

Results: Hyperforin is excreted into breast milk at low levels. However, the compound was at the limit of quantification in the 2 infants' plasma samples (0.1 ng/mL). Milk/plasma ratios ranged from 0.04 to 0.13. The relative infant doses of 0.9% to 2.5% indicate that infant exposure to hyperforin through milk is comparable to levels reported in most studies assessing antidepressants or neuroleptics. No side effects were seen in the mothers or infants.

Conclusion: These results add to the evidence of the relative safety of St. John's wort while breast-feeding found in previous observational studies.

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Received April 13, 2005; accepted Aug. 15, 2005. *From the Departments of Child and Adolescent Neuropsychiatry (Drs. Klier and Schäfer) and Psychiatry (Drs. Schmid-Siegel and Lenz), Medical University Vienna, Vienna, Austria; the Division of Neurochemistry, Department of Psychiatry, Medical University Innsbruck, Innsbruck, Austria (Drs. Saria and Zernig); and the Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada (Ms. Lee).*

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Corresponding author and reprints: Claudia M. Klier, M.D., Department of Child and Adolescent Neuropsychiatry, Medical University Vienna, A-1090 Wien, Währinger Gürtel 18-20, AUSTRIA (e-mail: claudia.klier@meduniwien.ac.at).

St. John's wort (*Hypericum perforatum*), a perennial herb indigenous to Europe, Asia, and Africa, has been used as a medicinal plant for centuries. Although the plant contains at least 10 classes of biologically active compounds, only 2, i.e., hypericin and hyperforin, and their metabolites pseudohypericin and adhyperforin, seem to be the most important for their neuropharmacologic properties. Recent studies have provided cumulative evidence to suggest that hyperforin may be the key constituent responsible for the antidepressant property of St. John's wort.[1] This compound may have a similar mechanism of action as the conventional tricyclic antidepressants and selective serotonin reuptake inhibitors.[1]

With respect to toxicology, there are few adverse drug reactions associated with St. John's wort use, with an overall incidence of 2.4%.[2] A rare adverse drug reaction associated with St. John's wort use at high doses is photosensitization, including dermal erythema, rash, and pruritus. Two potential cases of induced mania have been reported in bipolar patients taking 900 mg of St. John's wort extract daily.[3] Interaction of St. John's wort with antidepressants can cause serotonin syndrome, and 5 such cases are published.[4] In addition, there are concerns regarding

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numerous potential herb-drug interactions due to the ability of St. John's wort to induce the metabolic activity of cytochrome P450 (CYP). Drugs most prominently affected and contraindicated for concomitant use with St. John's wort are metabolized via both CYP3A4 and P-glycoprotein pathways; they include human immunodeficiency virus (HIV) protease inhibitors, HIV nonnucleoside reverse transcriptase inhibitors (only CYP3A4), the immunosuppressants cyclosporine and tacrolimus, and the antineoplastic agents irinotecan and imatinib mesylate.[5] Providing that certain precautions and contraindications are followed, the safe and effective use of quality-tested St. John's wort products can be ensured.[5]

Twenty percent to 30% of the general North American population are estimated to use alternative/complementary medicine.[6] The use of at least 1 of 16 alternative therapies during the previous year increased from 33.8% in 1990 to 42.1% in 1997 ($p \leq .001$) in the United States.[7] A survey of 242 Canadian physicians, naturopaths, and medical students found that 49% of naturopaths would recommend St. John's wort to pregnant women.[8] However, only 1 physician out of 60 would recommend the herb. Physicians seem to be more aware of the potential risk of herbal preparations.[8] Another study found that herbal preparations seem to be very popular with midwives: in North Carolina, 73% of midwives recommend herbal therapies for pregnant women.[9] Most women use herbs by self-medication due to the perception that because herbal preparations are from a natural source, they are considered to be safe, despite a lack of reproductive safety data. The growing interest in alternative medicine has created the need for accurate information that is accessible to all health care providers.

A prospective, observational cohort study with 33 breastfeeding women receiving St. John's wort and their infants (group 1) was conducted.[10] These women were compared with 101 disease-matched women (group 2) and 33 age- and parity-matched healthy control women (group 3). No statistically significant differences were found in maternal adverse events. However, whereas only colic was reported in 1 infant each in groups 2 and 3, there were 2 cases of colic, 2 of drowsiness, and 1 of lethargy in group 1 ($p < .01$; group 1 vs. group 2, $p < .01$; group 1 vs. group 3, $p = .20$). The symptoms were not severe, and specific medical treatment was not required. No significant difference was observed in the frequency of maternal report of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life.

The only published report describing pharmacokinetic data for St. John's wort use while breast-feeding showed that only hyperforin, not hypericin, is excreted into breast milk, at detectable, although very low, levels. Hyperforin was below the lower limit of quantification in the infant's plasma, and no side effects were observed in the mother or infant.[11] The milk/plasma ratio of hyperforin was very low (milk/plasma ratio = 0.02), indicating no accumulation in the breast milk. These results allow the focus to be on hyperforin excretion in the current study.

The current study adds to the growing body of information on the safety of St. John's wort during breastfeeding. The goal of the study was to measure levels of hyperforin in maternal and infant plasma and maternal breast milk and to calculate milk/plasma ratios and the estimated infant daily dose. The benefit of this study is to further challenge the safety of a widely used over-the-counter drug by breastfeeding women without being under supervision of health professionals.

METHOD

Subjects

After giving informed consent, 5 somatically healthy patients were enrolled in this study, which was approved by the Ethics Committee at Vienna University (Vienna, Austria). Two mothers also consented to have their infants evaluated for plasma hyperforin levels and complete laboratory analyses. The patients were recruited from the outpatient psychiatry department of the university clinic (Medical University Vienna). Their diagnoses were major depressive episode according to DSM-IV criteria ($N = 4$; 1 of these patients had comorbid obsessive-compulsive disorder) and panic disorder ($N = 1$). All subjects had been taking St. John's wort for at least 4 weeks before entering the study. All women were taking the same preparation of St. John's wort (LI 160 [Jarsin], Lichtwer Pharma GmbH; Berlin, Germany), 300 mg 3 times a day. The average hyperforin content in this preparation is 7.48 mg (2.49% on a weight basis).[12] No formal assessment of severity of the mothers' illness or of the development of the infants was made. Mothers were asked at intake if the behavior of their infants had changed since the beginning of treatment with St. John's wort. Data were gathered from January 2001 to February 2002.

Sampling Procedures

The milk samples were obtained by the mothers during an 18-hour period. Mothers took samples before and after breastfeeding to allow for foremilk and hindmilk concentration measurements. Milk was collected by manual expression and stored by the mothers at home at –20°C. The samples were transported to the clinic in a cooler the next day when the mothers came in for assessment.

Maternal and infant blood was drawn only once, approximately 5 hours postdose, when plasma hyperforin levels of the infants were supposed to be highest. The timing of the plasma level determinations was chosen according to existing data regarding the oral bioavailability

Table 1. Milk and Plasma Concentrations, Milk/Plasma Concentration Ratio, and Estimated Infant Dose in Samples From 5 Lactating Women Treated With St. John's Wort[a]

Patient	Time Postpartum, wk	Hyperforin Concentration, ng/mL, Mean (range)[b]		Maternal Plasma Hyperforin Concentration, ng/mL	Milk/Plasma Concentration Ratio	Infant Plasma Hyperforin Concentration, ng/mL	Relative Dose of Hyperforin Received by the Infant, %[c]
		Foremilk	Hindmilk				
1	22	3.4 (1.0–11.7)	7.3 (5.3–8.1)	60.2	0.09	0.1	2.5
2	10	3.3 (1.3–6.0)	2.0 (0.2–5.6)	65.2	0.04	0.1	1.1
3	13	3.3 (0.3–10.1)	1.6 (0–31.5)	32.2	0.08	NA	0.9
4	15	5.6 (0.6–8.6)	2.4 (0.6–4.1)	34.8	0.11	NA	1.6
5	12	2.1 (0.1–5.1)	4.0 (2.6–10.3)	22.8	0.13	NA	1.3

[a]All women were taking a St. John's wort dose of 900 mg/day, and all were exclusively breast-feeding their infants.
[b]Calculated using the area under the curve.
[c]Infant hyperforin dose per kg body weight expressed as a percentage of the maternal hyperforin dose per kg body weight.
Abbreviation: NA = not available.

of hyperforin. Steady state is reached after 4 days, peak level of hyperforin is reached at 3.5 hours, and half-life and elimination time are 9 and 12 hours, respectively.[13] Blood was collected at the outpatient department of the adult psychiatry department and the pediatric outpatient department and centrifuged within 30 minutes. Milk and plasma were frozen at –20°C until analysis.

Analytic Procedures

Plasma levels of hyperforin were quantified by tandem mass spectrometry[14] on a Micromass Quattro Ultima (Waters Corporation; Milford, Mass.; www.waters.com) using the mass transitions 537.0 > 276.8 for hyperforin. Hypericin did not yield a useful signal under the conditions employed in the present study. Plasma or breast milk was extracted by acetonitrile precipitation (190 μL plasma or breast milk, 10 μL internal standard chlorpromazine [1 μg/mL], 50 μL 500 mM zinc sulfate, and 500 μL –20°C cold acetonitrile). Ten μL of extract was directly injected into the LC/MS/MS instrumentation. Chromatographic separation of the analytes was performed on a reverse-phase C18 column (Symmetry 300, 5 μm, 2.1 × 150 mm; Waters Corporation; Milford, Mass.; www.waters.com) with a mobile phase of 50% acetonitrile, 50% water, 1.5 mM ammonium acetate, and 0.1% formic acid at a flow rate of 0.35 mL/minute. The standard curve (internal standard, 50 ng/mL d3-methadone) was essentially linear up to 25 ng/mL for breast milk and 50 to 100 ng/mL for plasma, with breast milk lowering the signal by a factor of 2 in comparison to plasma. The r values of the standard curves were 0.99 (0–100 ng/mL) and 0.996 (0–50 ng/mL) for plasma and 0.9992 for breast milk. The limit of detection was 0.05 ng/mL, and the limit of quantification was 0.1 ng/mL. Signal-to-noise ratios at 1 ng/mL were approximately 45:1. Interday imprecision (i.e., standard deviation as percentage of mean) was 16%.

Average foremilk and hindmilk concentrations were calculated using the area under the curve of the time-concentration curve for each woman. The concentration used to calculate the relative dose received by each infant was calculated using the mean of the infant hyperforin dose per kg body weight [(mg/mL of hyperforin in milk × 150 mL/kg infant × kg infant)/kg infant] and is expressed as a percentage of the maternal hyperforin dose per kg body weight (mother = 22.44 mg hyperforin/kg mother).

RESULTS

The women who participated in this study were white; their ages ranged from 26 to 35 years. Their infants were 3 boys and 2 girls whose ages ranged from 10 to 22 weeks. None of the women had taken St. John's wort during pregnancy, and none had taken any other drug during breastfeeding.

A total of 36 milk and 7 plasma samples were analyzed. Breast milk concentrations of hyperforin ranged from 0.1 to 31.5 ng/mL in individual samples, with mean foremilk and hindmilk samples for individual patients ranging from 2.1 to 5.6 ng/mL and 1.6 to 7.3 ng/mL, respectively (Table 1). Maternal plasma hyperforin concentrations ranged from 22.8 to 65.2 ng/mL. The 2 infants' plasma levels were at the limit of quantification (0.1 ng/mL). The percentages of the infant plasma level in relation to the maternal plasma level were 0.17% and 0.15%. Variance of the analytic method was tested with drug-free infant plasma and drug-free breast milk spiked with 100 ng/mL of hyperforin each. Interday imprecision (i.e., coefficient of variation expressed as percentage of mean) was 15% for infant blood plasma (N = 3) and 5% for breast milk (N = 5).

The milk/plasma ratios of hyperforin were in the range 0.04 to 0.13. The relative mean dose received by the infant per kg in percent of the maternal dose ranged from 0.9% to 2.5%. The mothers observed no adverse effects or unusual behavior in the infants, and the infants thrived normally during maternal St. John's wort treatment. Specifically, the mothers were inquired regarding gastrointestinal symptoms, lethargy, rashes, photosensitivity, and changes in sleep pattern.

DISCUSSION

The relative infant doses of between 0.9% and 2.5% indicate that infant exposure to hyperforin through milk is comparable to the 1% to 10% reported in most studies assessing antidepressants or neuroleptics.[15–19]

This low infant exposure was confirmed by the lowest detectable plasma hyperforin level of the 2 infants (0.1 ng/mL) assessed. In the first reported case,[11] the infant had levels below 2 ng/mL. It is notable that only 1 out of 48 studies assessing plasma levels of various drugs in mothers and/or infants had a limit of quantification below 1 ng/mL,[20] 8 studies did not report on limit of quantification, and the mean of the limit of quantification in the remaining 45 studies is 8 ng/mL, ranging from 1 to 50 ng/mL.[19] Therefore, although infant levels were very low in this sample, they could be detected due to the analytic method employed, i.e., tandem mass spectrometry.

There is discussion about the usefulness of obtaining infant serum drug concentration,[21] as there are methods of calculating infant exposure from maternal plasma and milk levels. Infant serum concentrations alone provide little information about metabolic capacity, and, with more data, medication exposure could be estimated without the need to perform an infant blood draw.[22] Other researchers argue against relying on breast milk samples alone to estimate the extent of exposure to the infant. The infant's ability to metabolize the drug can be a much stronger determinant of plasma levels than the amount of drug ingested through breast milk.[19] For some mothers, it might be reassuring to have their infant's plasma levels checked if they observe changed behavior in the infant. This can now be performed within 1 day for any psychotropic agent on the market by the technique of tandem mass spectrometry and can inform the treating doctor about possible accumulation of a drug in case of behavior change.

Our study was limited by a small sample size because it is difficult to recruit patients who self-medicate with herbal remedies, as they usually avoid psychiatric care. In addition, only 2 mothers consented to have infant serum levels assessed. Another limitation is that only hyperforin, and not any of the other active constituents of St. John's wort, was measured. Moreover, it must be taken into account that LI 160 is only one of several St. John's wort products marketed, and it has excellent toxicology and tolerability data.[23] Furthermore, we need long-term studies on neurodevelopment in infants whose mothers were taking medication while breast-feeding. All infants in our study were full-term older infants (10–22 weeks), and the findings may not apply to younger or premature infants.

Based on the low levels of hyperforin excreted into the breast milk and the lack of adverse events, these data suggest that St. John's wort may be considered relatively safe in lactating women who are breast-feeding healthy term infants, as has been shown in a previous prospective, observational study.[10] Nevertheless, the same risk/benefit assessment should be applied for "natural" over-the-counter drugs as for any synthetic drug. Infants' ability to metabolize substances is very low at birth but increases during the first few weeks. St. John's wort is metabolized by the liver, and the 2 infants' plasma levels in this study and the one in the previous study indicate that dose-related adverse drug reactions are unlikely to affect the infant. On the other hand, adverse drug reactions may occur idiosyncratically, as with any conventional drug, and it remains difficult to quantify the risk of such reactions.

Because of the possibility of rare adverse events with any drug, mothers who are breast-feeding while taking St. John's wort should be alert to changes in infant behavior and should be closely supervised by a pediatrician. If the mother is taking other medications, she should be informed that drug-herb interactions are possible.

The importance of this study stems from the fact that many women take St. John's wort and assume it is safe because it is natural. The reason for the popularity of herbal preparations and self-medication may be the stigma associated with being diagnosed with depression and being prescribed an antidepressant. The results of this study provide reassurance that with some precautions the St. John's wort extract LI 160 is safe during breastfeeding.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), cyclosporine (Gengraf, Neoral, and others), imatinib (Gleevec), irinotecan (Camptosar), tacrolimus (Prograf and Protopic).

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