

# No Camphor Toxicity in Cambodian Infants

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## Abstract

Thiamine deficiency and beriberi are prevalent in Cambodia, although most infants with nonspecific clinical symptoms of beriberi, including tachypnea, lack echocardiographic evidence diagnostic of the disease. Camphor activates transient receptor potential vanilloid 3 (TRPV3), a nonselective ion channel expressed in the medial preoptic nucleus of the hypothalamus and thought to be important for thermo-sensitivity. Because camphorated ointments are used commonly among Cambodian infants, we hypothesized that topical camphor modulates thermoregulatory behaviors, causing beriberi-simulating tachypnea, separate from any influence of thiamine deficiency. We assessed 9 tachypneic and 10 healthy infants for Tiger Balm use and for presence of camphor in whole blood. However, no camphor was found in blood from any infants, indicating that camphor is unrelated to tachypneic illness in Cambodian infants.

## Keywords

beriberi, thiamine deficiency, camphor, child nutrition disorders, poisoning

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## Introduction

Thiamine deficiency is common in parts of Southeast Asia. In some settings, as few as 1 in 30 breastfeeding mothers consumes the recommended daily allowance of thiamine.<sup>1</sup> This is unsurprising, as the per capita daily thiamine available in the Cambodian food supply is estimated to provide only half of the recommended daily allowance for breastfeeding women.<sup>2</sup> Postpartum traditions in parts of Southeast Asia, including consumption of glutinous white rice, dietary intake restriction, betel nut chewing, and consumption of thiaminase-containing food products such as fermented fish paste, also exacerbate low thiamine status in mother-infant pairs.<sup>1,3</sup> Unlike many micronutrients, the thiamine content of breast milk is negatively affected by maternal depletion,<sup>4,5</sup> placing infants at a greater risk for deficiency. Suboptimal levels of this essential micronutrient result in infantile beriberi, a disease characterized by respiratory distress and heart failure.<sup>6</sup> Infantile beriberi was responsible for 40% of infant deaths during early settlement of the Maela refugee camp on the Thai-Burmese border.<sup>6</sup> Heart failure associated with infantile beriberi is still thought to account for death in up to 3% of Cambodian children before age five.<sup>7</sup>

While thiamine deficiency is widely prevalent, fulminant infantile beriberi is far less common. In a study of cardiac function among thiamine-deficient Cambodian children, abnormal echocardiograms were observed only in sick children with exceptionally low thiamine levels.<sup>8</sup> Moreover, children with signs and symptoms of beriberi (eg, tachypnea, tachycardia, vomiting, lethargy, and hepatomegaly) exhibited moderately low thiamine concentrations comparable to those of healthy Cambodian controls.<sup>9</sup> Accurately distinguishing children with true infantile beriberi from those children with other illnesses is difficult.<sup>10</sup>

What causes illness in children who have signs of beriberi and moderate thiamine deficiency without any

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evidence of cardiac dysfunction? Previous work done by Porter et al<sup>8</sup> and Keating et al<sup>10</sup> revealed a positive correlation between respiratory rate and the extent to which Tiger Balm was applied to infants (unpublished observations;  $r = .41$ ,  $P < .01$ ). Tiger Balm is a petroleum-based ointment that Cambodian mothers commonly apply to infants with pain or colic. There are various formulations of Tiger Balm used among Southeast Asian populations, but camphor is one of the main active ingredients across all brands.<sup>11</sup> Camphor activates transient receptor potential vanilloid (TRPV) and transient receptor potential ankyrin (TRPA) channels, super families of nonselective ion channels that are involved in sensory transduction.<sup>12</sup> Specifically, TRPV3 channel proteins are important for thermo-transduction.<sup>13</sup> TRPV channels are expressed in the medial preoptic nucleus of the hypothalamus and may be important for hypothalamic thermo-sensitivity.<sup>14</sup>

Thus, we hypothesized that camphor from Tiger Balm could alter temperature regulation proteins in nuclei of the hypothalamus and stimulate tachypnea as an alternative temperature-regulating behavior, separate from any influence of thiamine deficiency. Therefore, the objective of this secondary analysis investigation was to quantify concentrations of camphor in blood of tachypneic infants and healthy controls in order to determine if symptoms in thiamine-deficient infants without echocardiographic abnormalities could possibly be associated with camphor toxicity from Tiger Balm.

## Methods

In the original study,<sup>8</sup> infants aged 2 weeks to 12 months participated in an observational, case-control study at the Svay Chrum Health Clinic in the Mesang District of Prey Veng Province, Cambodia. We enrolled 20 sick infants meeting clinical criteria for beriberi diagnosis<sup>7,9,10,15,16</sup> and 42 healthy control infants from the surrounding village between July 10, 2012, and August 3, 2012. All mothers gave informed consent for their infants' participation in the study, and a survey was given to mothers of all enrolled infants assessing dietary and environmental exposures, including Tiger Balm use, as described previously.<sup>9</sup>

In the present study, we assayed residual frozen whole-blood samples from 9 tachypneic infants meeting clinical criteria for beriberi<sup>8</sup> and 10 healthy control infants, all without either an abnormal echocardiogram or a profoundly low (<30 nmol/L) whole blood thiamine diphosphate (TDP) concentration. Median whole blood TDP concentrations were 61.3 nmol/L (range = 41.3-114.0 nmol/L) in tachypneic infants and 46.6 nmol/L (range = 38.0-59.4 nmol/L) in healthy control infants ( $P = .08$ ; Table 2).

Camphor analysis of whole blood samples was performed using an established laboratory method (NMS Labs, Willow Grove, PA). Briefly, after extraction with chloroform, aliquots were analyzed using capillary gas chromatography with a flame-ionization detector. Sample concentrations were determined by comparing the ratio of the area under the peak of camphor with an internal standard and calculating by linear regression against the standard curve. Camphor was linear from 0.02 to 0.50  $\mu\text{g/mL}$ , and the standard curve was calibrated at the following concentrations: 0.02, 0.05, 0.10, 0.20, 0.30, and 0.50  $\mu\text{g/mL}$ .

Data were recorded as median (range) or as percentages and analyzed using JMP software (SAS Institute Inc, Cary, NC). Statistical significance was determined using the Wilcoxon rank sum test. Analyses used a 2-sided 5% type I error rate.

The Mayo Clinic Institutional Review Board and the Cambodian National Ethics Committee for Health Research granted ethics approval for the original study,<sup>8</sup> and the Mayo Clinic Institutional Review Board approved the additional camphor analysis (No. 12-003939).

Detailed information regarding data collection, analysis, interpretation, and ethics approval is available on request from the corresponding author.

## Results

Basic descriptive data and statistics of enrolled tachypneic and healthy control infants are presented in Table 1. There was no difference in gender ( $P = .81$ ) between study groups. However, there were significant differences observed by age ( $P = .001$ ) and by number of people over age 10 who share meals in the household ( $P = .01$ ).

Tiger Balm use among enrolled infants in both study groups was common (Table 2). Eight (88.9%) mothers of tachypneic infants and 7 (70%) mothers of healthy infants reported presently using Tiger Balm on their child ( $P = .36$ ). Six mothers of tachypneic infants and 7 mothers of healthy infants reported applying Tiger Balm daily on their infant. Among infants on whom Tiger Balm was applied daily, the median number of applications per day was 1.5 (range = 1-4 applications per day) for tachypneic infants and 1 (range = 1-2 applications per day) for healthy control infants ( $P = .41$ ).

No case subject and no healthy control subject had any detectable camphor in the blood.

## Discussion

Children of the Mesang District of Prey Veng Province, Cambodia, vary widely in their thiamine status, from normal blood concentrations to severe thiamine

**Table 1.** Demographics of Enrolled Infants.

	Tachypneic Infants, n = 9	Healthy Control Infants, n = 10	P
Gender, male, n (%)	5 (55.6)	6 (60)	.81
Age, weeks, median (range)	8 (4-13)	22 (7-44)	.001
Household size (>10 years), median (range)	5 (2-6)	2.5 (2-5)	.01

**Table 2.** Tiger Balm Use Among Enrolled Infants and Thiamine Diphosphate (TDP) Concentration.

	Tachypneic Infants, n = 9	Healthy Control Infants, n = 10	P
Using Tiger Balm presently, n (%)	8 (88.9)	7 (70)	.36
Number of days used per week, median (range)	7 (0-7)	7 (0-7)	.92
Daily users			.41
n	6	7	
Uses per day, median (range)	1.5 (1-4)	1 (1-2)	
Whole blood TDP, nmol/L, median (range)	61.3 (41.3-114.9)	46.6 (38.0-59.4)	.08

deficiency,<sup>7-10</sup> although clinical illness compatible with beriberi diagnosis correlates poorly with thiamine level.<sup>8,9</sup> We analyzed blood samples in tachypneic and healthy control infants for camphor concentrations, testing the hypothesis that camphor from Tiger Balm use could stimulate tachypnea in Cambodian children. Failure to detect even trace amounts of camphor in blood samples suggests camphor toxicity is unrelated to symptomatic clinical illness in these children. It is conceivable that camphor elicits effects at the tissue level without accumulating in the blood. This explanation is unlikely, however, due to the lipophilic nature and high volume of distribution of camphor.<sup>17,18</sup> Mothers of ill children may be more prone to use Tiger Balm on their infants in response to irritability or other symptoms associated with their illness, potentially explaining the correlation with respiratory rate. However, other ingredients are included in Tiger Balm formulations with the potential to cause illness. High doses of salicylates, for instance, are known to cause metabolic acidosis,<sup>19</sup> which could lead to a compensatory increase in respiration. If any significant amount of salicylates was present, however, camphor would be expected to be observed in the blood, as well. Nevertheless, a causal relationship between other components of Tiger Balm and illness in thiamine-deficient Cambodian infants cannot be completely ruled out.

Camphorated products are commonly sold in Cambodian markets and are used extensively as a treatment of colic and abdominal discomfort in infants by lay caregivers, and among all ages for various other maladies, including headache, dizziness, and insect bites. The safety of camphorated products being sold over-the-counter is actively debated, due to toxicity risks.<sup>18,20,21</sup>

Camphor toxicity is reported in cases of ingestion, inhalation, and prolonged skin contact, with symptoms ranging from mild oropharyngeal, skin, and respiratory irritation to seizures, coma, or death.<sup>18,21-23</sup> Seizures, a cardinal symptom of toxicity, are often the only manifestation of camphor intoxication.<sup>20</sup> Onset of symptoms depends on route of exposure: toxicity due to ingestion often manifests within 5 to 90 minutes,<sup>24</sup> whereas in the relatively few cases of dermal intoxication, symptoms appeared within 4 hours to 3 weeks.<sup>25</sup> Symptoms generally resolve within 24 hours but may persist for longer periods, especially in cases of dermal intoxication.<sup>22,26</sup>

Toxicity is reached at serum concentrations of 0.3 to 0.4 µg/mL; concentrations of 1.7 µg/mL can lead to coma or death.<sup>27</sup> While ingestion is the most common means of toxicity, repeated or prolonged dermal exposures may also result in symptomatic plasma concentrations: one report revealed 0.45 µg/mL of camphor 17 hours after repeated applications.<sup>25</sup> Among reports of asymptomatic camphor ingestion, plasma concentrations ranged from undetectable to 0.015 µg/mL.<sup>26</sup> Peak plasma concentration after dermal exposure to camphor patches was reached at 4 hours after application,<sup>28</sup> corresponding with onset of symptoms in dermal intoxication. Similarly, maximum serum concentration occurred within 3 hours following camphor ingestion.<sup>20</sup> Camphor from dermal patches was undetectable in blood plasma within 8 to 12 hours after exposure,<sup>28</sup> consistent with normal time of symptom dissolution.

Important limitations of this retrospective investigation include imprecise and variable dosage of Tiger Balm among infants and failure to record time from last exposure to initial blood draw. However, because no camphor was detected in blood drawn from

concurrently symptomatic infants, it is unlikely that their symptoms were due to any significant degree of camphor toxicity. Stability of camphor in frozen blood has also not been evaluated, a potential concern for our investigation, as samples were stored for upwards of 30 months before analysis. However, camphor is stable at room temperature for 5 years.<sup>29</sup> Infant ages also varied between study groups, although all cases were less than 5 months old, the age range during which beriberi typically presents.

Infantile beriberi can be a devastating disease, and yet it has a simple, actionable solution: thiamine supplementation via direct administration, food fortification, or agricultural intervention. Reports of infantile beriberi are relatively limited to Southeast Asia where polished rice is a staple food<sup>1,6,9</sup>; even in Sub-Saharan Africa where up to a third of disability-adjusted life years have been attributed to malnutrition,<sup>30</sup> beriberi is rarely observed, likely because staples contain even small amounts of thiamine. Even though not all thiamine-deficient children develop infantile beriberi, this childhood disease is never seen in populations with adequate maternal thiamine intake. Therefore, while there is still an important scientific question as to the pathophysiology behind the presentation of beriberi, there is unequivocal evidence that adequate thiamine status is required to prevent infantile beriberi. Future work among thiamine-deficient populations should account for both the urgency of a curable disease and the need to understand progression from asymptomatic thiamine deficiency to fulminant beriberi for early, accurate diagnosis and prevention of disease. Public health initiatives on the local, national, and international levels will be especially important in early relief efforts, although a sustainable solution will likely require collaborations between government, health professionals, researchers, and public health workers.

Future investigations of tachypneic infants in regions with endemic thiamine deficiency could benefit from exploration of additional vitamin or mineral statuses. Thiamine is important for several metabolic processes and interacts with many other intrinsic and extrinsic factors, implying a need to understand more about the overall nutritional status of tachypneic children in Cambodia. Other avenues of future investigation include dietary interventions to curb thiamine deficiency, such as was demonstrated recently by Whitfield et al<sup>31</sup> through fortification of fish sauce used in Cambodian households. Furthermore, although this study and others<sup>9</sup> failed to correlate environmental exposures with illness, the possibility of toxicity from environmental contaminants, including Tiger Balm, remains to be excluded.

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## Author Contributions

CRJ: Contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SGP: Contributed to conception and design; contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

DC: Contributed to conception and design; contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KCW: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KM: Contributed to conception and design; contributed to acquisition and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

MDT: Contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

PRF: Contributed to conception and design; contributed to analysis and interpretation; drafted manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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