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Pediatrics 2005;116;648-653

DOI: 10.1542/peds.2004-2218

This information is current as of November 8, 2005

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/116/5/e648>

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Sublingual Sugar Administration as an Alternative to Intravenous Dextrose Administration to Correct Hypoglycemia Among Children in the Tropics

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ABSTRACT. *Background.* Hypoglycemia is a common determining factor of poor prognosis for children with severe malaria in sub-Saharan Africa. Intravenous dextrose administration is rarely available. Oral mucosal delivery may be an alternative to parenteral administration. A randomized, clinical trial was performed in Burkina Faso among moderately hypoglycemic children, comparing sublingual sugar administration with oral water, oral sugar, and dextrose infusion administrations.

Methods. Sixty-nine children with glucose concentrations of <0.8 g/L were assigned randomly to 1 of 4 methods of administration, 1 with 3 different doses of sugar, as follows: oral group (OG) ($n = 15$): 2.5 g of sugar; sublingual group (SG) ($n = 27$): 2.5 g of sugar under the tongue, with 3 treatment subgroups, ie, 0.1 g/kg, 0.15 g/kg, and 0.2 g/kg; intravenous group (IG) ($n = 8$): 8 mL of 30% dextrose in a single bolus; water group ($n = 11$). Eight children received sublingual sugar twice, ie, 0.1 g/kg at baseline and 20 minutes later. Blood glucose concentrations were measured every 20 minutes for 80 minutes. Treatment failures, peak glucose concentrations, times to glucose concentration normalization, and kinetic profiles were evaluated.

Results. No treatment failures were observed in the SG and IG, compared with 8 (53%) and 9 (81.8%) failures in the OG and water group, respectively. SG children exhibited glucose kinetic profiles and bioavailabilities (77%, 99%, and 81% in the 3 SG groups) similar to those of IG children. Bioavailabilities were 84% and 38% in the SG and OG, respectively. Children >7 years of age required repeated sublingual administrations to maintain normoglycemia.

Conclusions. The sublingual administration of sugar proved to be effective among moderately hypoglycemic children. It is a simple and promising method to control hypoglycemia among children in both developing and developed countries. This pediatric practice should be investigated in more detail among children with severe malaria. *Pediatrics* 2005;116:e648–e653. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2218; *hypoglycemia, tropics, sublingual, malaria*.

ABBREVIATIONS. OG, oral group; SG, sublingual group; IG, intravenous group; WG, water group; C_{\max} , blood glucose concentration gain; AUC, area under the concentration-time curve.

Hypoglycemia aggravates many severe clinical conditions, including malnutrition, intoxications, and malaria, leading to higher morbidity and mortality rates for affected children in sub-Saharan Africa. Hypoglycemia related to malaria represents by far the best example, because it contributes to a significant proportion of the 225 000 yearly deaths among African children <5 years of age with malaria.¹ Hypoglycemia is present for 10% to 20% of comatose children with cerebral malaria.² Reasons for the occurrence and severity of malaria-associated hypoglycemia are multiple and still controversial. Hypercatabolism, stress, inhibition of gluconeogenesis, and anaerobic glycolysis have all been suspected.^{3–7} Quinine, a drug used frequently in the treatment of severe malaria in Africa, is also responsible for hypoglycemia, because it is a powerful inducer of insulin secretion.^{8,9} For these reasons, an infusion of dextrose is strongly recommended for severe malaria among children, as a complement to antimalarial drugs.² However, infusion requires trained staff and equipment that often are not available in peripheral health care settings. Frequently this results in delays in adequate management of severe malaria. Malaria-associated hypoglycemia, and not the direct effects of malaria parasites, may be an additional contributor to early deaths among comatose children before they reach a health center.¹⁰ Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods.¹¹ Because the sublingual mucosa is highly vascularized, drugs that are absorbed through the sublingual mucosa enter the systemic circulation directly, bypassing the gastrointestinal tract and metabolism in the liver. For some drugs, this results in a rapid onset of action through a more comfortable and convenient delivery route than the intravenous and intramuscular routes. Moreover, administration is not painful and has no risk of blood-borne pathogen transmission and no neurologic risk of sciatic nerve trauma, a frequent consequence of inappropriate intramuscular injections among African children.

In Burkina Faso, hospital management of severe malaria among children involves a loading dose of

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Accepted for publication May 12, 2005.

doi:10.1542/peds.2004-2218

No conflict of interest declared.

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16 mg/kg quinine base delivered through slow infusion in 5% dextrose over 4 hours. This is equivalent to delivering ~2.5 g of dextrose to a 10-kg child in 1 hour. Only 30% dextrose in 10-mL vials is available in hospitals and private pharmacies. In resource-poor settings, where frequently infusion is not available or is not operational, the sublingual administration of sugar could represent a noninvasive, painless, and practical alternative treatment.¹² It is also widely available, cheap, and user-friendly for home treatment that could be extended to all cases of hypoglycemia among children in the tropics, whatever the level of care.

The most important advantage of the sublingual route is its potential use among comatose children who are not able to swallow. The sublingual route was used occasionally by our team in Niger, with good results (H. B. and M. A. Sani, MD, unpublished data, 2000). As a first step in confirming this hypothesis, we conducted the first clinical trial aimed at evaluating whether early correction of hypoglycemia could be achieved with sublingual administration of dextrose among moderately hypoglycemic children, with or without malaria, in Burkina Faso.

METHODS

Study Design, Site, and Patients

A randomized, open, clinical trial of oral, sublingual, and intravenous dextrose administration was launched in the Hamdalaye Health Center, in Bobo-Dioulasso (500 000 inhabitants), during the high malaria transmission period (October to December 2002). Children 1 to 15 years of age who presented with moderate clinical symptoms were recruited among the 2 main pathologic conditions observed in the health center outpatient department, ie, acute *Plasmodium falciparum* malaria and moderate respiratory tract infections. Moderate respiratory tract infection was defined by the presence of cough without signs of pneumonia (fever of <3-day duration and no modification of respiratory rhythm).

After appropriate care was administered, a nurse asked the parents if they would agree to return early the next morning. If so, children were directed to the physician for information on the study. After informed consent was obtained, an appointment was made for early the next morning, after fasting overnight (starting after dinner). The children were enrolled in the trial if they had blood glucose concentrations between 0.5 g/L and 0.8 g/L and no severe clinical symptoms of hypoglycemia requiring immediate treatment. To ensure the absence of early swallowing in the sublingual group (SG), children who swallowed the sugar within 10 minutes were dropped from the study; the next child entering the study was assigned to the same SG. The mean time for complete disappearance of sugar from under the tongue was estimated at 20 minutes in a pilot phase of the present study. A first physician (the same one throughout the study) performed the patients' enrollment and the treatment administration. A second physician collected and analyzed the data, in a blinded manner. Children were allocated randomly to 1 of the 4 methods of administration, 1 with 3 different doses of sugar, as follows: SG: 2.5 g of wet sugar under the tongue, defining 3 treatment subgroups, ie, ≤ 0.1 g/kg (SG-1), 0.15 g/kg (SG-1.5), and 0.2 g/kg (SG-2), according to the child's body weight; intravenous group (IG): 8 mL of 30% dextrose administered in a single bolus; oral group (OG): 2.5 g of sugar on the tongue; water group (WG): one-half tablespoon of water.

If children required immediate treatment for symptoms of severe hypoglycemia, then they received intravenous administration of 10 mL of 30% dextrose, followed by 5% dextrose infusion. They were monitored until complete recovery. As soon as a child completed follow-up monitoring, he or she received a meal at the hospital before departing.

Because the sublingual volume is limited and does not allow administration of large amounts of sugar (2.5 g), we also evaluated the kinetic profile of repeated administration for older children.

Eight children 10 to 12 years of age received 0.1 g/kg sugar at baseline and again 20 minutes later, under the tongue. They were matched with 1 child of the same age, gender, and sugar dose who was enrolled just before or just after.

Laboratory Methods

Before enrollment, 0.1 mL of blood was collected through finger prick, with a Glucomatic lancet (Bayer Diagnostics, Leverkusen, Germany), to confirm the baseline blood glucose level. After treatment administration, this measurement was repeated every 20 minutes until a blood glucose level of ≥ 0.9 g/L (defined as normoglycemia) was achieved. At least 4 measurements were performed for each child within 80 minutes. Glucose was measured in blood with a precision of 0.01 g/mL, by means of a Glucomatic mini-automate system (Bayer Diagnostics) based on glucose oxidase and glucose peroxidase. The reproducibility of this technique was 5.7% at a concentration of 1 g/L and 8.3% at 0.5 g/L. The Glucomatic performance was quality-controlled in the Centre Muraz laboratory with the biochemistry automate LabSysteme FP-140 (LSI, Cergy Pontoise, France), before the beginning of the study and after each series of 50 measurements. The mini-automate was also quality-controlled with the Glucomatic Esprit control solution after each 50 measurements.

For all children, malaria parasite density was assessed on the day preceding study enrollment, by counting asexual *P falciparum* parasites, relative to white blood cells, in thin films. The presence of >1000 parasites per μ L and a body temperature of >37.5°C defined an acute episode of malaria.

Study Outcomes and Definitions

The treatment failure rate and early treatment failure rate were the primary outcomes. The treatment failure rate was defined as the proportion of children who did not reach glucose concentrations of ≥ 0.9 g/L during the study period. The early treatment failure rate was the proportion of children with no blood glucose gain at 20 minutes. The maximal blood glucose concentration gain (C_{\max}) was the difference between the peak glucose concentration and the initial glucose concentration. C_{\max} and the time to obtain normoglycemia were observed values. The area under the curve (AUC) of glucose concentrations (difference between measured and initial values) versus time was calculated for each child, according to the linear trapezoidal rule, from 0 to 80 minutes. The relative bioavailability through the sublingual route was calculated as the ratio of the mean sublingual AUC to the mean intravenous AUC from 0 to 80 minutes.¹³ The treatment delay was the time from confirmation of the hypoglycemic level until the beginning of treatment. These criteria were chosen as secondary outcomes.

Ethics

The study protocol was approved by the Centre Muraz institutional ethics committee and the regional health district authorities. All parents were informed about the study in vernacular language, and written consent was obtained. Only children with moderate clinical disease were included in the trial. This trial can be considered a preliminary exploration of a novel method of administering glucose. As a first step, we wanted to test our hypothesis among moderately ill children, whose lives were not endangered. Children were told to have dinner as usual the day before enrollment and to present to the health center before breakfast on the following day, for a fasting blood test. All samples were collected with an analgesic EMLA patch (Astra Zeneca, Rueil-Malmaison, France), which reduced discomfort to a minimal level. All children were under constant medical supervision during the study period. Infusion dextrose material and sugar were readily available in case of symptomatic hypoglycemia. Treatment of the disease episode and transportation costs for attending the clinics were free of charge and reimbursed, respectively. Instead of a no-treatment arm, use of a water-treatment arm was considered, because rehydration (as well as administration of antibiotics, when appropriate) is an important component of standard care for children with benign or moderate infections.

Statistical Analyses

In this open study, the allocation sequence was generated by an independent researcher from Centre Muraz. The randomization

list was provided by EpiInfo 6 software¹⁴ and was concealed until interventions were assigned. The randomization took place at enrollment, once the eligibility criteria were met. The sample size was based on the assumption of expected rates of recovery to normoglycemia of ~10% in the WG and 85% in the treated groups ($\alpha = .05$, $\beta = .8$; $n = 8$ in each group). Normally distributed continuous data were compared with Student's *t* test and analysis of variance (*F* test). Bartlett's test was used to verify the homogeneity of variances. The nonparametric Kruskal-Wallis test was used when appropriate. The probability of normalized glucose concentrations according to time was assessed with Kaplan-Meier survival curves. Probability values of $<.05$ were regarded as statistically significant, and results were expressed as mean \pm SD.

RESULTS

During the study period, 156 children attended the outpatient department of the Hamdallaye Health Center with moderate clinical signs of respiratory tract infection or acute malaria. Sixty-nine children fulfilled the enrollment criteria and were included in the trial (Fig 1). Sixty-one received a single sugar administration. Their demographic and pharmacologic characteristics are presented in Table 1. The other 8 children (age: 11.1 ± 1.1 years) received 2 sublingual sugar administrations (0.11 ± 0.01 g/kg) and were compared with 8 matched children (age: 11.7 ± 1.5 years) who received a single sublingual sugar administration (0.07 ± 0.01 g/kg).

There were no differences in terms of age and gender among the 4 treatment groups. On the basis

of the design of the study, the age and weight differed among the 3 SG subgroups, because older children received the lower sugar dose (Table 1). Overall, 18 children had malaria. In the OG, children were first compared according to their malaria status. There was no difference in blood glucose kinetic profiles according to the presence or absence of malaria (data not shown). Therefore, children from the OG were pooled together.

Ten children had deeper hypoglycemia of <0.6 g/L (mean: 0.52 ± 0.02 g/L), with moderate dizziness, at baseline (1 in the WG, 2 each in the IG and OG, and 5 in the SG). No adverse clinical effects at enrollment or during the follow-up period were observed among hypoglycemic children, and all treatments were well tolerated.

There were no treatment failures in the SG and IG, compared with 8 (53%) and 9 (81.8%) in the OG and WG, respectively ($P < .05$) (Table 2). In the latter group, one child's glucose concentration remained at 0.6 g/L during the 80 minutes of the study, without appearance of clinical symptoms. That child received orally administered sugar (in addition to the snack) before departing with normoglycemia. There were also more early treatment failures and lower early blood glucose gains in the OG and WG than in the SG and IG ($P = .004$). In the OG, glucose concentrations increased slowly for all children but 4 received

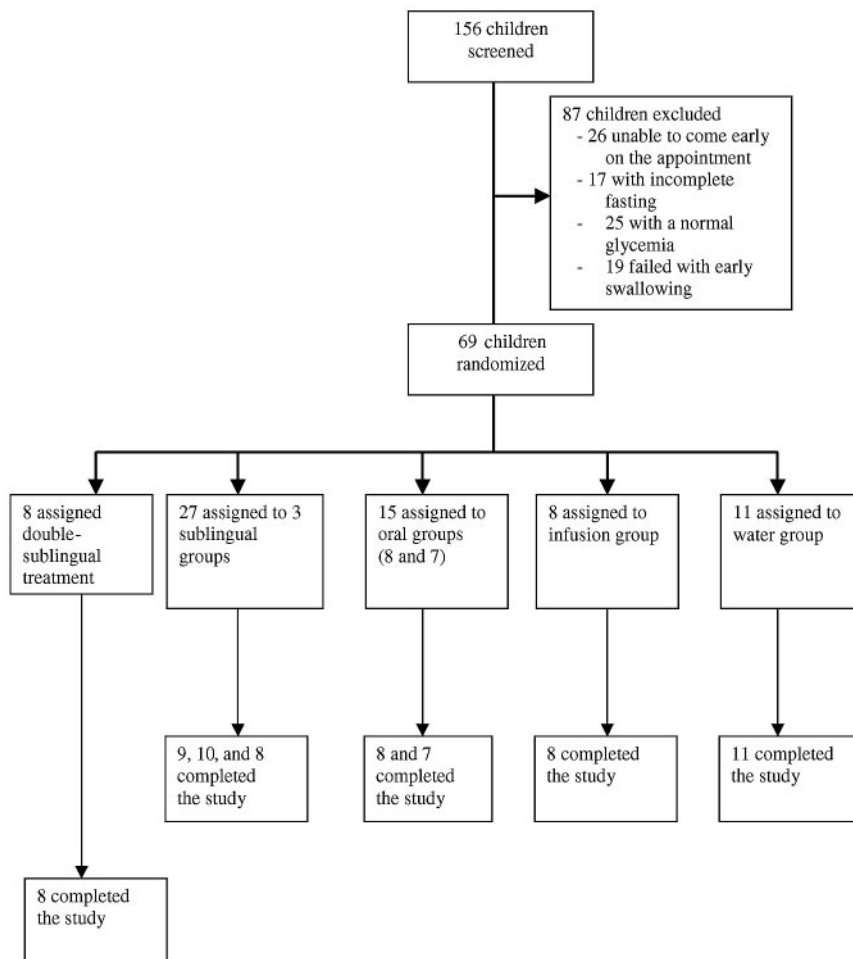


Fig 1. Diagram of sublingual sugar study in Burkina Faso.

TABLE 1. Baseline Demographic Characteristics and Treatment Group Descriptions

	SG, 0.1 g/kg	SG, 0.15 g/kg	SG, 0.2 g/kg	SG (Total)	OG	IG	WG
No.	9	10	8	27	15	8	11
Age, y	12.0 ± 1.0	7.7 ± 2.7	3.3 ± 1.1	7.8 ± 3.8	6.6 ± 4.2	6.1 ± 2.8	6.4 ± 3.4
Weight, kg	33.8 ± 5.6	24.0 ± 6.13	13.1 ± 1.8	24.0 ± 9.5	19.5 ± 6.1	18.5 ± 6.2	20.5 ± 6.8
Glucose concentration, g/L	0.75 ± 0.03	0.69 ± 0.07	0.63 ± 0.16	0.69 ± 0.1	0.7 ± 0.1	0.69 ± 0.07	0.73 ± 0.07
No. with malaria (%)	2 (22)	3 (33)	4 (50)	9 (33)	9 (60)	2 (28)	3 (27)
Sugar dose, mg/kg	79.5 ± 14.7	125.1 ± 12.9	194.2 ± 30.2	130.2 ± 44.6	138.7 ± 37.5	157.7 ± 51.8	0

Values are mean ± SD unless stated.

TABLE 2. Clinical and Biological Responses to Dextrose or Water Administration Among Children With Moderate Hypoglycemia

	SG	OG	IG	WG
No. (%) of children with Treatment failure	0	8 (53.3)*†	0	9 (81.8)*‡
Early treatment failure	2 (7.2)	4 (26.7)	0 (0.0)	6 (54.5)*†
C_{max} , g/L	0.46 ± 0.21	0.24 ± 0.18†	0.58 ± 0.17	
T_{iv} , min	28.5 ± 10.6		25.7 ± 9.5	
AUC_{0-80} , g/L · h	0.34 ± 0.21	0.16 ± 0.17†	0.49 ± 0.09	
F , %	84	38	100	

Values are mean ± SD unless stated. T_n indicates time to glucose concentration of ≥ 0.9 g/L; AUC_{0-80} , AUC from 0 to 80 minutes; F , approximate bioavailability.

* $P < .005$ versus SG.

† $P < .05$ versus IG.

‡ $P < .005$ versus IG.

<0.10 g/kg sugar (Fig 2). The latter group exhibited the same profile as the WG (data not shown).

The increase in glucose concentrations was rapid for all SG children (Fig 2). SG children exhibited a kinetic profile and bioavailability similar to those of IG children and a blood glucose profile higher than that of OG children (Table 2). Among the SG children, C_{max} values were similar in the SG-1.5 and SG-2 subgroups and higher than in the SG-1 subgroup (0.50 ± 0.20 , 0.53 ± 0.26 , and 0.34 ± 0.14 mg/L, respectively). AUC_{0-80} values were also similar in the SG-1.5 and SG-2 groups and higher than in the SG-1 group (0.40 ± 0.15 , 0.41 ± 0.25 , and 0.19 ± 0.14 g/L · hour, respectively). Because of the choice of a standard sugar dose, the sugar dose per body weight decreased with the age of the children (Table

1). The older SG children received <0.1 g/kg sugar but repeated sugar administration maintained the blood glucose level at >0.9 g/L at 40 minutes (Fig 3). Although infusion equipment and trained staff members were available in this health center, the delay for initiating treatment was shorter for the SG children than for the IG children (mean: 11.2 ± 9.1 and 18.5 ± 29.3 minutes, respectively; $P < .05$).

DISCUSSION

This study showed that sublingual administration of sugar was able to restore normoglycemia rapidly among moderately hypoglycemic children. Children with moderate hypoglycemia after an overnight fast were recruited among children exhibiting nonsevere malaria or moderate respiratory tract infections.

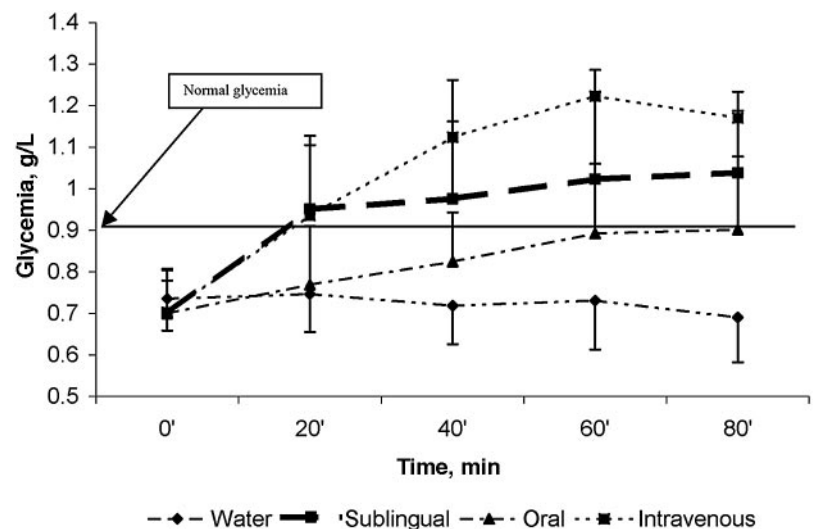
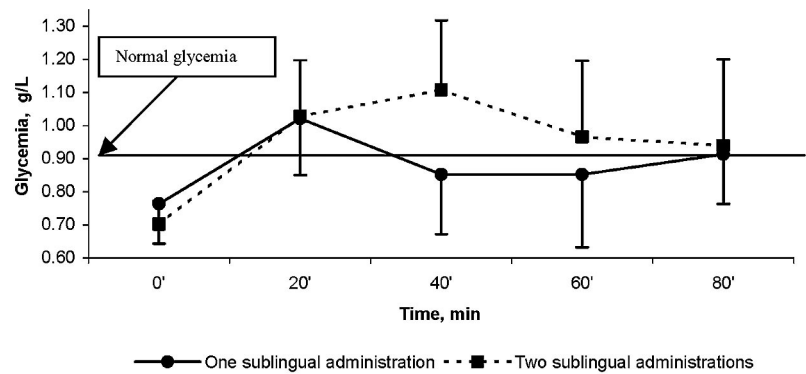


Fig 2. Glucose concentrations among hypoglycemic children after sublingual administration of sugar, oral administration of sugar, intravenous administration of dextrose, or oral administration of water (mean ± SD).

Fig 3. Glucose concentrations among hypoglycemic children (>7 years) in the SG-1 group after 1 or 2 sugar administrations (mean \pm SD).



Therefore, our results must be confirmed among children with spontaneous and more severe hypoglycemia. A possible bias in selection might be suggested, because 159 eligible children were screened to enroll only 69 in the study. However, examining the reasons why the children were not included (Fig 1), we could not find any trend for such a bias. The limitations of sublingual administration may result from the early swallowing of sugar that occurred for ~12% of screened children.

The sublingual mucosa represents an alternative route to parenteral administration for many drugs, including nitroglycerin, analgesics, sedatives, hormones, and bioactive peptides, because it offers excellent accessibility and avoids gastrointestinal absorption and first-pass hepatic metabolism.¹¹ The high vascularization of the mucosa allows an absorption rate similar to that for intravenous injection. Sugar bioavailability after sublingual administration seemed to be twice that observed after oral administration, because of direct passage to the systemic circulation, bypassing both gastrointestinal and hepatic metabolisms. However, the small surface of the sublingual area does not allow delivery of amounts of >0.2 g/kg, even for the youngest children. The current dose may seem insufficient in comparison with the usual recommended dextrose dose (0.5 g/kg) to cure severe hypoglycemia, and a second administration may be required. After sublingual administration of 2.5 g of sugar, all children, 1 to 7 years of age, became normoglycemic within the first 1 hour. Sugar doses ranging from 0.1 to 0.15 g/kg need to be repeated after 20 minutes to prevent recurrence of hypoglycemia among older children (weighing >10 kg) and to maintain normoglycemia up to 80 minutes. Hypoglycemia attributable to fasting is likely to be corrected more easily than hypoglycemia induced by more severe conditions. Moderate malaria did not alter the rate or extent of glucose concentration recovery, compared with children without malaria. At the peripheral health care level, where dextrose infusions often are not available, sublingual administration is a simple, low-cost, effective method that could be used early to prevent the occurrence of hypoglycemia among young children with potentially severe, evolving malaria. In developing countries, the sublingual route could also be used in the field for children of non per os status (with nausea, vomiting, dizziness, or coma), to prevent

them from developing severe hypoglycemia. In developed countries, this approach could be indicated as a home treatment for acute hypoglycemia among children or could be investigated in different situations involving hypoglycemia, such as neonatal hypoglycemia, intractable vomiting, or acute hypoglycemia among diabetic subjects.

This study should be considered a preliminary exploration. The significance of our conclusions is limited by the fact that the study was not conducted among patients anticipated to benefit most from this treatment, such as children with severe malaria and/or coma. These 2 conditions should be included in future clinical trials, to confirm and to extend our present observations.

ACKNOWLEDGMENTS

Financial support was provided by Impact Malaria, Sanofi-Synthelabo (Gentilly, France).

We thank the nursing staff of Hamdallaye Health Center, N. Diallo and P. K'Poda of Centre Muraz Epidemiologic Unit, the laboratory staff of Centre Muraz in Bobo-Dioulasso, E. Dembèlè, and E. Papa. We are grateful to F. Rasoanandrasana-Barenes for quality control of malaria diagnosis on blood films and to M. L. Srouf for reviewing the document. We are also grateful to the French Ministry of Foreign Affairs for technical assistance.

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