Control of Hyperbilirubinemia in Glucose-6-Phosphate Dehydrogenase-deficient Newborns Using an Inhibitor of Bilirubin Production, Sn-Mesoporphyrin

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ABSTRACT. Background. Hyperbilirubinemia in newborns with glucose-6-phosphate dehydrogenase (G6PD) deficiency is a serious clinical problem because of the severity and unpredictability of its course. An innovative approach to this problem is suggested by previous experience with Sn-mesoporphyrin (SnMP), a potent inhibitor of bilirubin production, in moderating neonatal hyperbilirubinemia caused by ABO incompatibility, immaturity, and unspecified mechanisms.

Objective. To compare the effectiveness of the preventive and therapeutic uses of SnMP in ameliorating the course of bilirubinemia of G6PD-deficient neonates.

Methods. Neonates born at the Metera Maternity Hospital, Athens, Greece, and found to be G6PD-deficient by cord blood testing were stratified by sex and gestational age (210–265 days and >265 days) and randomized in pairs to receive SnMP (6 μmol/kg birth weight, intramuscularly) either on the first day of life (preventive use) or if and when the plasma bilirubin concentration (PBC) level reached an age-specific threshold level for intervention (therapeutic use). In the case of failure of SnMP to control the rise of PBC levels, the protocol defined precisely the threshold PBC levels for switchover to phototherapy (PT) and, if necessary, exchange transfusion. PBC was measured daily until a declining value was obtained and the case was closed.

Results. A total of 86 G6PD-deficient neonates were randomized: 42 in the preventive arm and 44 in the therapeutic arm. Of the latter, 20 (45%) reached PBC levels requiring therapeutic intervention and thus received SnMP. Regardless of the trial arm, none of the 86 neonates required PT, whereas in a previous study in the same population, 33% of G6PD-deficient neonates required PT. In the intrapair sequential analysis, the favored arm was decided on the criterion of the age at closure of the case being shorter by at least 1 day. After plotting 30 untied pairs in the sequential analysis graph, the preventive use of SnMP proved to be the favored arm, and the trial was stopped. At this point, there were 2 unpaired neonates, 12 tied pairs, 22 pairs in which the preventive use of SnMP was favored and 8 pairs in which the therapeutic use of SnMP was favored. In the group analysis, infants in the preventive group, compared with those in the therapeutic group, had a lower maximum PBC level (8.2 ± 3.1 and 10.9 ± 2.8 mg/dL, respectively), which was reached at an earlier age (63.5 ± 34.8 and 82.2 ± 24.7 hours, respectively) as well as a lower closing PBC level (7.2 ± 2.9 and 9.6 ± 2.5 mg/dL, respectively) and an earlier age at closing (89.1 ± 35.6 and 110.8 ± 23.6 hours, respectively). Moreover, a PBC level of ≥8.0 mg/dL, a level at which jaundice is clearly visible, was not reached by 52% of the neonates in the preventive arm and 16% of the neonates in the therapeutic arm.

Conclusions. In G6PD-deficient neonates, a single dose of SnMP administered preventively or therapeutically entirely supplanted the need for PT to control hyperbilirubinemia. The preventive use of SnMP offers practical advantages in populations with a high enough prevalence of G6PD deficiency to justify cord blood screening. Pediatrics 1998;101(5). URL: http://www.pediatrics.org/cgi/content/full/101/5/e1; G6PD-deficiency, hyperbilirubinemia, heme oxygenase, Sn-mesoporphyrin, neonatal jaundice.

ABBREVIATIONS. G6PD, glucose-6-phosphate dehydrogenase; PT, phototherapy; MMH, Metera Maternity Hospital; ET, exchange transfusion; HO, heme oxygenase; SnMP, Sn-mesoporphyrin; GA, gestational age; PBC, plasma bilirubin concentration; BW, birth weight; Hb, hemoglobin.

In Greece, severe neonatal jaundice associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency historically has been the most important cause of kernicterus1–5 and, in recent years, of the failure of phototherapy (PT) to control hyperbilirubinemia.6 In a prospective study of the use of PT at the Metera Maternity Hospital (MMH) in Athens, 33% of G6PD-deficient neonates required light treatment, and it was only in this etiologic group that PT failed to control hyperbilirubinemia and exchange transfusion (ET) needed to be performed (unpublished observations). Moreover, the course of hyperbilirubinemia in G6PD-deficient neonates often is unpredictable, resulting in the need for prolonged inpatient observation.2,5 Thus, in populations in which G6PD deficiency is a frequent cause of hyperbilirubinemia before plasma bilirubin concentrations reach levels potentially toxic to the central ner-
ous system.7–9 These inhibitors have proved to be both safe and effective in ameliorating neonatal hyperbilirubinemia, as we have shown previously in a series of clinical trials carried out at MMH.10–12 In infants with direct Coombs-positive ABO incompatibility and in preterm infants, Sn-porphyrin administration within the first day of life (ie, preventive use of the inhibitor) significantly moderated, in a dose-dependent manner, the course of hyperbilirubinemia and reduced substantially the need for PT.10,11 In term and near-term newborns, the heme analogue Sn-mesoporphyrin (SnMP) administered at the time PT ordinarily would have been initiated according to the criteria in use at MMH (ie, therapeutic administration of the inhibitor) was shown to be superior to special blue light PT and eliminated the need for light therapy in managing nonspecific hyperbilirubinemia.12

In the present study, we have compared the preventive and therapeutic uses of SnMP to control hyperbilirubinemia in a randomized, sequentially analyzed clinical trial in G6PD-deficient newborns. The results indicate that a single dose of SnMP, used in either the preventive or the therapeutic mode, was able to entirely supplant the need for PT in these infants. Preventive use of the inhibitor, however, was the favored modality. Thus, in all etiologic groups we have studied to date, suppression of bilirubin production by an inhibitor of HO activity has proved to be highly effective in controlling the severity of hyperbilirubinemia and in diminishing or eliminating the need for PT.

METHODS

The study was approved by the institutional review boards of the collaborating institutions, ie, The Rockefeller University, the Tufts–New England Medical Center Hospital, and the MMH. In addition, the use of SnMP as an investigational new drug in newborns is approved by the US Food and Drug Administration (IND 29,462) and the Hellenic Drug Organization.

Study Population and Design

The enrolled neonates were delivered at MMH during the first 6 months of 1996. At MMH, an unclotted cord blood sample is collected at delivery from all live births, and the blood group, the red cell G6PD activity, expressed as units per gram of hemoglobin (Hb), was determined. The Diamed-ID card microtyping system (Diamed, Cressier, Switzerland) was used for ABO and Rhesus blood group typing and direct Coombs testing in cord blood. The red cell G6PD activity, expressed as units per gram of hemoglobin (Hb), was determined using the Sigma Diagnostics (St Louis, MO) reagent kit and procedure (no. 395-UV). On the basis of analysis of the

Fig 1. The daily PBC values chart, which includes the threshold lines for management decisions. Line A is the threshold for administering SnMP to neonates randomized to the therapeutic arm of the trial. Line B is the threshold at which PT was to be initiated and breastfeeding interrupted in neonates randomized to either arm of the trial. Line C is the threshold for ET to be performed. DCBF indicates discontinue breast feeding.

SnMP administration were identical to those used at MMH for initiating PT (Fig 1, line A), as were the critical levels at which ET had to be performed. For the purpose of the present trial, we placed the crossover from SnMP to PT (and interruption of breastfeeding) at PBC levels midway between the treatment and ET thresholds (Fig 1, line B). Four stratification groups were created according to sex and GA (>265 days and ≤265 days). Enrolled neonates were randomized in pairs within each of the four stratification groups. The assignment codes, created by the method of random numbers, were placed in serially numbered sealed envelopes; a series was created for each of the stratification groups.

The daily care of the neonates was the responsibility of the private pediatricians and the nursing staff at the six normal nurseries at MMH. With few exceptions, mothers breastfed their infants; however, a night formula feeding was given throughout hospitalization and supplemental formula was routinely used in the first 2 to 3 days of life until adequate lactation was established. All infants received 1 mg of vitamin K1 (Konakion, Roche Laboratories, Nutley, NJ) intramuscularly at birth. Blood samples (two microhematocrit tubes) were obtained every morning by heel stick. Additional samples were required if during the period of ascending PBC levels, the threshold for PT was approached. The PBC level of each case was plotted daily in the bilirubin graph (Fig 1), a copy of which was incorporated in the clinical chart, so that the attending pediatricians were kept informed of the course of hyperbilirubinemia and its management. Blood sampling continued up to the time that a declining PBC was established, based on the daily morning sample, at which time the case was closed. If this did not occur during routine hospitalization (4 to 5 days) of the mother–infant pair, additional samples were obtained in the outpatient clinic.

SnMP was administered as a single intramuscular injection at a dose of 6 μmol/kg birth weight (BW) from a 24 μmol/mL solution prepared as described previously. A volume of 0.25 mL/kg BW was administered. The SnMP solution was stored in darkness at 4°C.

Laboratory Methods

The Diamed-ID card microtyping system (Diamed, Cressier, Switzerland) was used for ABO and Rhesus blood group typing and direct Coombs testing in cord blood. The red cell G6PD activity, expressed as units per gram of hemoglobin (Hb), was determined using the Sigma Diagnostics (St Louis, MO) reagent kit and procedure (no. 395-UV). On the basis of analysis of the
frequency distribution of activity levels in the cord blood, the critical level for diagnosing G6PD deficiency was ≤6.0 U per gram of Hb and ≤8.0 U per gram of Hb in male and female neonates, respectively.

Total and apparent unbound PBC was determined using the automated digital UB analyzer (Arrows Company, Osaka, Japan). The accuracy and reproducibility of the instrument for total PBC were checked using the ACA liquid bilirubin calibrator (DuPont, Wilmington, DE); the coefficient of variation was 0%, 2.2%, and 1.5% for PBC levels of 1.7, 11.1, and 21.3 mg/dL, respectively (eight assays at each PBC level).

Data Collection and Statistical Analysis

All pertinent family, maternal, and neonatal clinical and laboratory information was entered in a computerized database. The principle of intent to treat was followed for intrapair analysis. The pair was considered untied if, in one of the members of the pair, the threshold PBC level for PT or ET was reached or if there was a difference of at least 1 day in the age at the closing of the case. Untied pairs were plotted on the sequential analysis chart (Fig 2). In addition to the sequential intrapair analysis, intergroup analyses comparing the two intervention modalities—preventive and therapeutic—were performed after the trial had ended. For continuous variables, the unpaired two-tailed t test, and for categorical variables, Fisher’s exact test were used. For practical reasons and to avoid the effect of circadian variation in PBC level, the daily blood samples were drawn in the morning. Thus, the exact age at sampling varied depending on the time of delivery. Age is an important determinant of PBC level at least for the first 2 to 3 days after birth during the phase of rapid bilirubin accumulation. To reduce this variability, using the actual PBC levels and the respective exact age, we calculated the rate of PBC change per 24 hours from cord blood to first blood sample and from first to second blood sample.

To place the present trial in perspective, an additional group (n = 60) of consecutive G6PD-deficient infants born over a 2-month period at MMH in 1994 was used for comparison purposes. The course of neonatal bilirubinemia in this group was examined with clinical and laboratory methods identical to those used in the present trial; however, the responsibility for the management of hyperbilirubinemia with PT rested with the attending physicians. In effect, this group represents the prevailing conditions at MMH for the management of neonatal hyperbilirubinemia with PT rested with the attending physicians. In effect, this group represents the prevailing conditions at MMH for the management of neonatal hyperbilirubinemia with PT rested with the attending physicians.

RESULTS

Comparison of Preventive and Therapeutic Use of SnMP

A total of 86 G6PD-deficient neonates were enrolled in the clinical trial. In addition, 2 neonates were excluded and parental consent was refused in 6 cases. The distribution of infants enrolled in the four stratification groups and the results of the sequential analysis are described in Table 1. Two female infants, both randomized to the therapeutic use of SnMP, remained unpaired when enrollment was closed. Thus, 42 neonates were enrolled in the preventive arm, and 44 neonates were enrolled in the therapeutic arm of the trial. All infants enrolled completed the period of observation, and none crossed the threshold for PT, ie, no supplemental PT was required in either treatment arm or for ET. Thus, the favored arm within each pair was decided on the basis of the age at the closing of the case.

The preventive use of SnMP was found to be superior to the therapeutic use of SnMP after 30 untied pairs were plotted in the sequential analysis chart (Fig 2). At this point, the trial protocol required that enrollment to the inferior arm, ie, therapeutic use of SnMP, be terminated and that the study be continued as an unrandomized, open-ended preventive use of SnMP in G6PD-deficient neonates. The trial is ongoing.

In the following analysis, the cases were grouped according to the arm to which they were randomized (Table 2). At entry, the two arms were comparable in demographic characteristics, which included ratio and number of males/females, GA, and BW, and in severity of hyperbilirubinemia as exemplified by the PBC in cord blood and in the first blood sample (Table 2). All neonates in the preventive arm were administered SnMP immediately after the first blood sample was drawn (26.0 ± 4.2 hours), whereas in the therapeutic arm, only 2 of the 44 neonates qualified to receive SnMP based on the PBC level of the first blood sample. Thus, the difference in the rate of change per 24 hours in PBC level from the first to the second blood sample between the preventive and therapeutic arms (1.02 ± 1.6 and 2.99 ± 1.65 mg/dL, respectively; P < .0001) represents the effect of SnMP in inhibiting HO activity, with a consequent reduction in the bilirubin production rate. All other differences between the two groups (Table 2) result from the fact that all neonates in the preventive arm received SnMP immediately after the first blood sample was drawn, whereas only 20 of the 44 neonates in the therapeutic arm were administered SnMP and at a later time when the threshold for clinical intervention was reached (55.2 ± 18.0 hours; range, 37.2 to 117.5 hours). To these facts we must ascribe the lower, in the preventive arm compared with the therapeutic arm, maximum PBC level (8.2 ± 3.1 and 10.9 ± 2.8 mg/dL, respectively) and closing PBC level (7.20 ± 2.9 and 9.58 ± 2.5 mg/dL, respectively), as well as the lower age at maximum PBC level (63.5 ± 34.8 and 82.2 ± 24.7 hours, respectively), and at closure of the cases (89.1 ± 35.6 and 110.8 ± 23.6 hours, respectively) (Table 2, Fig 3A).
A number of important differences between the two treatment groups from the standpoint of the management of neonatal jaundice under usual clinical practices emerged from a detailed examination of the individual cases. The PBC level of the first blood sample also was the maximum PBC level in 12 of 42 cases (29%) in the preventive arm, whereas this occurred in only 1 of 44 cases (2%) in the therapeutic arm ($P = .0006$). A PBC level of $8.0 \text{ mg/dL}$, the level at which jaundice is clearly visible, was not reached by 22 (52%) of the cases in the preventive arm and by only 7 (16%) of the cases in the therapeutic arm ($P = .0005$). Of the 20 infants in the therapeutic arm who required SnMP, only 11 (55%) did so on the basis of the PBC level at 24 to 48 hours of age (Fig 4). This number increased to 17 of 22 (77%) if a lower threshold (6mg/dL at 24 hours) was used. Nevertheless, even at the lower threshold, 5 of the 44 cases (11%) in the therapeutic arm would have escaped early detection of the severity of their hyperbilirubinemia (Fig 4).

The residual red cell G6PD activity in the G6PD-deficient males (1.03 ± 0.88U/g Hb; range, 0.1 to 5.4 U/g Hb) was markedly less than that in females, all of whom were heterozygotes (6.19 ± 1.19, U/g Hb; range, 3.5 to 7.85 U/g Hb). The difference in G6PD activity was not reflected in a significant sex difference in PBC levels at entry or in response to SnMP, but sample size limited the statistical power of the comparison (data not shown). None of the mothers were exposed in the perinatal period to vicia fava, naphthalene moth balls, or any drug known or suspected of triggering hemolysis in G6PD-deficient individuals. None of these drugs were administered to the neonates. Finally, none of the SnMP-treated neonates presented any local reaction, photosensitivity erythema, or other discernible effects of inhibitor treatment. A 5-year follow-up and surveillance are in progress.

### Comparison of the Therapeutic Use of SnMP to PT

As described in “Methods,” a cohort of G6PD-deficient neonates was studied over a 2-month period at the MMH in 1994. This allowed us the opportunity to compare the therapeutic use of SnMP with PT in the management of hyperbilirubinemia in G6PD-deficient Greek Newborns—Group Analysis
The criteria for intervention in the two trials were identical, but during the present trial, they were strictly applied by one physician (T.V.), who was solely responsible for the conduct of the trial, whereas during the 1994 study, the management decisions were made individually by the private attending pediatricians. The two series are comparable in demographic characteristics and in measures of hyperbilirubinemia. In the present study, 20 (45%) of the 44 neonates in the therapeutic arm received SnMP in lieu of PT, and in the 1994 cohort, 20 (33%) of the 60 neonates were treated with PT (Table 3, Fig 3B). The percentages of neonates treated are not statistically different, but in any case, the smaller percentage of neonates treated with PT in 1994 can be ascribed to a less strict application of the intervention criteria. As a consequence of this fact, PT was initiated in 1994 later than the age at which SnMP was administered in the present trial (73.4 ± 28.8 and 55.2 ± 18.0 hours in groups C and A, respectively; \( P = .0288 \)) and at a slightly but not significantly higher PBC level (12.6 ± 2.3 and 11.6 ± 1.8 mg/dL in groups C and A, respectively). The difference in the proportion of neonates treated between the two series means that in terms of the spectrum of severity of hyperbilirubinemia the cutpoint in the earlier series was higher than that in the present trial. This is the explanation for the differences between groups A and C and groups B and D in the first blood sample and maximum PBC values (Table 3).

As expected, in both series the treated groups A and C were significantly different in all measures of hyperbilirubinemia from the respective nontreated groups B and D. However GA, BW, and sex did not significantly influence the need for intervention (Table 3). PT was used for an average of 52.2 (± 24.2) hours in the 1994 cohort. Units of five daylight fluorescent lamps emitting 7 to 8 \( \mu W/cm^2/nm \) to the infant’s skin were used routinely. More intense PT combining special blue lamps and Halogen spotlights delivering 18 to 22 \( \mu W/cm^2/nm \) was reserved for neonates whose PBC level continued to rise after 24 hours of routine PT. There were no significant differences in the course of hyperbilirubinemia after the initiation of intervention between the neonates that received SnMP (group A) and those treated with PT in 1994 (group C). Consequently, the efficacy of the two treatment modalities, SnMP and PT, in controlling hyperbilirubinemia in G6PD-deficient neonates was comparable. However, one heterozygous
female neonate who received PT also required two ET (maximum PBC level, 26.7 mg/dL at 55 hours of age) after failure of intense PT initiated at 30 hours of life (PBC level, 11.7 mg/dL) to control the rapid rise of PBC level. No evidence of exposure to an exogenous hemolytic agent that could explain the high levels of PBC in this neonate could be found.

**DISCUSSION**

The present randomized clinical trial was designed to compare the preventive with the therapeutic use of SnMP to control hyperbilirubinemia in G6PD-deficient neonates. SnMP, regardless of its use preventively or therapeutically, was able to substitute entirely for PT in controlling hyperbilirubinemia associated with G6PD deficiency. As a result of the elimination of the need for PT in the SnMP-treated newborns, the age at closing the clinical monitoring of cases became the only criterion by which the preventive or therapeutic use of the inhibitor could be compared in the sequential intrapair analyses. In 22 of the 30 untied pairs, the age at closing was shorter by at least 1 day in the newborns randomized to the preventive arm of the trial (Table 1, Fig 2). This difference, although crucial in deciding the outcome of the sequential analysis, does not express fully, in clinical terms, the advantages of the preventive use of SnMP in G6PD-deficient neonates. There was no, or only faintly visible, jaundice in 52% and 16% of the newborns in the preventive and therapeutic arms, respectively (\(P = .0005\)). Consequently, if the preventive use of SnMP was to become routine in the management of G6PD-deficient neonates, for >50% of this population, there would be no clinical indication to measure the PBC level even once. In contrast, if SnMP was to be used therapeutically, >80% of the G6PD-deficient infants would need to be followed by measurement of the PBC level to determine who would develop hyperbilirubinemia significant enough to require clinical intervention.

In the trial reported here, the rate of PBC change in the 24 hours after administration of SnMP was decreased by 66%, from 2.99 ± 1.65 mg/dL to 1.02 ± 1.6 mg/dL (Table 2). This is comparable with the decrease documented with the same SnMP dose (6μmol/kg BW) in preterm infants and is similar to the effect of the preventive use of PT in G6PD-deficient neonates studied in Singapore. For PT, it may be argued that efficacy can be increased by using stronger sources of irradiance and multidirectional exposure. However, in our previous dose–effect study of SnMP, there was no evidence of an efficacy plateau having been reached with the single 6 μmol/kg BW dose used. Thus, variation of the dose, time of administration of SnMP, or repeat administrations of the inhibitor according to initial or subsequent rates of PBC increase and the etiology of jaundice can be envisioned such that efficacy of the agent would be enhanced if that is required. However, it is unrealistic to expect that interventions favorably altering neonatal bilirubin metabolism can totally replace ET in the management of marked hemolytic states in the neonate. In the presence of severe isoimmunization with rapid removal from the circulation of the antibody-coated red cells or massive red-cell age-independent oxidative injury of G6PD-deficient red cells after exposure to an exogenous hemolytic agent, prompt performance of ET will replace the vulnerable with normal red cells, thus eliminating the consequences of hemolyis.

The option of the preventive use of SnMP in neonates born in maternity units that test cord blood for G6PD deficiency is a potential management choice that merits comment. The cost-effectiveness of such a policy depends on the prevalence of G6PD deficiency and the associated spontaneous, severe neonatal hyperbilirubinemia in the population as well as on the postpartum length of stay. With cord blood screening, prolonged in-hospital observation and, when necessary, treatment of the G6PD-deficient neonates with PT, early discharge of the G6PD-normal and otherwise healthy neonates proved safe in Singapore, a population with a high incidence of kernicterus associated with G6PD deficiency in the past. For such populations, routine cord blood testing of G6PD activity and preventive use of SnMP would offer the advantages of simplicity and high efficacy in the control of hyperbilirubinemia. The more important question, concerning whether G6PD-deficient neonates receiving preventive SnMP...
would need to be monitored for the presence of hyperbilirubinemia, can be answered only after studies have been conducted in populations large enough to provide the statistical power necessary to exclude the possibility of additional interventions being needed in rare cases. Such a study currently is in progress at Matera Maternity Hospital.

The problem is more complex for many Northern European countries and for North America where, through immigration and intermarriage, the G6PD-deficiency gene has become established in the population. The prevalence of this enzyme deficiency and the related neonatal hyperbilirubinemia is so low in these infant populations that it would be difficult to justify testing the cord blood of all live births. Whether the type of G6PD deficiency common in the African-American population places such infants at special risk for spontaneous severe neonatal jaundice cannot be answered at present in the absence of adequate studies. However, it should be stressed that although the preventive use of SnMP offers clinical advantages over therapeutic administration of the inhibitor, the latter use of SnMP, as shown in this study, was equally effective in controlling hyperbilirubinemia to the extent that the need for supplemental PT was eliminated entirely.

The results of the trial reported here demonstrate, in another major population of newborns, the effectiveness of the HO inhibitor SnMP in controlling neonatal hyperbilirubinemia. Moreover, in the management of this neonatal problem in general, it is increasingly clear that interdicting bilirubin production offers distinct advantages over other interventions in which attempts are focused on disposing of the bile pigment after it has already reached threatening levels in the bloodstream. In the ongoing dilemma surrounding the bilirubin problem, inhibiting production of this potentially neurotoxic bile pigment in the immediate postnatal period carries a powerful logic, and the effectiveness of SnMP for this purpose, whether used therapeutically or preventively, is evident.

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