EFFICACY OF CLOFIBRATE ON SEVERE NEONATAL JAUNDICE ASSOCIATED WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY (A RANDOMIZED CLINICAL TRIAL)

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Abstract. Glucose-6-phosphate dehydrogenase (G6PD) deficiency may cause severe hyperbilirubinemia with bilirubin encephalopathy unless intervention is initiated. The aim of this study was to assess the efficacy of clofibrate in full term G6PD deficient neonates with jaundice. A randomized clinical trial study was performed in two groups of full term G6PD deficient jaundiced neonates (clofibrate treated group, n=21; control group, n=19). Infants in the clofibrate group received a single oral dose of 100 mg/kg clofibrate, whereas control group received nothing. Both groups were treated with phototherapy. Serum total and direct bilirubin levels were measured at the onset of treatments, 16, 24 and 48 hours later. On enrollment, the mean total serum bilirubin (TSB) level in the clofibrate treated group was 18.40 ± 2.41 and in the control group was 17.49 ± 1.03 (p= 0.401). At 16, 24 and 48 hours of treatment, the mean TSB in the clofibrate group were 15.2 ± 1.9, 12.6 ± 2.4, and 10.1 ± 2.4 and in the control group were 16.5 ± 1.2, 13.3 ± 2.2 and 11.4 ± 2.4, respectively (p=0.047). At 48 hours, 7 (33%) cases in the clofibrate group and one (5%) case in the control group were discharged with a TSB <10 mg/dl (p=0.031). No side effects were observed on serial examinations during hospitalization, or on the 1st and 7th days after discharge. The results show that clofibrate induces a faster decline in serum total bilirubin level, a shorter duration of phototherapy, and hospitalization with no side effects in full term G6PD deficient neonates with jaundice.

INTRODUCTION

Over the past 40 years, severe neonatal jaundice and kernicterus have emerged as the most important clinical manifestations of glucose-6-phosphate dehydrogenase (G6PD) deficiency and have been responsible for significant neonatal morbidity and mortality in populations of the Mediterranean littoral, the Middle East, the Arabian Peninsula, Southeast Asia, and Africa (Kappas *et al*, 2001). According to the WHO world map of G6PD deficiency, there is a 10-14.9% prevalence of G6PD deficiency in Iran (WHO, 1989). In the neonate, hyperbilirubinemia is usually due to increased production, decreased elimination and increased intrahepatic circulation of bilirubin or a combination of them (Rubaltelli, 1998; Dennery, 2002).

The pathogenesis of hyperbilirubinemia in approximately 30% of neonates affected by glucose-6-phosphate dehydrogenase

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deficiency is not clear (Iolascon *et al*, 1999). In these neonates, decreased conjugations are probably more important than hemolysis for causing jaundice (Murki *et al*, 2005). Five to 10 percent of all newborns require intervention for pathologic jaundice (Agrawal *et al*, 2001). Phototherapy is commonly used for the treatment of neonatal jaundice, whereas exchange transfusion has an important role in the treatment of hyperbilirubinemia of newborns in order to prevent kernicterus (Weisz *et al*, 1996).

Despite our understanding of the enzymatic pathways leading to bilirubin production and elimination, the role of some pharmacological agents like D-penicillamine, phenobarbital, metalloporphyrins and clofibrate may yet prove to be useful in the prevention or treatment of neonatal jaundice (Dennery, 2002). The safety and efficacy of this therapy needs to be confirmed prior to widespread use.

Clofibrate is an activator of peroxisome proliferators activated receptors (PPARs), and thus it affects lipid metabolism (Bourget *et al*, 1995; Brun *et al*, 1999). This drug can also increase bilirubin conjugation and excretion (elimination of bilirubin) (Kutz *et al*, 1984). In a double blind controlled study of infants without ABO incompatibility, 47 infants treated with a single oral dose of clofibrate demonstrated significantly lower bilirubin levels after 16 hours of treatment compared to 46 infants given corn oil alone(Lindenbaum *et al*, 1981). Clofibrate treatment also resulted in a shorter duration of jaundice and a reduced use of phototherapy in neonates with no risk factors for hemolytic jaundice (Lindenbaum *et al*, 1981, 1985; Mohammadzadeh *et al*, 2005). In this trial we evaluated the effectiveness of oral clofibrate in the treatment of hyperbilirubinemia in G6PD deficient term neonates.

MATERIALS AND METHODS

From February 2006 through July 2007, forty neonates with jaundice, admitted to the neonatal center of Amirkola Teaching Children Hospital, Babol University of Medical Science Iran, were enrolled in this study. This referral children hospital serves people living in the three cities located in the Province Mazanderan. The ethics committee of our university approved the study. After explanation of the purpose of our study to the parents, informed consent was obtained.

Inclusion criteria were G6PD deficient jaundiced babies, delivered between the 38th and 41st weeks of gestational age with a birth weight of ≥2,500 g, born from an uncomplicated pregnancy, had a total serum bilirubin (TSB) ≥15 and <20 mg/dl at >48 hours after birth. All the babies drank their own mother's milk. Exclusion criteria were hemolytic disease (Rh or ABO incompatibility), a positive Coombs' test, a conjugated bilirubin >1.5mg/dl or 15% of total serum bilirubin, dehydration, infection (congenital or acquired), and a history of phenobarbital intake by mother or infant.

The clinical examination, birth weight, sex, age and weight at enrollment, serial TSB, direct bilirubin and duration of phototherapy were recorded. Laboratory tests included a complete blood count, reticulocyte count, serum bilirubin level (total and direct), erythrocyte glucose-6-phosphate dehydrogenase (G6PD) level, T_4 and TSH. Total and direct serum bilirubin were estimated by the Jendrassic Grof colorimetric method. Red cell G6PD activity expressed as units/gram of hemoglobin was determined with the use of the Chem Enzyme (reagent kit and procedure). The critical level for diagnosing G6PD deficiency was <7.5 U/g of hemoglobin. Sample size were calculated by using one type error of 5%, a power test of 80%, a case group variance $(1.75)^2$, control group variance$(1.5)^2$ and a difference between the mean bilirubin levels in the two groups of 1.2 mg/dl.

The subjects were divided randomly into two groups, the clofibrate group (*n*=21) and

the control group (n=19). Infants in the clofibrate group received a single oral dose of clofibrate (100 mg/kg) whereas those in the control group received nothing. All neonates in both groups received phototherapy. Each phototherapy unit consisted of 4 special blue lamps (made by Philips, Germany) and adjusted to 25 cm above the infant cot. Total and direct serum bilirubin levels were determined at the beginning of treatment, at 16, 24 and 48 hours after phototherapy. Bilirubin levels were measured until the TSB declined to less than 10 mg/dl, the level at which phototherapy was discontinued and the babies were discharged. All infants in this study were examined during hospitalization and 1 and 7 days after discharge from the hospital at the outpatient clinic to evaluate for jaundice or any side-effects of the drug.

Data were analyzed with SPSS version 13. Numerical variables were compared between the two groups using the t-test and Fisher exact test. Outcomes of therapy were compared using the chi-square test. P-values of less than 0.05 were considered statistically significant.

RESULTS

In the clofibrate group 21 neonates with a mean birth weight of 3,195.2± 403.7 g, and in the control group 19 neonates with a mean birth weight of 3,326.3±553.6 g were evaluated (p>0.05). The demographic features and mean total bilirubin levels at the time of enrollment in these two groups are shown in Table 1.

Table 1
Demographics and bilirubin levels at enrollment in the control and clofibrate groups.

Demographic/ Plasma bilirubin level	Control group (n= 19) Mean ± SD	Clofibrate group (n=21) Mean ± SD	p-value
Weight at enrollment (g)	3,326.3 ± 553.6	3,195.2 ± 403.7	0.643
Age at enrollment (days)	4.37 ± 1.77	5.81 ± 2.54	0.362
Bilirubin at enrollment (mg/dl)			
Total	17.49 ± 1.03	18.40 ± 2.41	0.199
Direct	0.77 ± 0.16	0.80 ± 0.20	0.158

Table 2
The mean plasma bilirubin level during treatment in the control and clofibrate groups.

Plasma bilirubin level (mg/dl)	Control group (n=19) Mean±SD	Clofibrate group (n=21) Mean ±SD	p-value
16th hr bilirubin			
Total	16.5 ± 1.2	15.2 ±1.9	0.019
Direct	0.694 ± 0.131	0.676 ± 0.117	0.74
24th hr bilirubin			
Total	13.3 ± 2.2	12.6 ± 2.4	0.026
Direct	0.62 ± 0.09	0.57 ± 0.09	0.24
48th hr bilirubin			
Total	11.4 ± 2.4	10.1 ± 2.4	0.026
Direct	0.52 ± 0.05	0.55 ± 0.08	0.191

The mean TSB in the Clofibrate group was significantly lower than the control group by 16, 24 and 48 hours of treatment (Table 2). At the end of 48 hours, 7 (33%) neonates in the clofibrate-treated group and 1 (5%) neonate from the control group were discharged (TSB<10mg/dl, p=0.031). On serial examinations during hospitalization, and at 1 and 7 days after discharge from the hospital, no side effects were seen. None of the neonates in either group needed to be re-hospitalized after discharge.

DISCUSSION

In this study we found that clofibrate had a significant effect on the reduction of total serum bilirubin in severe neonatal jaundice associated with glucose-6-phosphate dehydrogenase deficiency. The present study may be the first clinical study which shows the beneficial effects of this agent for reducing bilirubin levels in jaundiced babies due to G6PD deficiency and decreasing the hospital stay in these neonates. Other investigators have shown the efficacy of clofibrate and phenobarbital in neonatal jaundice without any risk factors such as Rh or ABO incompatibility or G6PD deficiency (Caballero et al, 2001). The results of our study emphasize the efficacy of clofibrate in neonatal jaundice with the risk factor as G6PD deficiency, a finding that has not been reported previously. Other studies in Iran and France have confirmed the benefit effect of clofibrate for reducing of TSB in babies with no risk factors for hemolysis (Lindenbaum et al, 1981; Mohammadzadeh et al, 2005; Zahedpasha et al, 2007). In the present study, administration of a single dose of clofibrate was well tolerated and no side effects were observed during our follow-up of the infants up to 7 days after discharge from the hospital. This finding is in agreement with the work of Mohammadzadeh et al (2005) and Bourget et al (1995) who demonstrated that a single dose of 50-100 mg/kg of clofibrate was well tolerated with no side effects (Bourget et al, 1995; Mohammadzadeh et al, 2005).

Clofibrate in adults when used as an antilipidemic agent has some side effects such as nausea, gastrointestinal disturbances, vomiting and loose stool. Other possible complications include muscle cramps, fatigue, pruritus, and alopecia (Steiner et al, 1991). In the neonatal study with a single dose of clofibrate none of these side effects were reported (Lindenbaum et al, 1981; Mohammadzadeh et al, 2005). Similar to phenobarbital, clofibrate increases bilirubin conjugation and excretion as well as being a better enhancer of glucuronosyl transferase induction causing 100% increase of hepatic bilirubin clearance within 6 hours (Gabilan, 1998).

Phenobarbital has a long half-life and its effects on severe jaundice are questionable (Dennery, 2002). Phenobarbital also causes drowsiness in neonates and may alter the oxidation of bilirubin in the brain leading to worse bilirubin toxicity (Hansen and Tommarello, 1998). Some new pharmacological agents are also utilized in the prevention and treatment of neonatal jaundice. Tin protoporphyrin and Sn-mesoporphyrin are hemoxygenase inhibitors used successfully either for prevention or treatment of jaundice in neonates suffering from glucose-6-phosphate dehydrogenase deficiency in two randomized-sequentially analyzed trials of term and near term infants, however, it is not yet available outside research protocols (Valaes et al, 1999; Kappas et al, 2001). In this study we found a single dose of clofibrate caused a dramatic decrease in serum total bilirubin and a shorter duration of phototherapy and hospitalization with no side effects in full term G6PD deficient neonates with jaundice.

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REFERENCES

Agrawal R, Aggarwal R, Deorari AK, Paul VK. Jaundice in the newborn. *Indian J Pediatr* 2001; 68: 977-80.

Bourget P, Broise I, Quinquis-Desmaris V, Gabilan JC. Pharmacokinetics of clofibrate in jaundiced newborn infants at term. *Arch Pediatr* 1995; 2: 722-8.

Brun S, Carmona MC, Mampel T, *et al.* Activators of peroxisome proliferator-activated receptor-alpha induce the expression of the uncoupling protein-3 gene in skeletal muscle: a potential mechanism for the lipid intake-dependent activation of uncoupling protein-3 gene expression at birth. *Diabetes* 1999; 48: 1217-22.

Caballero NB, Hernandez PS, Rodriguez JBE, *et al.* Clofibrate effects associated with phototherapy on bilirubin concentration in newly-born babies. *Rev Mex Pediatr* 2001; 68: 176-80.

Dennery PA. Pharmacological interventions for the treatment of neonatal jaundice. *Semin Neonatal* 2002; 7: 111-9.

Gabilan JC. Pharmacologic treatment of neonatal jaundice. A new approach. *Arch Pediatr* 1998; 5: 1274-8.

Hansen TW, Tommarello S. Effect of phenobarbital on bilirubin metabolism in rat brain. *Biol Neonate* 1998; 73: 106-11.

Iolascon A, Faienza MF, Perrotta S, Meloni GF, Ruggiu G, Del Giudice EM. Gilbert's syndrome and jaundice in glucose-6-phosphate dehydrogenase deficient neonates. *Haematologica* 1999; 84: 99-102.

Kappas A, Drummond GS, Valaes T. A single dose of Sn-mesoporphyrin prevents development of severe hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns. *Pediatrics* 2001; 108: 25-30.

Kutz K, Kandler H, Gugler R, Fevery J. Effect of Clofibrate on the metabolism of bilirubin, bromosulphophthalein and indocyanine green and on the biliary lipid composition in Gilbert's syndrome. *Clin Sci* (Lond) 1984; 66: 389-97.

Lindenbaum A, Hernandorena X, Vial M, *et al.* Clofibrate for the treatment of hyperbilirubinemia in neonates born at term: a double blind controlled study. *Arch Fr Pediatr* 1981; 38 (suppl 1): 867-73.

Lindenbaum A, Delaporte B, Benattar C, *et al.* Preventive treatment of jaundice in premature newborn infants with clofibrate. Double-blind controlled therapeutic trial. *Arch Fr Pediatr* 1985; 42: 759-

Mohammadzadeh A, Farhat ASh, Iranpour R. Effect of clofibrate in jaundiced term newborns, *Indian J Pediatr* 2005; 72: 123-6.

Murki S, Dutta S, Narang A, Sarkar U, Garewal G. A randomized, triple-blind, placebo-controlled trial of prophylactic oral Phenobarbital to reduce the need for phototherapy in G6PD-deficient neonates, *J Perinatol* 2005; 25: 325-30.

Rubaltelli FF. Current drug treatment options in neonatal hyperbilirubinaemia and the prevention of kernicterus. *Drugs* 1998; 56: 23-30.

Steiner A, Weisser B, Vetter W. A comparative review of the adverse effects of treatments for hyperlipidaemia. *Drug Saf* 1991; 6: 118-30.

Valaes T, Drummond GS, Kappas A. Control of hyperbilirubinemia in glucose-6-phosphate dehydrogenase-deficient newborns using an inhibitor of bilirubin production, Sn-mesoporphyrin. *Pediatrics* 1999; 103: 536-7.

Weisz B, Belson A, Milbauer B, Reif S. Complications of exchange transfusion in term and preterm newborns. *Harefuah* 1996;130:170-3.

World Health Organization. Working group, World map of G6PD deficiency. Geneva: WHO, 1989; 67: 601.

Zahedpasha Y, Ahmadpour-Kacho M, Hajiahmadi M, Naderi S. Effect of clofibrate in jaundiced full-term infants: a randomized clinical trial. *Arch Iran Med* 2007; 10: 349-53.