Original Article

Iran J Ped
June 2007, Vol 17 (No 2), Pp:108-112

Determination of effect of low dose vs moderate dose clofibrate on decreasing serum bilirubin in healthy term neonates

Mohammad Ashkan Moslehi [1*], MD; Narges Pishva[1], MD

1. Department of Pediatrics, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, IR Iran

Received: 25/12/06; Revised: 5/03/07; Accepted: 20/04/07

Abstract

Objective: This study was performed to determine the effect of low doses (25 mg/Kg) vs. moderate doses (50 mg/Kg) of clofibrate in treatment of non-hemolytic hyperbilirubinemia in healthy term neonates.

Material & Methods: A clinical randomized controlled trial was performed in three groups of healthy term neonates. One group was treated with a single low dose of clofibrate (25 mg/Kg) while another group received a single moderate dose (50mg/kg) both orally plus phototherapy; the results were compared with those of a control group that received only phototherapy.

Findings: The mean total serum bilirubin (TSB) levels of 12th and 24th hours were significantly lower in the two clofibrate-treated groups as compared with the control group (P=0.002 and P=0.003, respectively). There was no statistically significant difference between the mean of TSB levels in the two clofibrate-treated groups. Treatment with clofibrate also resulted in a shorter duration of jaundice and a decreased use of phototherapy (P=0.01). No side effects were observed.

Conclusion: The present study demonstrated that there was no significant difference between a low (25mg/Kg) and moderate (50mg/Kg) doses of clofibrate in reducing TSB levels and also decreased need of phototherapy in healthy breastfed term newborns with marked hyperbilirubinemia (TSB>16 mg/dL).

Key Words: Clofibrate, Neonatal hyperbilirubinemia, Phototherapy, Jaundice

Introduction

Neonatal hyperbilirubinemia is a frequent occurrence during the neonatal period. It is the most common condition requiring medical attention in newborns. Phototherapy has been used world-wide in the treatment of mild hyperbilirubinemia in newborn infants[1].

*** Correspondence author**
Address: Department of Pediatrics, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail: moslehim@sums.ac.ir

Although some pharmacological agents oral charcoal, metalloporphyrins and clofibrate are suggested to treat neonatal jaundice, further studies are needed to confirm the safety and efficacy of these drugs prior to their routine clinical use[2].

Clofibrate is an activator of peroxisome proliferator-activated receptors (PPARs), hence decreases serum cholesterol and triglyceride levels and has been used for many years as an effective hypolipidemic agent in adults[3]. Clofibrate also is a glucuronyl transferase inducer and can increase bilirubin conjugation and excretion[4]. This drug has been proposed for prevention and treatment of neonatal hyperbilirubinemia[5,6]. Clofibrate, when used as an antilipidemic agent in adults, has some side effects such as nausea, gastro-intestinal disturbance, vomiting and loose stools. Other possible complications are muscle cramping, fatigue, pruritus, and alopecia[5]. In the neonatal study with a single dose of clofibrate, none of these side effects were reported[7]. In a double blind controlled study on the therapeutic effect of clofibrate in full term infants with non-hemolytic hyper-bilirubinemia[8]. Mohammadzadeh et al determined the effect of optimal doses (100 mg/kg) of clofibrate on TSB levels in term infants with non-hemolytic hyperbilirubinemia for the first time in Iran[9]. The aim of the present study was to compare the effects of a low dose (25 mg/Kg) versus a moderate dose (50 mg/Kg) oral clofibrate in treatment of non-hemolytic hyperbilirubinemia in healthy term neonates.

Material & Methods

From March 2006 to July 2006, 90 neonates with jaundice who were admitted to the Neonatal Ward of Nemazee Hospital, affiliated to Shiraz University of Medical Sciences in southern Iran, entered our study.

The study included healthy, full term neonates (between 38th and 41th week of gestational age), with a birth weight of 2500-3500 gr, breastfed, and having a total serum such as D-penicillamine, henobarbital, agar, bilirubin between 17-24.9 mg/dL. The excluding criteria were presence of any congenital anomaly, hemolytic disease (Rh or ABO incompatibility and a positive Coombs test), infection (congenital or acquired), dehydration, glucose-6-phosphate dehydrog-anase (G6PD) deficiency, conjugated bilirubin >2.0 mg/dL or TSB>25 mg/dL.

Written consent was provided from patients' parents. The neonates were allocated to three equal groups of 30 neonates by a simple randomization method using a table of random numbers. Group one was the control group and the other two groups consisted of treatment cases. Group two was treated with a low dose (25 mg/Kg) and the last group received a moderate dose (50 mg/Kg) of clofibrate (administered orally in a mixture of corn oil) ½ hour before breast feeding.

All neonates in the three groups received standard phototherapy. Each phototherapy unit contained six special white lamps and was adjusted to 20 cm above the infant's cot. The lamps were changed regularly after 250 hours of usage.

Serum total and direct bilirubin levels were measured at the beginning and every 12 hours in the first 24 hours of treatment. Other laboratory investigations included a complete blood count, blood group typing of neonates and their mothers, direct Coombs test (DCT), reticulocyte count, serum bilirubin level (total and direct) and erythrocyte G6PD activity.

The findings of the clinical examination, gestational age, birth weight, sex, age and weight at admission, serial TSB levels, and duration of phototherapy were recorded. TSB levels were determined using a Unistat® Bilirubinometer (Reichert-Jung, Germany). Direct bilirubin was estimated by the colori-metric method of Lathe and Ruthven. All infants in this study were examined 2 days after discharge in the outpatient clinic for icterus and any eventual side effects of the drug.

Data were analyzed using SPSS soft ware version 13 for Windows. P values less than 0.05 were considered statistically significant.

Findings

The minimum of age in all groups was 3 days and maximum 15 days. The mean age in group one was 5.3±1.87 days, in group two 5.25±1.99 days, and in group three 5.18±2.03 days. Of the total 90 infants, 30 neonates (16 boys, 53.3%; 14 girls, 46.7%) were considered as the control group, 30 neonates (17 boys, 56.7%; 13 girls 43.3%) assigned to the low dose, and finally 30 neonates (14 boys, 46.7%; 16 girls, 53.3%) to the moderate dose of clofibrate-treated group. The minimum of birth weight in all groups was 2500 and the maximum 3500 gr. There was no statistically significant difference between the groups regarding sex, birth weight, gestational age, reticulocyte count, hematocrit, hemoglobin and TSB levels at enrollment distribution (P=0.1). Except for jaundice, the infants were healthy and did not show any evidence of hemolytic disease. Thus the three (two clofibrate-treated and one control) groups were comparable (Table 1).

The mean of TSB levels in low and moderate doses of clofibrate-treated groups were statistically less than those in control group after 12 and 24 hours (P=0.002 and P=0.003, respectively) (Table 2). There was no statistically significant difference between the mean levels of TSB in the low and moderate doses of clofibrate-treated groups (P=0.1).

None of neonates in treated groups required phototherapy after 18 hours but 15 neonates (50%), 10 neonates (33.3%) and 5 neonates (16.6%) in the control group received phototherapy up to 24, 48 and 60 hours, respectively.

The duration of phototherapy significantly reduced with clofibrate administration from 38 (±14.8) hours in the control group to 14 (±12.9) hours in the low dose clofibrate-treated group and 14 (±12.6) hours in the moderate dose clofibrate-treated group (P=0.01) (Table 2). There was no statistically significant difference between the duration of phototherapy in the two clofibrate-treated groups (P=0.4).

Table 1: Patient characteristics in three groups of neonates

Variables	*Control (n=30)*	*Clofibrate-treated (Low dose) (n=30)*	*Clofibrate-treated (Moderate dose) (n=30)*	*P-value*
Males in each group (n)	16	17	14	NS*
Gestational age (weeks)	39.3±1.2	38.4±1.5	38.8±1.9	NS
Birth weight (gms)	2539±585	2564±428	2525±628	NS
Reticulocyte count (% of RBCs)	1.2±0.95	1.1±0.33	1±0.38	NS
Hemoglobin (g/dL)	16.8±1.4	17.3±2.2	16.6±1.8	NS
Hematocrit (%)	50.4±5.45	51.3±5.63	50.1±5.40	NS
Age (days)	5.31±1.87	5.25 ±1.99	5.18 ± 2.03	NS
TBS levels (mg/dL) on admission	17.6±1.4	17.7±1.3	17.6±1.5	NS
Direct bilirubin levels (mg/dL)	0.4±0.25	0.5±0.17	0.5±0.19	NS
G6PD levels	Normal	Normal	Normal	NS

* NS: non-significant

Table 2: Outcome of phototherapy in three groups of neonates

Variables	*Control (n=30)*	*Clofibrate-treated (Low dose) (n=30)*	*Clofibrate-treated (Moderate dose) (n=30)*	*P-value*
TBS levels (mg/dL) after 12 hrs	14.1±1.45	11.2±1.46	11.49±1.32	0.002
TBS levels (mg/dL) after 24 hrs	11.5±1.05	6.8±1.11	6.7±0.96	0.003
Duration of phototherapy (hrs)	25.3±4.4	14.2±1.2	14.7±1.5	0.01

On serial examination during hospitalization and 2 days after discharge in the outpatient clinic, no side effects were observed. None of the neonates in both clofibrate-treated groups needed exchange transfusion and hyperbilirubinemia was simply controlled with phototherapy.

Discussion

A clinical controlled study of the therapeutic effect of low dose clofibrate (25mg/Kg), an inductor of bilirubin glucuronyl transferase, was performed in neonates born at term and presenting with physiologic jaundice.

The present study demonstrated that there was no significant difference between a low (25 mg/Kg) or moderate (50 mg/Kg) single dose of clofibrate in significantly reducing indirect bilirubin levels after 6 hours of treatment compared to control group and also decreases phototherapy requirement in healthy breastfed term newborn with marked hyperbilirubinemia (TSB>16 mg/dl).

Clofibrate is a better enhancer of glucuronosyl transferase induction than phenobarbital and causes 100% increase of hepatic bilirubin clearance within 6 hours. In the treatment of early jaundice in term neonates, it significantly reduces hyperbilirubinemia in 16 hours, and decreases the intensity and duration of jaundice and also phototherapy requirement[7]. Phenobarbital has a long half-life and its immediate effects in severe jaundice are questionable[3]. In addition, phenobarbital causes drowsiness in infants and also worsens bilirubin toxicity by alteration of bilirubin oxidation in the brain[7]. Although recent clinical trials have shown that a single dose of the tin-mesoporphyrin (SnMP), a hemoxygenase inhibitor, has the best efficacy with minimal side effects when used prophylactically in premature infants and also curatively in full-term neonates, it is not yet manufactured outside research protocols[10].

The limits of our study were that we could not measure serum clofibrate levels in treatment doses. Also the long term effect of this drug in high-risk infants such as prematures is still unclear and needs to be estimated with further studies.

Conclusion

These findings are consistent with the results of other studies that have demonstrated the efficacy of clofibrate in decreasing of indirect hyperbilirubinemia, but demonstrated that lower doses of clofibrate can be used with the same therapeutic efficacy in reducing TSB levels in term infants with non-hemolytic hyperbilirubinemia. Thus for decreasing TSB levels in healthy term neonate we can use lower doses of clofibrate with low side effects instead of higher doses.

Acknowledgment

The authors would like to thank the Office of

Vice Chancellor for Research of Shiraz University of Medical Sciences for financial support of this study.

We would also like to express sincere appreciation to Ms. Shadab Moslehi for her grammatical support of this study.

References

1. Hosono S, Ohno T, Kimoto H, et al. Effects of albumin infusion therapy on total and unbound bilirubin values in term infants with intensive phototherapy. Pediatr Int. 2001; 43(1):8-11.
2. Dennery PA. Pharmacological interventions for the treatment of neonatal jaundice. Semin Neonatol. 2002;7(2):111-9.
3. Brun S, Carmona MC, Mampel T, et al. Activators of peroxisome proliferator-activated receptor-alpha induce the expression of the uncoupling pritein-3 gene expression at birth. Diabetes. 1999; 48(6):1217-22.
4. Kutz K, Kandler H, Gugler R, et al. Effect of clofibrate on the metabolism of bilirubin, bromosulphophthalein and indocyanine green and on the biliary lipid composition in Gilbert's syndrome. Clin Sci. 1984;66(4):389-97.
5. Lindenbaum A, Delaporte B, Benattar C, et al. Preventive treatment of jaundice in Preterm newborn infants with clofibrate. Double blind controlled therapeutic trial. Arch Fr Pediatr. 1985;42(9):759-63.
6. Bourget P, Broise I, Quinquis-Desmaris V, et al. Pharmacokinetics of clofibrate in jaundiced newborn infants at term. Arch Perdiatr. 1995;2(8):722-8.
7. 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.
8. Gabilan JC. Pharmacologic treatment of neonatal jaundice. A new approach. Arch Pediatr. 1998;5(11):1274-8.
9. Mohammadzadeh A, Farhat ASh, Iranpour R. Effect of clofibrate in jaundiced term newborns. Indian J Pediatr. 2005;72(2): 123-6.
10. Bhutani VK, Johnson LH. Newborn jaundice and kernicterus- health and societal perspectives. Indian J Pediatr. 2003;70(5):407-16.