The effect of low and moderate doses of clofibrate on serum bilirubin level in jaundiced term neonates

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***Aim*: This study was performed to determine the effect of low (25 mg/kg) and moderate doses (50 mg/kg) of clofibrate in the treatment of nonhaemolytic hyperbilirubinaemia in term healthy neonates.**

***Methods*: A randomised controlled trial was performed in three groups of healthy term neonates. All three groups received phototherapy. The treatment groups received a single oral dose of clofibrate (either 25 or 50 mg/kg). The control group received only phototherapy.**

***Results*: There was no significant clinical difference between the three groups with similar bilirubin levels. The mean total serum bilirubin (TSB) levels at 12 and 24 hours (h) were significantly lower in the two clofibrate-treated groups as compared with the control group (*t*-test, $P = 0.002$ and $P = 0.003$, respectively). There was no statistically significant difference between the mean 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 (*t*-test, $P = 0.01$). No side effects were observed.**

***Conclusions*: Low doses of clofibrate are as effective as moderate doses in the treatment of healthy term breastfed newborns with marked hyperbilirubinaemia.**

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Introduction

Hyperbilirubinaemia is common in the neonatal period. Approximately 60% of full term and 80% of premature infants develop jaundice during the first week of life. It is the most common condition requiring medical attention in newborns. Phototherapy is used worldwide in the treatment of mild hyperbilirubinaemia in newborn infants[1].

Although some pharmacological agents such as D-penicillamine, phenobarbital, agar, oral charcoal, metalloporphyrins and clofibrate have been 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. It decreases serum cholesterol and triglyceride levels and has been used for many years as an effective hypolipidaemic agent in adults[3]. Clofibrate is also a glucuronosyl transferase inducer and can increase bilirubin conjugation and excretion[4]. A single dose of clofibrate (100 mg/kg) has been proposed for

the prevention and treatment of neonatal hyperbilirubinaemia[5, 6]. Clofibrate in adults when used as an antilipidaemic agent has some side effects such as nausea, gastrointestinal disturbances, vomiting and loose stools. Other possible complications are muscle cramps, fatigue, pruritus, and alopecia[5]. In the neonatal study with a single high dose of clofibrate, none of these side effects were reported[7]. One double blind controlled study in full term infants with non-haemolytic hyper-bilirubinaemia suggested that a lower dose (50 mg/kg) was effective[8].

Our hypothesis was that low dose oral clofibrate (25 mg/kg) is as effective as a moderate dose (50 mg/kg). We therefore performed this study to directly compare these doses.

Methods

From March 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. Written consent was provided from each patient's parents and the study was approved by the University Ethical Committee.

The inclusion criteria were healthy and term neonates (between 38 and 41 weeks gestational age), breastfed, with a total serum bilirubin (TSB) level between 17.1 and 24.9 mg/dl (292 and 425 µmol/l) and a birth weight between 2500 and 3500 g.

The exclusion criteria were the presence of any congenital anomaly, haemolytic disease (Rh or ABO incompatibility and a positive Coombs' test), infection (congenital or acquired), dehydration, G6PD deficiency, and conjugated bilirubin >2.0 mg/dl (34 µmol/l) or TSB >25 mg/dl (427 µmol/l).

The neonates were allocated to three equal groups of 30 by a simple randomisation method using a table of random numbers. The random numbers were computer generated and slips bearing the allocated group were placed in serially numbered, opaque, sealed envelopes.

Group one was the control and the other two groups received treatment with clofibrate. In group two, a single dose of clofibrate (25 mg/kg, low dose) and in group three a single dose (50 mg/kg, moderate dose) of the drug was administrated orally in a mixture of corn oil, 30 minutes 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 infants' cots. The lamps were changed regularly after 250 hours of usage (Tosan Company, 2006, Iran).

A single neonatologist performed physical examinations and obtained blood specimens from all of the infants. After cleaning the site with Betadine solution, 100 µl of blood was withdrawn and serum total and direct bilirubin levels were measured at the beginning, and at 12 and 24 hours (h). Laboratory investigations included a complete blood count, blood group typing of neonates and their mothers, direct antibody tests, reticulocyte count, serum bilirubin level (total and direct) and erythrocyte G6PD level.

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 (a stat photometric analyser for determining total bilirubin concentration in newborn infants, Reichert-Jung, Germany). The determination of direct bilirubin was made by the colorimetric method of Lathe and Ruthven.

All infants in this study were examined by a single neonatologist during hospitalisation and two days after discharge in the outpatient clinic for evaluation of their jaundice and any side effects of the drug. The side effects, if present were recorded in a checklist by the neonatologist.

Data were analysed using SPSS software version 13 for Windows. Analysis of variance (ANOVA) was used to compare clinical characteristics of the three groups. Student's *t*-test was used to compare the effects of treatment with the control group or to compare low and moderate doses. *P* values of less than 0.05 were considered statistically significant.

Results

The mean age in all three groups was 5 days (range 3–15 days). All 90 neonates were term, healthy and breastfed, with no evidence of haemolytic disease. There was no statistically significant difference between the three groups regarding age, sex, birth weight, gestational age, reticulocyte count, haematocrit, haemoglobin and TSB levels at enrolment distribution (ANOVA, $P = 0.15$) (Table 1).

The mean TSB levels in the low and moderate doses of clofibrate-treated groups were significantly less than the control group after 12 and 24 h (*t*-test, $P=0.002$ and $P=0.003$, respectively) (Table 2). There was no statistically significant

Table 1 Patient characteristics

Parameters	Control	Clofibrate-treated (low doses)	Clofibrate-treated (moderate doses)
	(*n*=30)	(*n*=30)	(*n*=30)
Males	16	17	14
Gestational age (weeks)	39.3±1.2	38.4±1.5	38.8±1.9
Birth weight (g)	2539±585	2564±428	2525±628
Reticulocyte count (% RBCs)	1.2±0.9	1.1±0.3	1.0±0.4
Haemoglobin (g/dl)	16.8±1.4	17.3±2.2	16.6±1.8
Haematocrit (%)	50.4±5.5	51.3±5.6	50.1±5.4
Age (days)	5.3±1.9	5.2 ±2.0	5.2 ± 2.0
TBS on admission*	17.6±1.4	17.7±1.3	17.6±1.5
Direct bilirubin*	0.4±0.3	0.5±0.2	0.5±0.2
G6PD levels	Normal	Normal	Normal

Data shown are mean ± SD.
*Bilirubin levels are shown as mg/d.l

difference between the mean TSB in the low and moderate doses of clofibrate-treated groups (*t*-test, *P*=0.16).

None of the neonates in the groups that received clofibrate required phototherapy after 18 h. 15 neonates (50%) in the control group received phototherapy for 24 h or more (five needed 48 h and five needed 60 h). The duration of phototherapy significantly decreased with clofibrate administration in the two treated groups compared with the control group (*t*-test, *P*=0.01) (Table 2). There was no statistically significant difference between the duration of phototherapy in the two clofibrate-treated groups (*t*-test, *P* =0.48).

On serial examination during hospitalisation and two days after discharge in the outpatient clinic, no side effects were observed. None of the neonates needed exchange transfusion.

Discussion

The present study was performed to compare the therapeutic effect of low and moderate doses of clofibrate in neonates born at term and presenting with physiological jaundice. Our study demonstrated that both low (25 mg/kg) and moderate (50 mg/kg) single doses of clofibrate achieve a significant reduction of indirect bilirubin levels after treatment. This results in a decrease in the requirement for phototherapy.

Previous studies showed that clofibrate is an inducer of glucuronosyl transferase and causes 100% increase of hepatic bilirubin clearance within 6 h. Hence, clofibrate is considered for the treatment of early jaundice in term neonates[5-8]. Previous studies of doses of 50 and 100 mg/kg of clofibrate on TSB levels demonstrated efficacy in reducing bilirubin levels in neonates[8,9]. No previous study has evaluated the effect of a low dose of clofibrate.

Within a country such as Iran there are major advantages in reducing the stay in hospital for jaundiced babies who are otherwise healthy. There is always a shortage of beds and therefore early discharge allows other patients to be treated. From the parent's point of view, it is a lot easier, especially for mothers who have other children at home. There are also considerable financial savings for parents associated with an early discharge from hospital.

Although other recent clinical trials have shown that a single dose of the tin-mesoporphyrin (SnMP), a haemoxygenase 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 limitations of our study were that we were not able to measure serum clofibrate levels following treatment and also we were unable to evaluate any possible long term effects of this drug in high-risk infants such as premature infants. Further studies are needed to evaluate the long term safety of clofibrate.

Table 2 Clinical outcomes

Parameters	Control	Clofibrate-treated (low doses)	Clofibrate-treated (moderate doses)
	(*n*=30)	(*n*=30)	(*n*=30)
TBS after 12 h*	14.1±1.5	11.2±1.5	11.5±1.3
TBS after 24 h*	11.5±1.1	6.8±1.1	6.7±1.0
Duration of phototherapy (h)	25.3±4.4	14.2±1.2	14.7±1.5

Data shown are mean ± SD.
*Bilirubin levels are shown as mg/dl.

These findings are consistent with the results of other studies that have demonstrated the efficacy of clofibrate in decreasing the serum indirect bilirubin, but showed that lower doses of clofibrate can be used with the same therapeutic effect in term infants with non-haemolytic hyperbilirubinaemia. Thus, we can use lower doses of clofibrate that is beneficial in reduction of the possible long term side effects. There is still controversy on the potential risks involved in this treatment and other treatment regimens might also be considered.

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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;43:8-11.
2. Dennery PA. Pharmacological interventions for the treatment of neonatal jaundice. Semin Neonatol 2002;7:111-119.
3. 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;48:1217-2122.
4. 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 1984;66:389-397.
5. 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; 42:759-763.
6. Bourget P, Broise I, Quinquis-Desmaris V, Gabilan JC. Pharmacokinetics of clofibrate in jaundiced newborn infants at term. Arch Pediatr 1995; 2:722-728.
7. Gabilan JC. Pharmacologic treatment of neonatal jaundice. A new approach. Arch Pediatr 1998; 5:1274-1278.
8. Lindenbaum A, Hernandorena X, Vial M et al. Clofibrate for the treatment of hyperbilirubinaemia in neonates born at term: a double blind controlled study. Arch Fr Pediatr 1981;38:867-873.
9. Mohammadzadeh Ashraf, Farhat A Sh, Iranpour R. Effect of clofibrate in jaundiced term newborns. Indian J Pediatr 2005;72:123-126.
10. Bhutani VK, Johnson LH. Newborn jaundice and kernicterus – health and societal perspectives. Indian J Pediatr 2003;70:407-416.

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