

Fenofibrate: A novel approach in treating uncomplicated neonatal hyperbilirubinemia?

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Abstract:

Fenofibrate is one of the commonest drug to treat hyperlipidemia in adults (Marshall et al, 2011). However, apart from its hypolipidemic action, it also has the ability to induce bilirubin conjugation. The present study was aimed to find its effect on uncomplicated neonatal hyperbilirubinemia. The study was conducted on 40 normal term newborns who were admitted for uncomplicated jaundice at R.D. Gardi Medical College & Hospital, Ujjain from March 2010 to October 2010. The data included: age, sex, weight, serum bilirubin level, and duration of hospitalization. All newborns enrolled in this study, received phototherapy. The cases were divided into two groups viz. Fenofibrate group (B) consisting of 14 boys (70%) and 6 girls (30%) and a control group (A) with 11 boys (55%) and 9 girls (45%). There were no statistical overt differences between the two groups regarding sex distribution, age, weight and total serum bilirubin level at the time of admission. Mean values for total serum bilirubin in Fenofibrate group at 12, 24, 36, and 48 hours after starting of phototherapy were significantly lower than those for control group ($p < 0.001$). The mean time needed for phototherapy was also shorter in Group B than Group A. Fenofibrate appears to be an effective drug for neonatal hyperbilirubinemia. This decreases the duration of phototherapy and thus reduces the length of hospital stay.

Key Words: Fenofibrate, Serum Bilirubin, Neonates, Physiological Jaundice.

Introduction:

Destruction of R.B.C. and its haem component produces bilirubin which is then conjugated to a soluble form and excreted. In neonates, this becomes all the more significant because of high Red Cell mass and relative immaturity for bilirubin conjugation (Maisels & Kring, 2006). This free bilirubin deposits in the skin and mucous membranes and produces jaundice. It may also deposit in the brain where it has been implicated in causing transient dysfunction and, occasionally, permanent neuronal damage (Newman et al, 2006). "Kernicterus" refers to neurological consequences of the deposition of unconjugated bilirubin in brain tissue by damaging and scarring of the basal ganglia and brain stem nuclei (American Academy of Pediatrics, 2004). Clinicians usually suffer from "Vigintiphobia" i.e. a bilirubin level of more than 20mg/dl where there may be a high probability of development of "Kernicterus" (Harris & Roth, 1989).

There are several non pharmacological and pharmacological modalities for treating hyperbilirubinemia. Phototherapy has emerged as the most

widely used non pharmacological therapy for the treatment and prophylaxis of neonatal unconjugated hyperbilirubinemia, but it has several untoward complications such as deleterious effect to eyes, high temperature, loose stool and bronze baby syndrome (Piazza & Stoll, 2008). Pharmacological agents introduced for treatment of unconjugated neonatal jaundice include Phenobarbitone (Stern et al, 1970), Metalloporphyrins and D-penicillamine (Piazza & Stoll, 2008) but, so far they have not been proved very effective and safe in clinical use (Dennery et al, 2002).

Fibrates have been used for several years as a hypolipidemic drug (Bennet & Brown, 2008). Fibrates also increase bilirubin conjugation and excretion via induction of glucuronyl transferase activity (Kutz et al, 1984). Its potency to induce bilirubin conjugation is many times more than Phenobarbitone (Gabilan et al, 1990). The effect of Clofibrate on uncomplicated hyperbilirubinemia was proposed in some studies (Bourget et al, 1995; Mohammadzadeh et al, 2005).

Mohammadzadeh et al (2005) studied Clofibrate effect on reducing serum bilirubin level of neonates beyond the first week of life. Clofibrate, however, is no longer routinely used for hyperlipidemia in adults due to its adverse effect profile. Fenofibrate is now the most widely used fibrate in treating

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hyperlipidemia and has a comparatively much better safety profile than clofibrate (Scott et al, 2009). The present study was designed to assess the effect of Fenofibrate on uncomplicated hyperbilirubinemia of neonates during the first week of life.

Material and Methods:

This study was under taken from March 2010 to October 2010, at R.D. Gardi Medical College & Hospital, Ujjain (M.P.). Ethical committee approval was taken vide no. 68 dated 05/02/2010.

A total of 40 neonates were enrolled in this study after excluding jaundiced newborns presenting with infection, ABO or Rh incompatibility, G6PD deficiency, conjugated bilirubin above 2 mg/dl or exceeding 15% of total serum bilirubin (TSB) and congenital anomalies. All selected neonates were born at term (with gestational age of 38 to 41 weeks), breastfed, had total serum bilirubin (TSB) levels between 15 to 21.7 mg/dl and body weight between 2500gm to 3500gm.

These neonates were randomly allocated to the control group (A) and Fenofibrate group (B) with the permission of their parents and the ethical committee of hospital. Both groups received phototherapy under standard conditions with 4 special white 420-480 nanometer lamps, adjusted to about 30 centimeters above the neonate. Group B received a single oral dose of 10 mg/kg of nonmicronized Fenofibrate.

Blood samples were withdrawn immediately after admission and before starting any treatment from both the groups for laboratory tests such as complete blood count (CBC), total bilirubin (direct and indirect), reticulocyte count, Coomb’s test, G6PD assay and blood group (ABO and Rh of neonates and their mothers). Total serum bilirubin and indirect bilirubin were measured every 12 hours till the end of phototherapy. Statistical analysis of data was performed by unpaired *t* test and paired *t* test.

Results:

All the 40 newborns enrolled in the present study received phototherapy which included 14 boys (70%) and 6 girls (30%); in the Fenofibrate group, and rest of them were included in the control group with 11 boys (55%) and 9 girls (45%). There was no statistical overt difference between the two groups regarding sex, age, weight and Total serum bilirubin at the time of admission (Table I).

Table I: Age, Weight and total serum bilirubin in two group with neonatal hyperbilirubinemia.

Parameter	Control Group (A)	Fenofibrate Group (B)	<i>t</i> value	<i>p</i> value
Mean Age (Day)	4.60 ± 0.27	5.15±0.22	-1.59	0.12
Mean Weight (gm)	2857 ± 0.045	2808±0.051	0.73	0.47
Mean Total Serum Bilirubin (mg/dl)	19.06 ± 0.26	19.25±0.30	0.47	0.64

There was no persistent hyperbilirubinemia. The mean values for TSB at 24th, 36th and 48th hours after admission in group B were significantly less than group A (Table II).

All neonates in group B, after 48 hours of starting the treatment did not need phototherapy (Fig. I). But in group A, 9 out of 20 neonates needed it for 72 hours and 4 neonates for 96 hours. During hospitalization, and 48 hours after discharge, none of the neonate demonstrated any complication. All neonates were followed for a period of a month, and no complication was found in them.

Table II: Plasma bilirubin values during treatment in control and Fenofibrate group.

Time (Hours)	Control Group (A) Plasma Bilirubin (mg/dl)	Fenofibrate Group (B) Plasma Bilirubin (mg/dl)	<i>t</i> value	<i>p</i> value
0	19.06±0.26	19.25±0.30	0.47	0.64
12 th	18.81±0.24	18.55±0.27	0.73	0.47
24 th	18.33±0.23	17.32±0.25*	2.98	0.005
36 th	17.75±0.23	15.88±0.27*	5.32	<0.001
48 th	16.82±0.22	14.45±0.23*	7.33	<0.001

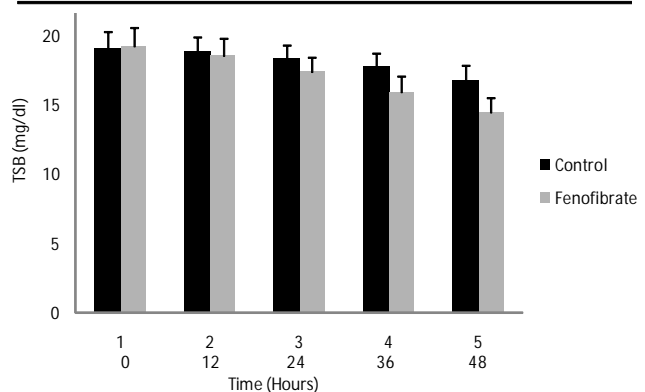


Fig. I: Plasma bilirubin values during treatment in control and fenofibrate group.

Discussion:

In the present study, the effect of combination therapy of single oral dose of Fenofibrate (10mg/kg)

and phototherapy (Group B) was compared with phototherapy alone (Group A) on TSB level.

Total serum bilirubin levels in group B at 24th, 36th and 48th hours after starting the treatment were significantly lower than those in group A. The mean time of phototherapy needed in group B was also lower than that in group A.

For uncomplicated unconjugated hyperbilirubinemia, phototherapy if unsuccessful, exchange transfusion remains the primary treatment modality to keep the total serum bilirubin level below the pathological levels (Piazza & Stoll, 2008). Intravenous immunoglobulin and metalloporphyrins are sometimes used prophylactically in cases of hyperbilirubinemia due to isoimmune haemolytic disease (Gottstein & Cooke, 2003; Kappas et al, 2001).

Although, unconjugated hyperbilirubinemia is a common neonatal problem, so far, very few drugs have been found to be effective in its treatment. Some of these drugs such as Phenobarbitone act by induction of the conjugation of bilirubin which makes the bilirubin soluble and thus fit for renal excretion. But, Phenobarbitone takes days to influence the enzyme and may produce sleepiness, sluggishness and feeding difficulty. It may also depress the respiratory centre. Compared to Phenobarbitone, Fibrates induce bilirubin conjugation much more effectively and readily converts unconjugated bilirubin to conjugated bilirubin, thus, hasten its clearance. Some studies have shown effectiveness of Clofibrate in treatment and prophylaxis of hyperbilirubinemia of infancy at a dose of >100 mg/kg (Mohammadzadeh et al, 2005). Fenofibrate is very similar to clofibrate in its mechanism of action. It is easily available, has a relatively much better safety profile and thus much safer to administer in pediatric age group than Clofibrate. Fenofibrate has some side effects in adults after prolonged use, such as gastrointestinal symptoms and muscle cramp (Bennet & Brown, 2008); in the neonatal period with a single dose of Fenofibrate, no side effects were observed in this study. No side effect in the patients was observed up to one month of follow up.

Conclusion:

The present study clearly shows that Fenofibrate decreases the time needed for phototherapy and lessens the duration of hospital stay. Thus, Fenofibrate appears to be an effective and probably safe drug for uncomplicated neonatal hyperbilirubinemia. Although, no side effects of Fenofibrates were observed after a single dose, further

studies with a more precise and longer follow up is needed for proving its safety to be used in the treatment of neonatal hyperbilirubinemia.

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