Relative roles of phototherapy and phenobarbitone in treatment of nonhaemolytic neonatal jaundice

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Wong, Y. K., and Wood, B. S. B. (1973). *Archives of Disease in Childhood*, **48**, 704. **Relative roles of phototherapy and phenobarbitone in treatment of nonhaemolytic neonatal jaundice.** Trials were carried out on 61 infants with plasma bilirubin over 15 mg/100 ml to compare effects of phototherapy alone, phenobarbitone by injection, and both treatments combined. Infants above 2.5 kg birthweight treated with phenobarbitone only behaved like untreated controls up to 60 hours, and only at 84 hours was a significant fall seen. Infants of 2.5 kg birthweight or less treated with phenobarbitone had significantly higher levels throughout the 84 hours of study. Phototherapy, either alone or combined with phenobarbitone, had its expected significant effect from 24 hours onwards in both groups of infants. Combined phototherapy and phenobarbitone treatment showed no difference from phototherapy alone. Phenobarbitone has no place in the management of established jaundice. Risks of phenobarbitone therapy and a possible explanation of contradictory results in previous trials are discussed. No changes were found in packed cell volumes, plasma albumin level, or residual albumin binding capacity at 48 hours from onset of treatment or between groups.

Since Trolle (1968a, b) suggested the use of phenobarbitone for treatment of neonatal hyperbilirubinaemia, a number of trials (Maurer *et al.*, 1968; Trolle, 1968b; Ramboer, Thompson, and Williams, 1969; Valaes, Petmezaki, and Doxiadis, 1970; Vest *et al.*, 1970; Stern *et al.*, 1970; McMullin, Hayes, and Arora, 1970; Yeung *et al.*, 1971) have shown that its administration to the mother before birth or to the infant soon after birth produced a significant reduction in plasma bilirubin levels from the 2nd to the 4th days of life. Phenobarbitone therapy started after the appearance of jaundice seemed to be far less effective, though some studies (Yeung and Field, 1969; Stern *et al.*, 1970; Sinniah, Tay, and Dugdale, 1971) have shown reduced need for exchange transfusions and lower plasma bilirubin levels, while others (Levin, McMullin, and Mobarak, 1970; Cunningham, Mace, and Peters, 1969) have found no significant difference.

The possible adverse effects of phenobarbitone on the neonate have been reviewed by Wilson (1969). There are theoretical risks that the liver cells affected by phenobarbitone may become more susceptible to hepatotoxic drugs or that an increase in microsomal

enzyme activity may accelerate the metabolism of certain drugs rendering them less effective (Burns, 1964; Fouts, 1964; Conney, 1967). Sexual and behavioural development might be affected as a consequence of possible alteration in steroid metabolism (Conney and Klutch, 1963; Kuntzman *et al.*, 1964; Kuntzman, Lawrence, and Conney, 1965). Large doses of barbiturates in mothers have also been reported to produce coagulation defects in newborn infants (Schulz and van Creveld, 1958; Mountain, Hirsh, and Gallus, 1970). As the excretion of barbiturates in the newborn is extremely variable (Melchior, Svensmark, and Trolle, 1967), significant levels may be present in some infants for days or weeks while others excrete the drug within 2 days. Intravenous barbiturates used for sedation in labour can affect the infant's ability to suck and lead to reduced milk intake (Kron, Stein, and Goddard, 1966). To date, however, no immediate or serious side effects have been reported from the clinical trials in which phenobarbitone was given to mothers and infants, though no long-term follow-up report has yet been published.

It was therefore decided to compare phenobarbitone treatment with phototherapy for the treatment of jaundice. Phototherapy has been

Roles of phototherapy and phenobarbitone in treatment of nonhaemolytic neonatal jaundice 705

shown to be effective (Broughton *et al.*, 1965; Lucey, Ferreiro, and Hewitt, 1968; Behrman and Hsia, 1969) even when treatment was not started until significant jaundice (plasma bilirubin > 15 mg/100 ml) had developed (Wong, Shuttleworth, and Wood, 1972). Furthermore, since the known mechanisms for reduction of jaundice by phenobarbitone and phototherapy are unrelated, it was decided to study the effect of these 2 treatments combined.

Materials and methods

Only those infants whose plasma bilirubin levels rose to 15 mg/100 ml and above were included. Infants with the following conditions were excluded. (i) Infants with rhesus haemolytic disease. (ii) Group A or B infants whose mothers were group O. (iii) Infants of diabetic mothers. (iv) Breast-fed infants. (v) Infants with any evidence of infection. Infants weighing 2.5 kg or less at birth were considered separately. The babies were allocated to one of three regimens by random selection.

- I. Phototherapy for 60 hours.
- II. Administration of phenobarbitone sodium BP by 3 daily intramuscular injections at a dosage of 8 mg/kg per day for a total of 10 doses.
- III. Combined treatment as in I and II.

It was not considered ethical to have controls, as results from a previous trial (Wong *et al.*, 1972) had shown that about a third of the controls required therapy because the bilirubin level was rising to 20 mg/100 ml. 8 babies from a previous trial were therefore used as controls.

Total bilirubin was measured by the spectrophotometric method of Scott (1959). Plasma albumin was measured by a modification of the bromocresol green dye binding method of Bartholomew and Delaney (1966). Residual albumin binding capacity (RABC) was measured using the HBABA dye method of Porter and Waters (1966) and was expressed as g albumin reserve/100 ml plasma (Wood, Comley, and Sherwell, 1970).

Results

Infants above 2.5 kg birthweight (Trial A). 14 infants were entered into the trial in each group and the mean values of birthweight, gestation, and age at onset of phototherapy in each group, with 1 SD, are shown in Table I.

All infants who received only phototherapy responded satisfactorily and no further treatment was required. Of the group given phenobarbitone alone, 3 had bilirubin levels reaching 20 mg/100 ml and were given other treatment, leaving 11 for comparison. In the combined group 1 infant was given an exchange transfusion as the bilirubin rose to 20 mg/100 ml, while 2 infants developed severe infections 36 to 48 hours after onset of treatment (see Discussion) so that again 11 were left. Of the 8 infants in the control group, 3 had to be given treatment as their bilirubin levels reached 20 mg/100 ml, leaving only 5 for comparison in the results.

The mean drop or rise was obtained by calculating the difference from the pretreatment level in each infant and then averaging the sum of the differences. The significance of the mean between groups was calculated using Student's 't' test. All results on differences were calculated in this way.

The changes in bilirubin levels are shown in Fig. 1, while the alterations in plasma albumin levels and

FIG. 1.—Bilirubin levels in infants above 2.5 kg birthweight in Trial A.

TABLE I
Group comparability in infants over 2.5 kg birthweight (Trial A)

Groups	No.	Mean birthweight (kg) (SD)	Mean gestation (wk) (SD)	Mean age at onset of treatment (hr) (SD)
Combined	11/14	3.02 (0.357)	37.8 (1.537)	84.8 (22.4)
Phototherapy only	14/14	3.27 (0.503)	39.0 (1.414)	84.8 (20.2)
Phenobarbitone only	11/14	3.04 (0.386)	38.6 (1.293)	85.5 (12.2)
Controls	5/8	3.39 (0.699)	38.6 (1.95)	83.4 (15.6)

Note: Differences between mean values are not significant. SD, standard deviation.

residual albumin binding capacity (RABC) are shown in Table II.

TABLE II

Plasma albumin and residual albumin binding capacity levels in infants over 2.5 kg birthweight (Trial A)

Groups	Mean differences after 48 hours (1 SD)	
	Plasma albumin (g/100 ml)	RABC (g/100 ml)
Combined	+0.09 (0.217)	+0.17 (0.295)
Phototherapy only	+0.15 (0.303)	+0.30 (0.299)
Phenobarbitone only	+0.03 (0.295)	+0.19 (0.281)

Note: Differences are not significant.

Packed cell volume (PCV) was also estimated but did not show any significant differences between the groups.

Infants 2.5 kg birthweight and below (Trial B). This trial was carried out on a total of 19 infants. Table III shows their comparability. No controls could be justified. 1 infant was removed from the phenobarbitone group because of rising bilirubin levels and the results are based on 6 infants in each group.

The changes in the various levels are shown in Fig. 2 and Table IV. Again there were no significant differences in the PCV between groups.

Discussion

In both trials the only differences between the groups lay in the bilirubin levels.

Despite higher starting levels, the group on phototherapy only and the combined groups had significantly lower bilirubin levels than both the control and the phenobarbitone groups within 24 hours of onset of treatment, and this was maintained at 60 hours. In the infants over 2.5 kg (Trial A) the phenobarbitone group fell no faster than the controls up to 60 hours, but at 84 hours the bilirubin level had fallen close to that of the other 2 treated

FIG. 2.—Bilirubin levels in infants of 2.5 kg birthweight or less in Trial B.

TABLE IV

Plasma albumin and residual albumin binding capacity levels in infants of 2.5 kg birthweight or less (Trial B)

Groups	Mean differences after 48 hours (1 SD)	
	Plasma albumin (g/100 ml)	RABC (g/100 ml)
Combined	+0.033 (0.362)	+0.15 (0.198)
Phototherapy only	+0.067 (0.25)	+0.30 (0.342)
Phenobarbitone only	-0.04 (0.305)	-0.06 (0.055)

Note: Differences are not significant.

groups. The smaller infants (2.5 kg and under), however, showed no such fall even at 84 hours. This suggests that while the larger, presumably more mature, baby will respond to phenobarbitone after 60 hours, the low birthweight infant fails to do so up to 84 hours. This accords with the report of Sinniah *et al.* (1971). Because of this considerable time lag of 48 to 60 hours during which 4 infants had

TABLE III

Group comparability in infants of 2.5 kg birthweight or less (Trial B)

Groups	No.	Mean birthweight (kg) (SD)	Mean gestation (wk) (SD)	Mean age at onset of treatment (hr) (SD)
Combined	6/6	2.01 (0.232)	34.3 (1.862)	93.8 (18.2)
Phototherapy only	6/6	2.17 (0.088)	34.5 (0.548)	9.38 (3.1)
Phenobarbitone only	6/7	2.04 (0.298)	34.3 (2.06)	9.48 (17.2)

Note: Differences are not significant. SD, standard deviation.

Roles of phototherapy and phenobarbitone in treatment of nonhaemolytic neonatal jaundice 707

to be given other treatment, it appears that in clinical practice the effect of phenobarbitone is too slow to control a rising plasma bilirubin level once it has reached 15 mg/100 ml or more.

Combining phototherapy with phenobarbitone did not produce any difference in bilirubin levels compared with phototherapy alone throughout the 60 hours of phototherapy. The rate of fall from 60 to 84 hours appeared faster in the combined groups compared with phototherapy only (Fig. 1 and 2), but the end points did not differ significantly.

Our results on combined therapy of infants >2.5 kg birthweight are in agreement with the findings of Valdes *et al.* (1971) and Blackburn, Orzalesi, and Pigram (1972) who showed no difference in plasma bilirubin levels when compared with those treated with phototherapy alone. In these studies, however, treatment was started within 24 hours after birth.

There were 2 deaths in the present trial; both received phenobarbitone combined with phototherapy. They were apparently normal healthy term neonates, but one developed septicaemia and the other meningitis after 36 hours. It is not possible to state categorically that the infections were not present before entry into the trial, but there were no signs apart from jaundice. However, the delay in diagnosis may have been partly due to phenobarbitone, which could modify or even totally suppress any fits, and partly due to difficulty in the assessment of subtle changes in the infants colour, e.g. cyanosis, once the infant is under the light. In view of this possibility and the results showing the combined therapy to be no different from phototherapy alone, the former treatment cannot be recommended. It is also suggested that infants under phototherapy should be kept under close scrutiny since jaundice may be the only sign of neonatal infection.

No immediate side effects were found in the other treated groups. The dosage of phenobarbitone given did not cause any lethargy or difficulties with respiration or feeding.

The present results obtained with phenobarbitone therapy in infants over 2.5 kg birthweight are in general agreement with the findings of Yeung and Field (1969), Stern *et al.* (1970), and Sinniah *et al.* (1971). They differ from those of Levin *et al.* (1970) and Cunningham *et al.* (1969) who administered phenobarbitone orally 5 to 15 mg/day for 3 days to infants who appeared jaundiced (plasma bilirubin level around 8 mg/100 ml) and found no significant drop of bilirubin when compared to controls.

Such contradictory findings may be explained in

part by the following considerations. With the exception of the present trial, all others quoted administered oral phenobarbitone. The possibility of variable absorption or vomiting of oral medication cannot be excluded. Furthermore, phenobarbitone itself is virtually insoluble in water and elixir phenobarbitone BP contains 36% ethanol v/v, so that infants weighing 3 kg who are given 8 mg/kg per day of elixir phenobarbitone would thus receive over 3 ml of 90% ethanol. Ethanol itself has been shown to have a similar effect to phenobarbitone when administered to the mother in the prevention of hyperbilirubinaemia in the newborn (Waltman *et al.*, 1969). In the study of Levin *et al.* (1970) phenobarbitone was given in linctus simplex (which also contains ethanol) and the controls also received linctus simplex, so that both groups received some form of enzyme inducer. In other studies phenobarbitone 'syrup' was given with no reference as to whether the controls received any syrup or not. It is probable that some of these infants received elixir phenobarbitone (with ethanol as vehicle) while others received phenobarbitone in another solvent or in a suspension. The differences in the findings could well be explained in this way.

Certain preparations of phenobarbitone sodium BP for injection contain alcohol, but in the present study phenobarbitone sodium BP (McCarthy's Ltd.) was used with propylene glycol as the vehicle, which has been shown to have no enzyme induction properties (Zarolinski, Browne, and Possley, 1971).

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