Acta Paediatrica Hungarica, 26 (4), pp. 297—302 (1985)

Treatment of Neonatal Hyperbilirubinaemia with Flumecinolone, a New Enzyme Inducing Drug

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The effect of flumecinolone, a new drug with enzyme inductor properties, on non-haemolytic hyperbilirubinaemia of term and premature newborns has been investigated. Prophylactic treatment with the drug prevented the development of severe hyperbilirubinaemia. Alone or in combination with phototherapy, flumecinolone inhibited the steep rise of serum bilirubin in premature infants. A similar effect has been shown in term babies with haematomas. The new drug is void of all side-effects of phenobarbital.

A significant proportion of neonatal hyperbilirubinaemias is caused by decreased glucuronyl transferase activity in the liver. The activity of this enzyme can be induced by phenobarbital. This knowledge was the basis for the introduction of phenobarbital treatment of icterus gravis neonatorum [7]. This drug is not any more widely used for this purpose because of its side-effects [1]: it takes 3—4 days to attain the maximum effect, the drug has to be applied intramuscularly, accumulation of the drug may lead to depressed respiration and it is less effective than phototherapy.

Flumecinolone, 3-trifluoromethyl-α-benzhydrol (Zyxorin®, Gedeon Richter Ltd. Budapest, Hungary) acts in the liver as an enzyme inductor but, in contrast to phenobarbital, it does not depress respiration, does not inhibit imprinting, nor leads to paradoxical irritability or hyperactivity, and can be applied by mouth [9]. After completion of pharmacological studies in adults the drug has now been tested in paediatric patients as well.

We have examined the effect of flumecinolone on the course of the bilirubin level of premature babies, to test whether the drug was suitable for the treatment of non-haemolytic hyperbilirubinaemia of premature infants. In addition, the prophylactic effect of the drug on hyperbilirubinaemia has also been tested in term babies having haematomas.

Material and Method

56 newborns with moderately low birthweight, all born after completion of the 35th week of gestation, were treated with flumecinolone, 30 mg/kg bodyweight in a single dose daily for 3 days. Their mean weight was 2285 g, mean gestational age

was 36.5 weeks. 52 babies had a five-minute Apgar score higher than 7, 4 had a value equal to or lower than 7. There was no case of Rh-incompatibility, ABO incompatibility was present in one case. Flumecinolone therapy was started whenever the level of indirect serum bilirubin increased above the value of 180 μmol/l.

Flumecinolone alone was applied in 19 cases, combined with phototherapy in other 19 cases. This latter was started if the serum bilirubin level remained at the margin of indication for exchange transfusion by 24 hours after introduction of flumecinolone treatment. 18 premature infants were treated only with blue light lamps (Medicor KLA-21). Serum bilirubin was determined by the method of Jendrassik and Gróf. During the first ten days of life blood and reticulocyte counts, prothrombin time, serum sodium and potassium, serum GOT, GPT and γ-GT, total protein and albumin, immune electrophoresis, serum creatinine, blood urea nitrogen, blood and urinary glucose were regularly checked; the same laboratory tests were carried out some time during the subsequent weeks. 15 term babies (mean birthweight 3320 g, mean gestational age 40.0 weeks) with extensive haematomata were treated with a single daily dose of 30 mg/kg flumecinolone for 4 days from the first day of life.

Results

The course of serum bilirubin of the 19 preterm babies treated with flumecinolone alone is represented by Line 1 in Figure 1. Line 2 shows the changes seen in the 19 premature babies treated with flumecinolone and additional phototherapy, while Line 3 stands for the mean values of the 18 prematures treated with phototherapy alone. Table I shows the numerical mean values and their standard deviations in the three treatment groups. From Figure 1 and Table I it can be seen that flumecinolone treatment, alone or in combination with phototherapy, keeps the bilirubin level below that observed in infants receiving only phototherapy. At first sight it seems curious

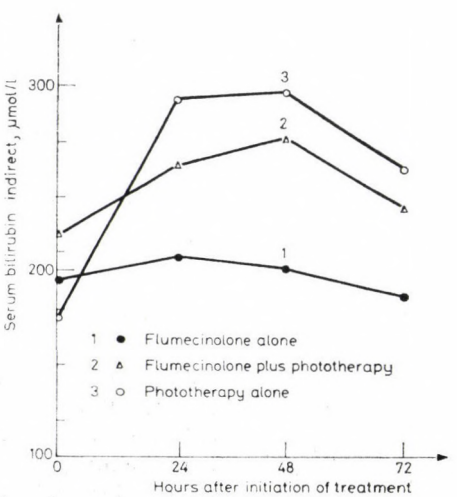

Fig. 1. The course of hyperbilirubinaemia in 56 preterm babies

TABLE I

Serum bilirubin levels in three groups of jaundiced preterm newborns, means and standard deviations

Treatment groups	n	Serum bilirubin, indirect, μmol/l							
		Before therapy		24 hours after initiation of therapy		48 hours after initiation of therapy		72 hours after initiation of therapy	
		mean	SD	mean	SD	mean	SD	mean	SD
Group 1									
Flumecinolone	19	195	51	205	85	205	83	185*	70
Group 2									
Flumecinolone plus phototherapy	19	220	65	255	39	270	51	235*	60
Group 3									
Phototherapy	18	175	65	290	51	295	62	255**	72

* no significant difference from initial value
** significant difference from initial value, $p < 0.01$ (paired t-test)

that Line 2 runs a higher course than Line 1; the mode of selection, however, fully explains this difference: since additional phototherapy was only introduced in case of a high bilirubin level observed 24 hours after initiation of drug treatment, i.e. in spite of flumecinolone treatment, the initial values were already higher in the babies needing subsequent additional phototherapy. The data show that flumecinolone, alone or combined with phototherapy, is capable of preventing a further rise in indirect serum bilirubinaemia without blood-group incompatibility. After 72 hours the mean serum bilirubin level of infants treated with flumecinolone alone was lower than their own initial mean value. In the group treated with flumecinolone plus phototherapy the 72-hour value did not differ from the initial value while in babies treated with phototherapy alone the mean value observed 72 hours after introduction of therapy was significantly higher than the initial mean of the same group.

In 15 term newborns affected by haematoma (face, limbs or cephalhaematoma) flumecinolone prophylaxis was started at the age between 12 and 24 hours. The results are demonstrated in Figure 2 and Table II. Figure 2 shows the course of serum bilirubin of normal and pathological newborns during the first week of life. The moderating effect of flumecinolone on the rise of serum bilirubin can clearly be seen. From Table II it can be noticed that the difference was significant from the third day of life. Exchange transfusion had to be carried out in one patient receiving flumecinolone prophylaxis and three patients left untreated.

Four cases deserve further attention.

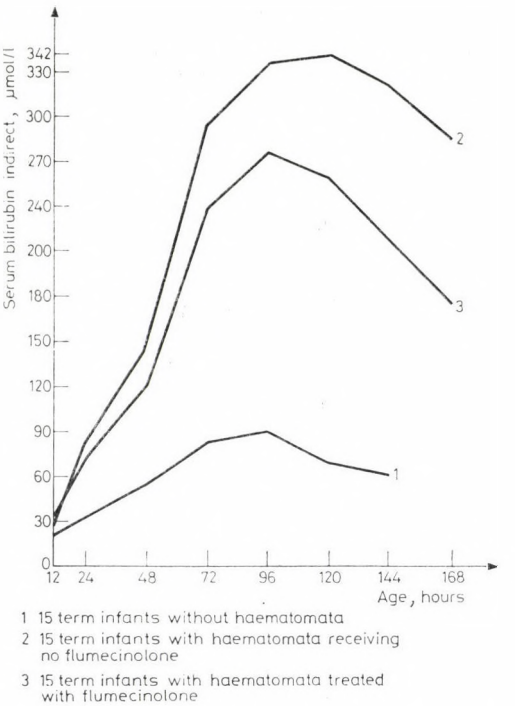

FIG. 2. The effect of flumecinolone on serum bilirubin of term newborns with and without heamatoma

In a newborn with a birthweight of 2700 g and a gestational age of 40 weeks, affected by AO incompatibility, flumecinolone combined with phototherapy did not prevent the rise of serum bilirubin to a level necessitating exchange transfusion.

In a newborn weighing 3100 g, and of 39 weeks gestational age, phototherapy had to be supplemented with D-penicillamine in order to avoid exchange transfusion. After blood-exchange a rebound ensued, the patient's serum bilirubin persisted a-

TABLE II

Effect of flumecinolone on serum bilirubin in term newborns with haematomas

Age in hours	n	Serum bilirubin, indirect, µmol/l means and standard deviations							
		12	24	48	72	96	120	144	168
No flumecinolone	15	mean 26	160	160	294	336	338	333	284
		SD 8	35	50	61	61	65	54	54
Flumecinolone	15	mean 32	74	140	240	278	260	216	174
		SD 10	33	48	60	63	66	55	52
Significance of difference	p<	—	—	—	0.05	0.02	0.01	0.001	0.001

round 350 μmol/l; this prompted us to initiate flumecinolone therapy on the 13th day of life. By 72 hours after introduction of the drug the serum bilirubin level had dropped to 140 μmol/l.

In two term babies affected by prolonged neonatal jaundice, flumecinolone treatment induced a rapid, marked fall in serum bilirubin.

No side-effects have been encountered. The parameters listed above (blood picture, prothrombin time, blood gases and electrolytes, serum total protein, liver and kidney function tests) remained normal during the first 10 days of life and showed no pathological changes at later checking, either.

Discussion

Introduction of phototherapy into treatment of hyperbilirubinaemia of term and preterm newborns has caused a marked fall in the number of exchange transfusions [2]. Lakatos et al have proposed the use of D-penicillamine for the same purpose [4]. Haemocarbo-perfusion has also proved useful in abolishing extreme hyperbilirubinaemia [6]. Phenobarbital alone or combined with diethylnicotinamide has been shown effective in preventing severe hyperbilirubinaemia [8] and clofibrate has also been used for treating jaundice of term newborns [5]. Flumecinolone has been demonstrated to induce bilirubin conjugation in the liver [10].

In this study preterm newborns needing no intensive care have been investigated. The mean serum bilirubin level 72 hours after initiation of treatment was significantly lower in the group treated with flumecinolone than in newborns treated with phototherapy; the same holds for the combined treatment using flumecinolone and phototherapy. We therefore recommend flumecinolone therapy in addition to phototherapy or D-penicillamine for treating hyperbilirubinaemia of preterm babies born after the 36th week of gestation because flumecinolone has been observed to moderate the hyperbilirubinaemia and to have no toxic or side-effects.

In addition, haematoma is an important factor in eliciting neonatal jaundice, ranking after blood-group incompatibilities, asphyxia and infection [3]. Flumecinolone, a compound void of the side-effects of phenobarbital, is the drug of choice in treating newborns affected by haematoma.

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Received 27 September, 1984

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