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D-penicillamine treatment of hyperbilirubinaemia in preterm infants

By

G. Korányi, Judith Kovács and Ildikó Vörös

Péterfy Hospital, Budapest

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In 41 hyperbilirubinaemic infants born before the 38th gestational week intravenous D-penicillamine treatment was applied in doses of 300 mg/kg body weight/day. As compared to 41 infants of identical gestational age and treated under identical circumstances, penicillamine ensured favourable results, especially in babies born after the 33rd gestational week. Some undesirable side-effects have to be taken into account, but they are infrequent if the indication is correct.

Elevation of the conjugated bilirubin level is a frequent occurrence in preterm infants. Both its incidence and level are the higher the shorter was the gestational time [10, 11]. The histotoxicity of bilirubin depends, however, also on the degree of simultaneous hypoxia and acidosis [3]. These factors should, therefore, be taken into account when indicating an exchange transfusion.

In order to state its optimum time, we have prepared a new chart (Fig. 1). In contrast to the well-known in-

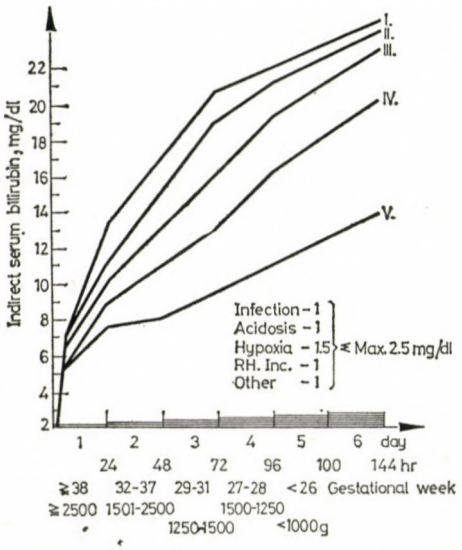

Fig. 1. Indication of exchange transfusion in preterm infants according to gestational age and pathologic conditions

dication charts [1, 9] we have taken into consideration in our chart the baby's gestational age in the first place and only secondarily its body weight. Then, in addition to hypoxia and acidosis, also infection, hypoglycaemia, hypocalcaemia, apnoea and the history of pregnancy were accepted as factors contributing to the severeness of jaundice and promoting central nervous system damage. Finally, with non-immunized infants delivered after the 36th week or of large body weight, the indication of exchange transfusion was put at a higher serum bilirubin level than in the other tables.

In addition to exchange transfusion, during the last two decades numerous procedures have been applied in the treatment of neonatal hyperbilirubinaemia. Among these, polyvinylpyrrolidone, agar-agar and corticosteroids failed to fulfil expectations. In term newborns barbiturate treatment is applied with satisfactory results but due to its depressive effect, it is contraindicated in somnolent, hypoxic premature infants [3]. Albumin infusions have been given extensively but by themselves they are satisfactory only exceptionally. The most widely used method today is phototherapy and its effect is unanimously considered excellent. In the treatment of preterm infants and chiefly those of very low body weight and short gestational age this therapy too meets with a number of problems [4, 8]. These experiences have justified the introduction of new methods. One of them is D-penicillamine treatment.

D-penicillamine (PA) or dimethylcysteine is a metabolite of penicillin excreted in urine. Similarly as numerous compounds containing a sulphhydryl group, the compound possesses a specific biological activity; this manifests itself chelate-formation, inhibition of collagen synthesis and a cytostatic effect [12]. As it binds metals, it ensured excellent results in Wilson's disease [14].

In the treatment of hyperbilirubinaemia of the newborn, Lakatos et al. [5, 6, 7, 13] were the first to apply PA orally and/or intravenously in a dose of 300 to 400 mg/kg body weight/day. According to their hypothesis, newborn infants have a low serum copper and coeruloplasmin level, whereas large copper reserves are stored in the liver. These are mobilized by PA and bilirubin is transformed into some non-toxic biliverdin-like compound, probably copper [5].

A pharmacological effect can be expected only from D-penicillamine, the L- and racemic modifications are ineffective. Among the three, D-PA is the least toxic. As the toxicity is dose- and time-dependent, in the course of the short neonatal treatment severe side-effects are exceptional [5, 6, 7]. If, however, PA is administered for a prolonged time, urticaria, albuminuria, leuko- and thrombocytopenia, even pemphigus foliaceus may occur [12].

Based on these considerations we have studied the effect of PA in the treatment of hyperbilirubinaemia in preterm infants.

Materials and Methods

The material included 82 preterm infants. Patients below 1000 g birth weight were excluded from the series. From April 1, 1975 to March 31, 1976, the hyperbilirubinaemic preterm infants were randomized: those born on even days received phototherapy and 5% glucose solution, with electrolytes when necessary. Those born on uneven days received PA in addition. Otherwise, the two groups were identical concerning body weight, gestational age and feeding methods as well as occurrence of infections, hypoxia or acidosis. Gestational age was estimated according to Dubowitz et al. [2].

PA (Metalcaptase®, Knoll, Ludwigshafen, FRG) was applied intravenously in doses of 300 mg/kg body weight, t. i. d., injected with a glass syringe very slowly. Of the 41 treated infants, PA treatment was started on the first day in 2, on the second in 4, on the third in 15, on the fourth in 13, on the fifth in 7, and on the ninth day in 1. For statistical evaluation of results, the chi square test was used.

Results

The efficiency of the methods applied in the treatment of hyperbilirubinaemia is indicated by the decrease in the number of exchange transfusions and of the serum bilirubin level.

Among the 41 children not treated with PA an exchange transfusion had to be performed in 19; among

Table I

Exchange transfusions performed in patients treated or not treated with D-penicillamine, according to birth weight

Birth weight, g	Not treated		Treated	
	number of patients	number of exchange transfusions	number of patients	number of exchange transfusions
1001—1250	5	4 (in 1 case 2×)	4	2
1251—1500	3	1	1	—
1501—1750	7	5 (in 1 case 2×)	6	2
1751—2000	6	1	8	3 (in 2 cases 2×)
2001—2250	12	4	13	4
2251—2500	7	4	6	2
2501—	1	—	3	—
Total	41	19	41	13

those treated with PA, in 13 babies. The indication was set on the basis of our chart (Fig. 1) in every case. From the aspect of exchange transfusions, statistical evaluation revealed no significant global difference between the two groups. Thus, the efficiency of PA in all the treated babies cannot be accepted.

Subsequently, we examined which are the factors that influence the effect of the drug and which among

TABLE II

Exchange transfusions performed in patients treated or not treated with D-penicillamine, according to gestational age

Gestational age (weeks)	Not treated		Treated	
	number of patients	number of exchange transfusions	number of patients	number of exchange transfusions
28	2	1	—	—
29	1	—	2	—
30	2	1	6	3
31	4	2*	3	2*
32	4	2	6	5*
28—32 Total	13	6	17	10
33	4	1	4	1
34	9	6*	5	—
35	9	5	5	—
36	5	1	6	1
37	1	—	2	—
38	—	—	2	1
33—38 Total	28	13	24	3
28—38 Total	41	19	41	13

* in 1 case 2×

them could be considered important. The results demonstrated that taking the body weight groups into consideration, no positive conclusions could be drawn from the number of the necessary exchange transfusions (Table I). On the other hand, if the efficiency of PA was examined as a function of gestational age, the favourable clinical experience was supported by statistical evaluation (Table II). Its result proved with 99% probability ($p < 0.01$) the efficiency of the drug in children born in the 33rd gestational week or later.

The distribution of the patients according to blood groups and Rh incompatibility is demonstrated in Table III.

To study by a similar method the connection between gestational age and the frequency of exchange transfusions in the PA treated infants, three age groups were formed: from

TABLE III

Exchange transfusions performed in patients treated or not treated with D-penicillamine, according to blood group incompatibility

Blood group incompatibility	Not treated		Treated	
	number of patients	number of exchange transfusions	number of patients	number of exchange transfusions
None	35	15	33	11*
ABO	2	1*	2	1
Rh	4	3*	3	1*
ABO + Rh	—	—	3	—
Total	41	19	41	13

* in 1 case 2×

TABLE IV

Exchange transfusions performed in the period 1974 to 1975, according to birth weight

Birth weight (g)	1974	1975
>2500	25	20
<2500	84	77
Total	109	97

28 to 32 weeks, from 33 to 35 weeks, and beyond 36 weeks. In this case the positive connection has again been proven.

Case Reports

Case 1. J. V., the fourth child from the 6th pregnancy (after 3 healthy children and 2 artificial abortions) was born at 36 gestational weeks with 2700 g body weight. No isoimmunization was present. The child was admitted on the 4th day of life, when the serum bilirubin level was 17.8 mg/dl. PA was prescribed. On the 5th day the bilirubin level was 21 mg/dl, a border value for exchange transfusion. Taking into consideration the satisfactory general condition of the newborn, the slow elevation of the bilirubin level and the gestational age, no blood exchange was performed. On the 6th day the level was 16.0, on the 7th day, 14.2 mg/dl, and on the following days the decrease remained even. The infant was discharged on the 12th day. Thus, in this case the exchange transfusion could be avoided by PA administration and recovery was undisturbed.

Case 2. T. H., the second child from 3 pregnancies (1 healthy child, 1 artificial abortion), was born at 38 gestational weeks with 2800 g body weight. He was admitted with Rh incompatibility and cardiorespiratory insufficiency. The direct Coombs test was negative. On due treatment the circulation had normalized, but on the 4th day of life the serum bilirubin level was 18 mg/dl. Then PA administration was introduced. On the 5th day, the bilirubin level was 20.3 mg/dl, on the 6th day, 15.8 mg/dl, then after a gradual decrease it became normal and the infant could be discharged at the age of 16 days.

In this seriously ill patient an exchange transfusion would have involved more risk than PA treatment, which was effective despite the additional pathological conditions. This case illustrates that after the 34th gestational week the efficiency of PA treatment is not affected by associated diseases.

Case 3. J. W., the first living child from 3 pregnancies (2 artificial abortions) was born at 36 gestational weeks with 2400 g body weight. On admission A-O incompatibility and respiratory distress were observed; the latter condition responded well to treatment. On the 3rd day the serum bilirubin level was 19.3 mg/dl, on the 6th day, 23.8 mg/dl, when an exchange transfusion had to be performed. This decreased the bilirubin level to 9.2 mg/dl. Then PA was given, but despite this therapy the bilirubin level was 17.1 mg/dl on the 8th day and decreased only on the 14th day to 9.5 mg/dl.

In this case it seems difficult to evaluate how far PA was effective, but it probably prevented the necessity of a second exchange transfusion.

Case 4. A. B., the first living child from the 6th pregnancy (3 spontaneous abortions, 2 stillborn babies) was delivered in the 31st gestational week with 2000 g body weight. No blood group incompatibility was present. Jaundice manifested itself on the first day of life, therefore PA, phototherapy and albumin infusion were applied. Despite this treatment the bilirubinaemia increased to 26.6 mg/dl by the 5th day when an exchange transfusion was performed. This resulted in a decrease of serum bilirubin to 11.0 mg/dl, but on the next day the level rose to 14.6 mg/dl. Despite continuous PA administration serum bilirubin on the 7th day reached the critical level of 19.2 mg/dl, the baby was faint and could not be fed and a second exchange transfusion had to be performed. The further course was uneventful.

In this infant of low gestational age, PA treatment started in the first 24 hours was ineffective.

Case 5. C. S., the first living child from 7 pregnancies (3 artificial, 2 spontaneous abortions, 1 dead preterm infant) was born at 32 weeks with 2200 g weight. No blood-

group incompatibility was present. The immediate postnatal period was undisturbed. PA treatment was started on the 4th day of life, when the bilirubin level was 19.0 mg/dl. On the 6th day it was 21.6, on the 7th 15.8 mg/dl, on the 8th day, 8.6 mg/dl. From the second day of PA administration anorexia, occasional vomiting, loss of weight were noted. These symptoms persisted even 4 days after discontinuing PA treatment and the baby's body weight decreased to 2000 g. He started to gain weight in the 4th week, and regained its birth weight only at 5 weeks. After 35 days hospitalization the infant was discharged.

The protracted course of the disease may have been connected with the PA treatment and the question seems justified whether an exchange transfusion performed on the 5th or 6th day of hospitalization would not have considerably shortened the course.

Discussion

The favourable effect of PA on hyperbilirubinaemia of term newborns was shown by Lakatos et al. [5, 6, 7]. In our preterm babies the results were not so uniformly satisfactory, due perhaps to the peculiarities of such patients. In our experience, the efficiency of PA depends on the gestational age rather than on birth weight and good results can only be expected from PA after the 33rd gestational week. The borderline seems to be between the 33rd and 34th weeks, when the baby's organism is sufficiently mature for utilizing PA.

Another aspect is the undesirable side-effects of PA. They are transitory during the usually short course of treatment which seldom lasts more than 5 to 6 days. Among our 41 cases, in 4 low-weight newborns, during and sometimes after PA treatment anorexia, vomiting, loss of weight and lagging development were observed. The severity of side-effects was directly proportional to the duration of treatment and inversely to the gestational age. Under the effect of PA, the serum bilirubin level may display a dramatic decrease in a number of cases, but at the same time recovery may considerably be prolonged owing to the side-effects.

Taking all these into consideration, PA represents an efficient drug in the therapy of hyperbilirubinaemia of newborns and especially in babies born after the 33rd week of gestation. Its combination with phototherapy is recommended and such treatment will often help to avoid exchange transfusions. Estimation of the serum bilirubin level is of course a precondition of successful treatment.

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G. Korányi M. D.
Péterfy Hospital.
Pf. 76
H-1441 Budapest, Hungary