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D-penicillamine therapy of neonatal jaundice: Comparison with phototherapy

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A total of 330 newborns suffering from haemolytic disaease of the newborn and hyperbilirubinaemia was treated with D-penicillamine. The therapy resulted in a significant decrease in the frequency of exchange transfusions and of high serum bilirubin levels among preterm and fullterm babies with or without sensitization. Concerning the drug's mechanism of action, reduction of the bilirubin level is achieved by means of the copper stored in the liver. The intravenous route is suggested for application of the drug. In preterm infants D-penicillamine treatment proved more effective than phototherapy.

Since its first use in the treatment of Wilson's disease [48] D-penicillamine (DPA) has found a number of applications [1, 7, 9, 10, 14—16, 19, 21, 24, 25, 37] and it has proved beneficial in neonatal hyperbilirubinaemia [32—34]. The present study was undertaken mainly in order to summarize our experience obtained in the treatment of a large number of patients with hyperbilirubinaemia.

Material and Methods

In the period March, 1973, to November, 1974, 330 hyperbilirubinaemic newborns were treated with DPA. Among them, 308 infants fulfilled the following criteria.

1. In 147 newborns with a birth weight of more than 2500 g without any detectable sensitization, the serum bilirubin level was above the limit defined as pathological [44] at the point of time when DPA treatment was started. The babies had had no previous exchange transfusion.

2. In 132 preterm babies without detectable sensitization, and a serum bilirubin level higher than 8 mg/100 ml during the first three days of life.

3. In 29 term and preterm infants with Rh and ABO sensitization with a direct positive Coombs test.

The serum bilirubin level was determined by the method of Mertz [36] as modified by Jezerniczky [29].

Dosage and route of application

DPA was applied orally and/or intravenously in a dose of 300—400 mg/kg body weight daily, divided into 4 equal parts. The period of treatment varied between 2 and 5 days. The drug was administered to 40 patients intravenously; to 189 patients orally; and to 79 patients by both routes.

The much more effective intravenous application could be chosen

only in the most severe cases, because suitable preparations were available in limited quantities.

Results

1. *Mature hyperbilirubinaemic infants without sensitization.*

The dye-levels measured at the beginning of DPA administration are indicated in Fig. 1 as a function of age in hours. The bilirubin values falling between the two solid lines are to be regarded as pathological [44] and require constant observation. An exchange transfusion becomes necessary if the dye concentration exceeds the higher limit (i.e. the upper line). Figure 1 reveals that 3 exchange transfusion were performed in the cases where the dye concentration had exceeded the limit of indication at the beginning of drug therapy. On the other hand, in 20 cases where the bilirubin concentration had exceeded the critical limit, the level could be reduced by intravenous DPA in 12—24 hours.

This group included a considerable number of early jaundice and hyperbilirubinaemia of such severity that occurs only in grave ABO haemolytic disease of the newborn or in cases of a severe conjugation defect [13].

2. *Preterm infants*

Table I demonstrates three groups of hyperbilirubinaemic preterm infants treated with different methods during the period 1971—74. Every

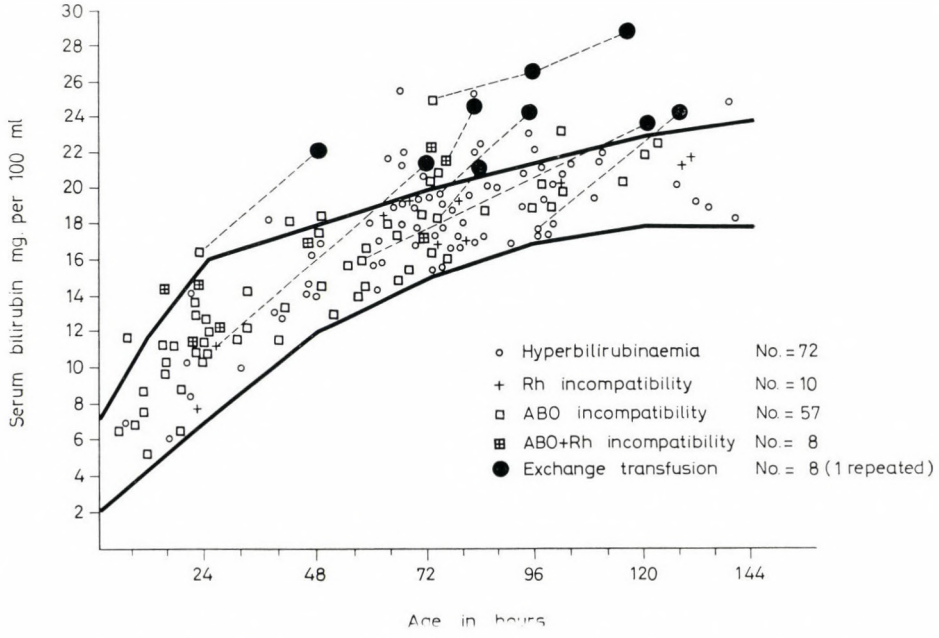

Fig. 1. Term infants with hyperbilirubinaemia without sensitization

TABLE I

Comparison of preterm infants treated with: (1) DPA; (2) phototherapy; and (3) glucose infusion (control group)

		DPA (N = 132)		Phototherapy (N = 125)		Controls (N = 162)	
Weight (g)	1000–1500	30		27		40	
	1501–2000	56		64		60	
	2001–2500	46		34		62	
Cause of jaundice	"Idiopathic"	65		69		84	
	ABO incompatibility	24		23		26	
	Rh incompatibility	7		7		11	
	ABO + Rh incompatibility	3		2		4	
	Respiratory distress syndrome and incompatibility	29		22		33	
	Respiratory distress syndrome	4		2		4	
Maximum Sebi. value (mg/100 ml)	8–12	27	(20.4%)	6	(4.8%)	15	(9.3%)
	12.1–16	40	(30.3%)	25	(20.9%)	36	(22.2%)
	16.1–20	48	(36.4%)	48	(38.4%)	37	(22.8%)
	20 <	17	(12.9%)	46	(36.8%)	74	(45.7%)
No. of Et.-s	Once	14		33		58	
	Twice	—		2		7	
	Three times	—		2		4	
	Total (Et./all cases)	14	(10.6%)	42	(34.4%)	84	(51.9%)

Et. = Exchange transfusion.

baby had a dye level higher than 8 mg per 100 ml during the first three days of life. The kind of treatment chosen was mostly determined by circumstances beyond our control.

a) In 1971, most cases were treated solely with 10% glucose infusion.

b) In 1972, about two thirds of the babies were subjected to phototherapy.

c) In the period March to October, 1973, DPA could be used only when it was available. In its lack, phototherapy and/or glucose infusions were applied.

d) In the period October, 1973, to August, 1974, a controlled clinical trial was performed. The infants were treated with DPA or phototherapy, or glucose infusion in the order of their admission (Fig. 2).

An exchange transfusion was carried out in babies with a birth weight of less than 2000 g at a serum bilirubin level between 18 and 20 mg per 100 ml and in babies exceeding that weight at dye levels between 20 and 22 mg per 100 ml.

As can be seen in Table I, DPA treatment was superior to phototherapy in reducing both the number of blood exchanges and the critical dye values. In cases with respiratory distress syndrome, the development of jaundice was prevented by DPA much more effectively than expected.

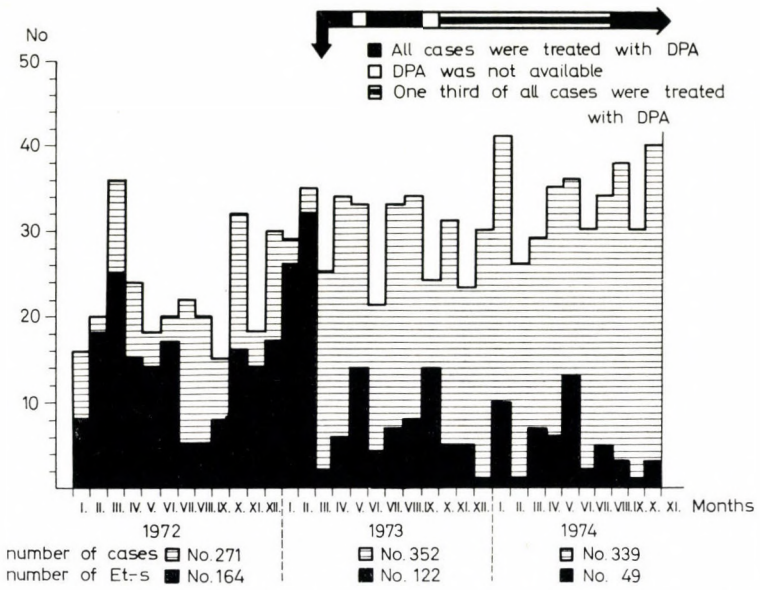

FIG. 2. Incidence of hyperbilirubinaemia and frequency of exchange transfusions in the period 1972 to 1974

3. *Coombs positive preterm and term infants with haemolytic disease.*

As demonstrated in Table II blood exchange became superfluous in about 60% of the 29 newborns treated with DPA.

TABLE II

Preterm and term Coombs positive infants treated with DPA

	No. of cases	No. of Et.-s
Rh incompatibility	22	9 (1 repeated
ABO incompatibility	6	2
ABO + Rh incompatibility	1	1
Total	29	12

Et. = Exchange transfusion.

MECHANISM OF ACTION

Our experimental work has revealed that:

(i) DPA has no direct effect on bilirubin;

(ii) reduction of the dye level by DPA is achieved by means of heavy metals, especially copper. In this respect DPA behaves like a chelating agent and the copper–DPA complex formed destroys bilirubin. This is supported by the following data.

a) Heavy metals, and copper in the first place, are known to accelerate bilirubin decay both in the dark and under light, suggesting an important role for bivalent cations under these conditions [12, 31, 35, 46].

b) The concentration of bilirubin was reduced by DPA only in the

presence of Cu^{++} ions both in aqueous alkaline and in albumin solutions.

c) The bilirubin decreasing effect of DPA in vitro in blood samples or icteric sera is inhibited by previously added EDTA.

d) In Gunn-rats pretreated with copper, DPA causes a rapid fall of the bilirubin level.

e) In the blood samples of newborns responding well to DPA treatment, plasma copper concentration increased during therapy. On the other hand, babies who were requiring blood exchange in spite of DPA treatment had low or unchanged copper values. This must have been due to the mobilization by DPA of the copper stored in the newborn's liver. Thus, from the point of view of DPA-therapy, it is favourable that the newborn infant has some biochemical traits of Wilson's disease: low serum coeruloplasmin and copper levels, and a high hepatic copper content [42].

(iii) The products of bilirubin arising on its decomposition by DPA are soluble in water.

There are certain data indicating that DPA can be of some benefit in haemolytic processes, by its influence on immune complexes and immunoglobulins [41, 47]. Thus, the production of bilirubin is also inhibited. Our clinical experience tends to support this hypothesis. It was unexpected to find that late anaemia developed only in three out of 17 cases without blood exchange; they only necessitated simple transfusions of blood.

Side effects

In the diseases requiring long-term DPA treatment, application of the drug is limited by the high incidence of side effects [3, 5, 17, 18 20]. They are troublesome but not grave and disappear on withdrawal of the drug.

Although DPA was administered to our babies in doses comparatively much higher than those used in adults, no dangerous side effects have so far been recorded. This may have been due to that treatment usually lasted less than 5 days. Besides, the adverse reactions were mainly allergic in nature [26, 27], as with all penicillin metabolites. Such manifestations, are however, unfrequent in the neonatal period [39]. The lack of dangerous side effects was clearly reflected by the mortality rate and the gain of weight of the babies treated with DPA in 1973 and 1974 (Tables III, IV). These data show the superiority of DPA over phototherapy and/or glucose treatment and seem to prove that neither DPA nor the products resulting from the decomposition of bilirubin by DPA have a harmful biological effect.

Most side effects occurred when DPA was administered orally; they consisted in vomiting, anorexia, loose stools, and frequent thrush. They originated probably from the local influence of the drug on the gastrointestinal mucosa.

On intravenous application, the only side effect was a mild erythema

TABLE III

Mortality rate and causes of death among preterm infants after three days of life in the period 1972—1974

Causes of death	DPA, N = 131				Controls, N = 141			
	Birth weight (g)							
	1000—1500	1501—2000	2001—2500	total	1000—1500	1501—2000	2001—2500	total
Intracranial haemorrhage	6	1		7	10	3	1	14
Pulmonary haemorrhage	2	2		4	2	1		3
Idiopathic respiratory distress syndrome	2			2	3			3
Pneumonia	5	2		7	6	5		11
Congenital anomalies	1		2	3	1	1	2	4
Total	16	5	2	23	22	10	3	35
per cent				17.5				24.8
in 1st week, per cent				11.4				17.7
after 1st week, per cent				6.1				7.1

TABLE IV

Gain in weight of preterm infants treated with (1) DPA; (2) phototherapy; and (3) glucose solution infusion

Age	Mean Body Weight (g)			Statistical significance
	(1) DPA	(2) Phototherapy	(3) Controls	
2 months (birth weight below 1500 g)	2200±320 (N = 25	2260±240 (N = 24)	1970±280 (N = 28)	1 : 2 — n.s. 1 : 3 — $p <$ 0.01 2 : 3 — $p <$ 0.0001
1 month (birth weight over 1500 g)	2240±230 (N = 55)	2090±290 (N = 60)	2030±250 (N = 60)	1 : 2 — p < 0.01 1 : 3 — p < 0.0001 2 : 3 — n.s.

± = Standard deviation.
n.s. = non significant.

in two cases; it responded readily to antihistaminics. Thus, intravenous treatment is more advantageous than oral application, not only in reducing the dye level, but also with respect to side effects. Serious side effects of DPA observed during long-term therapy, such as copper, iron and pyridoxine deficiency, thrombocytopenia, agranulocytosis, proteinuria and ne-

phrosis syndrome never occurred in our patients.

Three further questions have to be discussed in some detail.

Anaemia. As haemolytic disease of the newborn and prematurity are accompanied by anaemia, some of the cases treated with DPA displayed a low RBC, requiring late transfusion of blood. On the other hand, considerably less late transfusions were necessary among the DPA-treated patients than in the other groups. This is an indirect evidence that DPA causes no depression of the haemopoetic system.

Copper deficiency. This question has arisen in view of the physiologic importance of copper and of the chelating nature of DPA. It is difficult to induce a copper deficiency in normal infants [43], but some neonates maintained on unusual diets or fed parenterally for several weeks have developed copper deficiency presenting with anaemia, neutropenia, and vascular and bone changes which were relieved by oral copper treatment [2, 30]. In contrast, all our patients treated with DPA had a normal serum copper level and there was no need of supplementation. This is believed to have been due to the short course of treatment.

The copper content in the fetal and neonatal liver, muscle, skin, adrenal glands, thyroid, testes and uterus, is much higher than in adults [11, 45]. These elevated tissue copper levels decrease soon after birth, while there is a corresponding increase in plasma copper and coeruloplasmin concentration [22]. DPA seems to hasten this process without causing copper deficiency in such a short period of time. In addition, 8 cases have been reported [8] where before and during pregnancy women were treated with DPA for Wilson's disease or cystinuria, and they delivered normal babies except one who displayed Ehlers—Danlos's syndrome.

Immunosuppression. It has been established [23, 40] that DPA is not a cytotoxic-immunosuppressive agent in man. DPA treatment does not affect the immune system and does not predispose to tumour formation. Lymphocyte transformation and serum complement are not inhibited by DPA therapy. DPA seems to cause clinical improvement and normalization of immunological and serological abnormalities without immunosuppression. This is supported by its:

a) influence on antibodies fixed to cells [41];

b) splitting of intermolecular disulphide bridges of macromolecular and polymeric proteins [14];

c) changes of 7 S, 19 S and 22 S immunoglobulins [6];

d) mesenchymal suppressant effect [38];

e) reduction of C-reactive protein acting as phagocytosis promoting factor [14];

f) action on the recipient cells in tissue culture by increasing their resistance to viral infection [28].

These clinical and experimental findings may explain that the number of complications associated with immune inhibition did not increase

among our patients treated with DPA.

Conclusions

I. *When is DPA ineffective in hyperbilirubinaemia?*

1. In grave haemolytic disease with apparent jaundice where the dye values approach or exceed the limit indicating a blood exchange.

2. In the rare cases of a low hepatic mobilizable copper content (mostly in preterm infants).

3. In the course of oral administration when because of vomiting and gastrointestinal disturbances the absorption of DPA is affected.

II. *When to start DPA therapy?*

1. As early as possible if clinical symptoms or laboratory findings point to a haemolytic process;

2. in preterm infants with a dye level higher than 8 mg/100 ml during the first three days of life;

3. as early as possible in all cases of early jaundice due to incompatibility.

III. *When is DPA therapy not recommended?*

Jaundice in the first week of life is a symptom of several illnesses. It may be the earliest sign of infectious diseases, sepsis, bleeding or mild haemolytic anaemia not due to incompatibility. Because of obscuring the adequate diagnosis, DPA therapy should be started with great caution in such cases.

IV. *Are the babies treated with DPA without exchange transfusion exposed to the danger of bilirubin encephalopathy?*

Follow-up of patients with high neonatal serum bilirubin levels revealed no ill effects whatever in these babies of whom now several have past the age of two years.

To sum up, we believe that in the control of neonatal hyperbilirubinaemia, DPA treatment surpasses the effect of any other drug or of light therapy.

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