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Hyperbilirubinemia and urinary D-glucaric acid excretion in premature infants following antepartum dexamethasone treatment

I. Németh, T. Szeleczki, D. Boda

Department of Pediatrics, Medical University, Szeged, Hungary

1 Introduction

Contrary to the numerous reports on the promising results with antepartum glucocorticoid treatment of respiratory distress syndrome (RDS) [2–4, 13, 17, 20], little information is available on the risks of this form of therapy to the premature infant [2, 19]. Hyperbilirubinaemia with consequent jaundice is known to be by far the most common and potentially harmful abnormality associated with several neonatal pathological conditions (prematurity, RDS, acidosis, hypoxia, hypothermia, etc.) [16]. There are only very few and conflicting data regarding the correlation between prenatal glucocorticoid treatment and neonatal hyperbilirubinaemia. No significant increase in the serum bilirubin levels of newborn infants was found following antepartum maternal administration of betamethasone [13]. By contrast, prednisolon sodium succinate, when given to mothers, proved capable of aggravating hyperbilirubinaemia in their premature infants [23]. The possible influence on the neonatal serum bilirubin concentration of maternal treatment with dexamethasone, another glucocorticoid used to prevent RDS [20], has not yet been studied.

The present study was, therefore, undertaken to evaluate the effect of maternally administered dexamethasone on the serum bilirubin levels of premature infants. Since the hepatic microsomal enzyme glucuronyl transferase (UDPGT), which is immature in the newborn infant [1, 8, 24], plays a key role in the metabolism of both bilirubin and glucocorticoids [7], it was also of some interest to

Curriculum vitae

ILONA NÉMETH studied medicine at the University of Pécs, Hungary from 1963 to 1969. She received postgraduate training in biochemistry and pharmacology at the Szeged University of Medical Sciences and became specialist in clinical chemistry in 1972. Since 1973 she has been working at the Department of Pediatrics of the same university as Scientific Investigator. Her main research interest is clinical pharmacology of the perinatal period and childhood, including therapeutic and adverse effects of new pharmaceutical agents as well as monitoring drug levels in pediatric patients.

provide additional data by studying the influence of prenatal dexamethasone treatment on the urinary D-glucaric acid excretion of infants born prematurely.

2 Patients and methods

Premature infants of similar gestational age, birth weight, APGAR scores, CLEMENTS' test (Tab. I), severity of RDS and therapy (antibiotics, theophylline, phototherapy) were included in the study. Cases with maternal diabetes, hypothyroidism, oxytocin infusion during labour and evidence of blood group (ABO and Rh) incompatibility were excluded from this study as were those who suffered excess bruising or bleeding due to abnormal delivery.

Tab. I. Parameters of control and dexamethasone-treated premature infants at birth.

¹ Mean values $\pm$ S.E.² 10 mg i.m. dexamethasone was given to the mother at least 24 hours before delivery.

	Gestational age [weeks] ¹	Birth weight [gm] ¹	APGAR score				CLEMENTS' test				
			1 min		5 min		-	+	++	+++	++++
			< 5	$\geq$ 5	< 5	$\geq$ 5					
Controls	31.9 $\pm$ 0.7	2010 $\pm$ 110	2	10	1	11	2	4	2	1	2
	n = 18	n = 18	n = 12				n = 11				
Dexamethasone-treated infants ²	31.8 $\pm$ 0.9	2003 $\pm$ 134	2	10	1	11	2	2	3	1	4
	n = 16	n = 16	n = 12				n = 12				

16 premature infants received antenatal glucocorticoid therapy; 10 mg dexamethasone (Oradexon®-N. V. ORGANON, Oss, Holland) was given intramuscularly to the mothers 24 hours before delivery. 18 pre-term infants with similar parameters but without dexamethasone treatment served as controls. The indication for the antepartum steroid administration was based upon gestational age and biparietal cranial diameter. Serum levels of unconjugated (indirect) bilirubin was measured over the first 7 days of life by the method of JENDRASSIK et al. [6].

In order to assess the activity of the hepatic microsomal enzyme UDPGT, urine was collected for periods of 24 hours during the first week of life, and the excretion of D-glucuric acid ($\mu\text{M/kg/24 hours}$) was determined by the method of MARSH [15] as modified by SIMMONS et al. [18]. Statistical analysis of the results was carried out using Student's "t" test as well as χ^2 test with Yates correction.

3 Results

The serum bilirubin levels increased considerably in dexamethasone-treated premature infants throughout the first week of life (Tab. II). In addition, on days 3 to 4 of the postnatal period, the incidence of serum bilirubins over 15 mg/100 ml (256.56 $\mu\text{M/l}$) (the value thought to be the upper limit of the usual range in pre-term neonates [5]) was three times greater in the steroid-treated than in the control group (2 out of 17 controls vs. 7 out of 15 treated; $p < 0.05$).

On the other hand the difference between the D-glucuric acid excretion of infants with dexamethasone therapy and that of the untreated controls did not reach the level of statistical significance over the first 7 days of life. It was conspicuous, however, that the urinary excretion of D-glucuric acid showed some tendency to decrease in the dexamethasone-treated group of infants on the third and fourth postnatal days when the highest serum bilirubin concentrations were measured (Tab. II).

4 Discussion

The evidence presented in this paper suggests that dexamethasone may increase the serum level of unconjugated bilirubin in premature infants over the first 7 days of life. Apart from the antepartum maternal administration of dexamethasone and the subsequent elevation of serum bilirubin concentration the two groups of infants involved in our study were similar in every respect. It thus seems very likely that the observed phenomenon reflects a cause and effect relationship. In theory, hepatic uptake, transfer, conjugation and excretion of bilirubin may all be diminished by a drug inducing hyperbilirubinaemia. In neonates the hepatic concentration of Y and Z proteins is low and dexamethasone, similarly to other drugs [12], may compete with bilirubin for binding to these proteins, thereby decreasing the uptake and transport of bilirubin in the liver. The limiting factor in the hepatic conjugation of bilirubin is the adequacy and availability of the microsomal enzyme, UDPGT

Tab. II. Serum bilirubin concentrations and urinary D-glucaric acid excretion in premature infants over the first 7 days of life following antepartum administration of dexamethasone to the mother.

¹ Mean values $\pm$ S.E.

² see footnote in Tab. I.

Age [days]	Serum bilirubin concentration $\mu\text{M/l}$ [mg/100 ml] ¹			D-glucaric acid excretion $\mu\text{M/kg/24 hrs}$ ¹		
	1-2	3-4	6-7	1-2	3-4	6-7
Controls	139.8 $\pm$ 10.6 [8.18 $\pm$ 0.62] n = 17	199.9 $\pm$ 11.4 [11.69 $\pm$ 0.66] n = 17	153.5 $\pm$ 11.3 [8.98 $\pm$ 0.66] n = 16	0.22 $\pm$ 0.05 n = 17	0.20 $\pm$ 0.03 n = 17	0.20 $\pm$ 0.05 n = 16
Dexamethasone-treated infants ²	187.0 $\pm$ 12.9 [10.93 $\pm$ 0.75] n = 15	238.8 $\pm$ 10.6 [13.96 $\pm$ 0.62] n = 15	188.8 $\pm$ 11.4 [11.04 $\pm$ 0.67] n = 14	0.27 $\pm$ 0.09 n = 15	0.15 $\pm$ 0.03 n = 12	0.18 $\pm$ 0.03 n = 11
Statistical	p < 0.01	p < 0.02	p < 0.05	N.S.	N.S.	N.S.

[9, 10]. Deficiency of this enzyme is considered to be the principal factor underlying the development of the "physiologic" neonatal hyperbilirubinaemia both in full-term and in premature infants [1, 24]. Thus the major cause of the aggravation of the already existing hyperbilirubinaemia in the dexamethasone-treated preterm infants involved in our study could be a simultaneous and competitive binding of bilirubin and dexamethasone to UDPGT leading to a decrease in the glucuronidation of bilirubin and elevation of serum bilirubin levels.

D-glucaric acid excretion, which reflects the activity of hepatic microsomal enzymes has been found to increase in full-term infants during the first week of life [21, 22], whereas no considerable change and low basal excretion were found in the same period in the control premature infants included in our present study. The observed difference is presumably related to the known maturational delay in the hepatic microsomal enzyme systems of pre-term infants. The clearance of bilirubin administered intravenously does not change in premature infants, but increases progressively in full-term infants in the first week of life [11].

Recent reports on the functional heterogeneity of the enzyme UDPGT have revealed that transferase

activities toward different substrates (Group 1: e.g. 2-aminophenol; Group 2: e.g. bilirubin, chloramphenicol) develop at different periods and rates and respond differentially to a wide range of stimuli, including antepartum dexamethasone treatment [27].

Glucocorticoids, when administered antenatally, stimulate transferase activity in Group 1 ('steroid group'), but have negligible effect on those in Group 2 ('non-steroid group') [14, 25]. Conversely, phenobarbital was found to stimulate significantly Group 2 transferase activities under conditions in which Group 1 activities remained unaffected [26]. It appears likely that our observation regarding the most pronounced glucaric acid excretion of dexamethasone-treated premature infants on the 1st and 2nd postnatal days can, at least in part, be attributed to some increase in Group 1 transferase activities.

In the light of the results presented, more detailed clinical and experimental analysis of the effects of glucocorticoids on bilirubin metabolism of pre-term infants and investigations into the drug prophylaxis of steroid-induced hyperbilirubinaemia would be well worth while.

Summary

Dexamethasone (10 mg i.m.) administered to mothers 24 hours before delivery for the prevention of respiratory

distress syndrome caused a considerable elevation of the serum level of unconjugated bilirubin in premature infants

throughout the first week of life. On days 3 to 4 the incidence of infants with bilirubin levels exceeding 256.56 $\mu\text{M/l}$ (15 mg/100 ml) was found to increase (7/15 vs 2/17). The urinary excretion of D-glucuric acid, which reflects the activity of the hepatic microsomal enzyme systems, proved to be low in pre-term infants over the first 7 days of life, and it was not enhanced significantly by antenatal dexamethasone therapy.

In the light of the results presented, more detailed clinical and experimental analysis of the effects of glucocorticoids on bilirubin metabolism of pre-term infants and investigation into the drug prophylaxis of steroid-induced hyperbilirubinaemia are suggested.

Keywords: Antepartum dexamethasone treatment, D-glucuric acid excretion, hyperbilirubinaemia, premature infant.

Zusammenfassung

Hyperbilirubinämie und Ausscheidung von D-Glucursäure im Urin bei Frühgeborenen nach antepartaler Dexamethasonbehandlung

Die Applikation von Dexamethason (10 mg i.m.) 24 Stunden vor der Geburt zur Verhütung eines Atemnotsyndroms hat einen beträchtlichen Anstieg des unkonjugierten Bilirubins im Serum der frühgeborenen Kinder während der ersten Lebenswoche zur Folge. Erhöhte Bilirubinspiegel ($> 256.56 \mu\text{M/l} = 15 \text{ mg/100 ml}$) am 3. bzw. 4. Lebenstag waren signifikant häufiger (7 von 15 Frühgeborenen bei Dexamethasontherapie versus 2 von 17 ohne Behandlung). An der D-Glucursäureausscheidung im Harn läßt sich die

Aktivität des mikrosomalen Enzymapparates der Leber abmessen, welche bei frühgeborenen Kindern während der ersten 7 Lebenstage reduziert zu sein scheint. Die antenatale Dexamethasontherapie führt nicht zu einer Steigerung der Aktivität.

Wir meinen, daß unsere Ergebnisse detailliertere klinische und experimentelle Untersuchungen zur Wirkung von Glukokortikoiden auf den Bilirubinstoffwechsel bei Frühgeborenen erforderlich machen und daß Forschungen auf dem Gebiet der medikamentösen Prophylaxe von steroidinduzierten Hyperbilirubinämien einsetzen sollten.

Schlüsselwörter: Antepartale Dexamethasontherapie, D-Glucursäureausscheidung, Frühgeborenes, Hyperbilirubinämie.

Résumé

Hyperbilirubinémie excrétion urinaire d'acide D-glucarique chez les enfants prématurés après traitement antépartal à la dexaméthasone

L'administration de dexaméthasone (à raison de 10 mg. i.m.) à la mère 24 heures avant l'accouchement afin de prévenir le syndrome de détresse respiratoire provoque une élévation considérable du taux sérique de bilirubine libre chez les enfants prématurés pendant la première semaine de vie. Les jours 3 et 4 l'on a noté une augmentation de l'incidence des enfants avec des taux de bilirubine dépassant 256.56 mM/l (15 mg/100 ml), (7/15 contre 2/17).

L'excrétion urinaire d'acide D-glucarique, reflétant l'activité des systèmes enzymatiques microsomaux hépatiques, était basse chez les prématurés pendant les premiers 7 jours de vie et n'était pas significativement augmentée par l'administration anténatale de dexaméthasone.

A la lumière des résultats présentés il semble nécessaire d'obtenir d'avantage d'analyses cliniques et expérimentales détaillées sur les effets des glucocorticoïdes sur le métabolisme de la bilirubine chez les prématurés et de recherches sur la prophylaxie médicamenteuse de l'hyperbilirubinémie provoqué par les stéroïdes.

Mots-clés: Excrétion d'acide D-glucarique, hyperbilirubinémie, prématuré, traitement antépartal à la dexaméthasone.

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Ilona Németh, M.D.
Department of Pediatrics
Medical University
Szeged P.O. Box: 471
H-6701 Hungary