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Induction of bilirubin-eliminating processes by methylphenobarbital in mature newborn babies

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1 Introduction

Phototherapy has proven to be a very potent tool for the prevention as well as for the therapy of different forms of hyperbilirubinemia. This does not exclude different approaches to the problem, for instance the induction of bilirubin eliminating processes by drugs. This approach might be particularly promising in newborns, who suffer from additional disturbances such as hypoxia, infection, acidosis or hemolytic disease and extreme immaturity, which may facilitate the development of a bilirubin encephalopathy.

In 1968 TROLLE [20] introduced phenobarbital (PB) into the prevention of hyperbilirubinemia in newborns. Because of its marked sedative effect in dosages, which are necessary to reduce the plasma bilirubin concentration sufficiently, respiratory depression is frequently seen in infants, who are especially prone to develop bilirubin encephalopathy, such as very immature newborns or those with prior cerebral damage. Thus a combination with nikethamid, an analeptic with a good inductive effect, has been recommended [6, 7]. However, this combination was not with out dangerous side effects in those infants, who need a prophylactic treatment of hyperbilirubinemia.

Methylphenobarbital (MPB), an antiepileptic drug introduced by BLUM 1932 [1], is still in use for adults including pregnant women [14] as well as for infants. Because of its chemical configuration it is a racement of two optically active isomeres. The (+)isomer has no sedative effect [3, 4, 5]. The inductive activity acting on different metabolic systems in animals, however, is common for both isomers [8, 9, 13, 18, 21], and comparable to the activity of phenobarbital. MPB proved to be a potent inductor in man as well [5, 11]. Up to now there are no investigations on its inductive activity in newborns. From our own data, until now unpublished, as well as from investigations of HILL and coworkers [10], one may conclude that MPB is well absorbed from the gut after oral administration and that the half life of MPB, which is metabolized to PB and at least five minor metabolites [11], is less than 30 hours. SCHMID and BALLOWITZ [17] were able to show that MPB does not influence the bilirubin binding to albumin – this goes for both the racemete and the (+)isomer.

These results encouraged us, to investigate the effect of MPB-racemate on the bilirubin concentration of mature newborn babies in a double-blind trial.

2 Patients, design and methods of the study

198 newborn babies weighing more than 2500 g received MPB racemate or a placebo. MPB was mixed with glucose to form a powder. The single doses – MPB with glucose or glucose alone – were enclosed in paperenvelopes. Different brands of the verum were prepared containing 30 mg of MPB for babies weighing 2500 g to 3499 g or 40 mg for those weighing 3500 g to 4499 g in order to administer single doses of about 10 mg/kg body weight.

Envelopes with identical contents were combined into one set. The sets were prepared and blinded by a pharmacist, who kept the key locked up until the end of the study. Each baby was assigned to one set and received the first poweder between the 8th and 12th hour of life, the two others 8 and 16 hours later. Bilirubin was estimated from venous blood before the first administration and between 48 and 72 and 72 and 96 hours of life respectively. We used the method of JENDRASSIK and GROF [12] for the bilirubin analysis. Because of organizational problems most of the babies were discharged shortly after the 96th hour of life. Therefore the bilirubin level could be followed only up to four days after birth. Informed consent was obtained from each mother. For statistical analysis we used the u-test.

3 Results

Table I shows some basic data of the groups, which could be suspected to influence the bilirubin level. It is shown that there was no significant difference in gestational age, sex-ratio, birth weight and weight loss, body length and immediate postnatal adaptation. All babies passed meconium during the first 24 hours. In no baby did the bilirubin level exceed 230 µmol/l. Therefore no phototherapy was necessary. No other problems like such as, poor sucking, breathing difficulties or somnolence were observed.

Table II shows the results of the bilirubin concentration. Already on day three there is a slight however statistically not significant difference between the bilirubin concentration in the plasma of the two groups. One day later there is a decreased plasma bilirubin concentration in the study group on MPB, whereas the bilirubin concentration still increased in the babies on placebo. The difference between the bilirubin levels of the two groups on day four is statistically significant ($p < 0{,}001$). There is an insignificant difference, if one looks upon the two subgroups with different birth weights. The effect seems to be a little bit more pronounced in the infants with lower birth weight (figure 1).

Table I: Comparison of factors suspected to influence the bilirubin concentration (mean ± SD)

	Placebo	Methylphenobarbitone	significant differences
sample size	100	98	
gestational age (weeks)	39.47 ± 1.33	39.73 ± 1,32	n. s.
sex male/female	0.53	0.48	n. s.
body weight (g)			
1. day	3477 ± 436	3468 ± 438	n. s.
3. day	3333 ± 416	3345 ± 431	n. s.
decrease (%)	−4.11 ± 2.77	−3.54 ± 2.72	n. s.
body length (cm)	50.5 ± 1.74	50.5 ± 1.58	n. s.
APGAR			
1 min ≥ 9	73	68	n. s.
< 9	27	30	n. s.
5 min ≥ 9	96	90	n. s.
< 9	4	8	n. s.

Table II: Comparison of plasma bilirubin concentration (µmol/l) (mean ± SD)

age	Placebo	Methylphenobarbitone	significant differences
1. day	69.73 ± 26.16	72.78 ± 31.45	n. s.
3. day	108.57 ± 53.47	99.77 ± 47.01	n. s.
4. day	116.37 ± 65.28	87.28 ± 49.65	$p < 0.001$

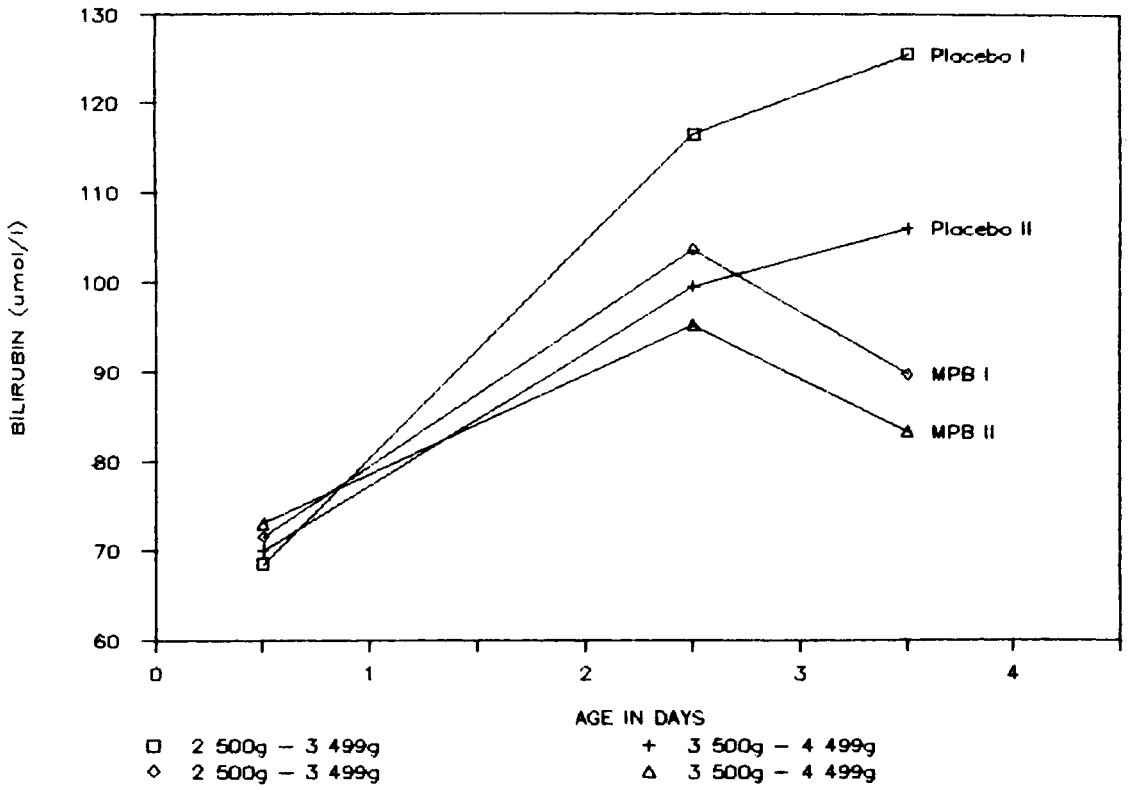

Figure 1: Plasma bilirubin-concentration in fullterm neonates of different birthweight after administration of 3 × 10 mg/kg MPB or placebo on the first day of life.

4 Discussion

Different drugs are in development and research for the prevention and therapy of neonatal hyperbilirubinemia, i.e. clofibrate [15, 16], flumezinol [2]. The unique properties of the (+)isomer of MPB, which is an excellent inductor of different enzymes and lacks the sedative effect of PB might make it well suited for the prevention and early therapy of neonatal hyperbilirubinemia. Up to now the (+)isomer of MPB was not available in sufficient amounts for clinical trials. Therefore we used the racemate for our preliminary investigation. The effect in mature newborns after early treatment is comparable to the results of GMYREK and coworkers [6] with PB and PB in combination with nikethamid. The difference in the plasma bilirubin concentration on day four in their series was 29,5 µmol/l between the group treated by verum and that on placebo. This difference amounted to about 25% of the concentration in the control babies. The differences found in our investigation on day four amounts to 29.1 µmol/l, i.e. 33% of the concentration in the control infants. Similar results were also obtained by STERN and coworkers [19] as early as 1970 using PB. On day four they had found nearly identical differences between the treated and the control group: 1.98 mg/100 ml (= 33.7 µmol/l) corresponding to 29% of the concentration in the control infants.

We suppose that the effect in premature babies, who might be in greater need for pharmacological treatment of hyperbilirubinemia than mature newborns would show analogous effects. The slight difference between the birth weight groups (figure 1) may be a weak suggestion that the effect of MPB is more pronounced in infants with lower gestational age. The difference in gestational age between the two groups, however, amounts to no more than 0.5 weeks with a slightly higher SD of 1.6 weeks.

The results of our study do not justify a recommendation of MPB for the treatment or prevention of neonatal hyperbilirubinemia, however, they promise interesting and useful results, if the investigations are carried out in premature babies using the (+)isomer alone. Performing some pharmacokinetic studies would be necessary as well.

Abstract

In order to find a drug for the prevention of metabolic hyperbilirubinemia of the newborn, which has less sedative effects than phenobarbital (PB) the effect of methylphenobarbital (MPB) on the plasma bilirubin concentration of newborns was studied in a double blind trial. MPB (3 × 10 mg/kg on the first day) reduced the plasma bilirubin level in mature newborns on day four by 33% in comparison to those on placebo. The results justify further investigations in premature babies, who frequently suffer from disturbances which may facilitate the development of bilirubin encephalopathy.

Keywords: Bilirubin elimination, icterus of the newborn, induction of enzymes, methylphenobarbital.

Zusammenfassung

Induktion Bilirubin eliminierender Prozesse durch Methylphenobarbital (MPB) bei reifen Neugeborenen

Die medikamentöse Induktion Bilirubin eliminierender Prozesse ist trotz der bewährten Fototherapie zur Prophylaxe des Neugeborenenikterus bei Neugeborenen in Erwägung zu ziehen, die durch zusätzliche Anpassungsstörungen, Hypoxie, Azidose, Hämolyse, Infektionen oder extreme Unreife besonders zur Entwicklung einer Bilirubinenzephalopathie neigen.

Methylphenobarbital (MPB), das als Antieleptikum im Gebrauch ist, ist ein Razemat zweier aktiver Isomere, deren (+)-Isomer keine sedative Wirkung hat. Demgegenüber haben beide Isomere in unterschiedlichen Systemen an Mensch und Tier eine dem PB vergleichbare Aktivität als Induktoren Bilirubin eliminierender Prozesse. MPB ist bisher am Neugeborenen nicht untersucht.

Wir untersuchten in einem Doppelblindversuch die Wirkung des MPB-Razemats auf den Plasma-Bilirubinspiegel reifer Neugeborener. 198 Neugeborene mit Geburtsgewichten von mehr als 2500 g erhielten dreimal in den ersten 24 Lebensstunden je 10 mg/kg MPB-Razemat. Der Bilirubinspiegel im Venenblut wurde vor der ersten Verabreichung, am dritten und vierten Lebenstag untersucht. Am vierten Lebenstag fiel die Bilirubinkonzentration im Plasma der MPB-Gruppe bereits wieder ab, während sie in der Plazebo-Gruppe noch anstieg. Der Konzentrationsunterschied am vierten Lebenstag zwischen den beiden Gruppen war statistisch signifikant ($p < 0{,}001$).

Die Eigenschaften des (+)-Isomers von MPB lassen es für den Einsatz in der Prophylaxe der Neugeborenenhyperbilirubinämie sehr geeignet erscheinen: es ist ein hervorragender Induktor verschiedener Enzyme und hat keinen sedativen Effekt. Derzeit ist das (+)-Isomer in hinreichenden Mengen für einen klinischen Versuch nicht verfügbar. Wir benutzten für unsere orientierenden Untersuchungen daher das Razemat. Seine Wirksamkeit ist der des PB und des PB in Kombination mit Niketha-mid, wie sie von GMYREK u. a. verwendet wurden, voll vergleichbar.

Weitere Untersuchungen an Frühgeborenen unter Verwendung des (+)-Isomers scheinen vielversprechend.

Schlüsselwörter: Bilirubinelimination, Enzyminduktion, Methylphenobarbital, Neugeborenenikterus.

Résumé

Induction de processus d'élimination de la bilirubine par le methylphenobarbital chez les nouveaux-nés matures

L'induction médicamenteuse des processus d'élimination de la bilirubine pourrait être une approche prometteuse de la prévention de l'ictère des nouveaux-nés qui souffrent de troubles associés tels que l'hypoxie, l'infection, l'acidose ou la maladie hemolytique et l'immaturité majeure, tous éléments qui facilitent l'apparition d'encéphalopathie à la bilirubine.

Le Méthylphénobarbital (MPB), médicament fréquemment utilisé comme antiépileptique et un racémique de deux isomères optiquement actifs. L'isomère (+) n'a pas d'effet sédatif. L'activité d'induction de différents systémes métaboliques chez l'annimal et chez l'homme est néanmoins spécifique des deux isomères et elle est comparable à l'activité du Phénobarbital. Nous avons étudié par une étude en double aveugle l'effet du MPB racémique sur la concentration plasmatique du bilirubine chez des nouveaux nés matures.

198 enfants pesant plus de 2500 g ont reçu du MPB racémique (3 × 10 mg/Kg au cours du premier jour de vie) ou un placebo. La bilirubine a été dosée dans le

sang veineux avant la première administration et entre respectivement 48 heures et 72 heures de vie et 72 et 96 heures.
Au quatrième jour il y a une diminution de la bilirubine plasmatique dans le groupe étudié, alors que dans le groupe placebo les concentrations de bilirubine continuent d'augmenter (tableau II). La différence entre les taux de bilirubine des deux groupes au quatrième jour est significative ($p < 0{,}001$).
L'effet est comparable aux résultats de GMYREK et coll avec le PB et le PB associé au nikéthamide (coramine). Les résultats de notre étude justifient l'étude chez les prématurés de l'isomère (+) seul.

Mots-clés: Elimination de la bilirubine, ictère du nouveau-né, induction enzymatique, Méthylphénobarbital.

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