MOTHERISK *UPDATE*

Antenatal phenobarbital for prevention of intraventricular hemorrhage in preterm infants

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ABSTRACT

QUESTION One of my patients, a 36-year-old, who has had three pregnancies and two live births, delivered her third baby at 32 weeks' gestation. Her first pregnancy was complicated by premature labour, which led to delivery at 30 weeks' gestation. She received antenatal phenobarbital before the first delivery because it was considered proven therapy for preventing intraventricular hemorrhage in preterm infants. I would like to know why it is no longer routinely used.

ANSWER Cumulative results from recent studies have failed to confirm the initial impression of effectivenes of antenatal phenobarbital. It is no longer recommended when preterm delivery is anticipated.

RÉSUMÉ

QUESTION L'une de mes patientes, âgée de 36 ans, a eu trois grossesses dont deux naissances d'un enfant vivant. L'accouchement de son troisième enfant s'est produit à 32 semaines de gestation. Des complications ont eu lieu durant sa première grossesse, notamment un travail prématuré qui s'est traduit par un accouchement à 30 semaines de gestation. Elle a reçu du phénobarbital prénatal avant son premier accouchement car ce médicament était considéré une thérapie éprouvée pour prévenir une hémorragie intraventriculaire chez les nouveau-nés avant terme. J'aimerais savoir pourquoi cette pratique n'est plus systématiquement suivie.

RÉPONSE Les résultats cumulatifs de récentes études n'ont pas réussi à confirmer l'impression initiale de l'efficacité du phénobarbital prénatal. Ce médicament n'est donc plus recommandé dans les cas où un accouchement avant terme est anticipé.

Improving the neurodevelopmental outcome of premature infants is one of the important aims of neonatal care. Intraventricular hemorrhage (IVH), one of the most common causes of brain injury in preterm infants, contributes greatly to adverse neurodevelopmental outcome. Any means of preventing this complication is of great importance but, because IVH occurs most frequently during the first day of life,[1] effective intervention would have to occur before birth or shortly after delivery.

Pathogenesis of IVH occurs due to a combination of factors, including immature and vulnerable germinal matrix in the periventricular region of the brain in association with hemodynamic instability resulting in fluctuations in blood flow to the susceptible area. One of the first treatments suggested as effective for reducing the incidence of IVH was antenatal phenobarbital. The protective effect of phenobarbital was explained by several mechanisms, among them, decreasing the cerebral metabolic rate as a way of decreasing the brain's susceptibility to injury and decreasing the variability of blood pressure changes to prevent surges in blood pressure that could cause or aggravate IVH.[2]

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Clinical trials of antenatal phenobarbital

The first clinical trial of antenatal phenobarbital that demonstrated a reduction in the rate of IVH was performed in 1981 by Donn et al.[3] Since this trial, several other trials have established the role of antenatal phenobarbital for preventing IVH.[4-9] In most of the trials performed in the 1980s, antenatal phenobarbital was shown to be beneficial in preventing either severe grades of IVH

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or all grades of IVH.[4-8] The only trial that failed to show its effectiveness used a subtherapeutic dose.[9]

Evidence for preventing IVH seemed so compelling that use of antenatal phenobarbital became a standard of care in many institutions.[10] A recent Cochrane Collaboration review presented a meta-analysis of all randomized controlled trials (RCTs) using antenatal phenobarbital. More than 1600 women were included in these trials, which showed a protective effect in reducing all grades of IVH (relative risk [RR] 0.75, 95% confidence interval [CI] 0.65 to 0.88) and severe grades of IVH (RR 0.49, 95% CI 0.32 to 0.74).[11]

Despite the apparent effectiveness of antenatal phenobarbital treatment, it is no longer employed in clinical practice. This is mainly due to two recent RCTs that have shed more light on phenobarbital's preventive effect.[12,13] Both trials showed that phenobarbital has no significant protective effect, thus contradicting previous results.

Why conflicting results?

Why do the results of these recent studies conflict with those of previous RCTs? Several explanations are possible. Not all RCTs were blinded, so a preferential bias toward treatment groups could exist. In some studies, treatment groups had more exclusion criteria, again possibly causing a bias in favour of treatment groups. The similarity in results of early studies suggests an uncontrolled confounding factor. When assessed for possible confounders, the most likely candidate would be antenatal steroid use, which has been proven to decrease IVH.[14]

In the studies performed in the 1980s, steroids were either uncontrolled or preferentially given to those in treatment (phenobarbital) groups. Because antenatal corticosteroid use has significantly increased over the last two decades, its possible confounding effect would cause an apparent decrease in the effectiveness of antenatal phenobarbital. If studies using antenatal phenobarbital are scrutinized in chronologic order, we see a clear trend toward decreasing effect of phenobarbital over time. This is consistant with an increase in use of antenatal steroids. Meta-analysis of clinical trials that were not confounded by antenatal steroid use[8,12,13] show no effect of antenatal phenobarbital in preventing IVH (RR 0.89, CI 0.74 to 1.06).

Thus, despite "statistical evidence," mainly influenced by early studies supporting use of antenatal phenobarbital for preventing IVH, the most recent evidence indicates that antenatal phenobarbital does not exert a synergistic effect on antenatal steroid treatment. Because it is possible that antenatal phenobarbital has a detrimental influence on intelligence,[15] there is no longer any role for it in preventing IVH.

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