

Phenobarbital uses in a Maternal-fetal infections suspected case

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Abstract

Introduction : Maternal-fetal infections (MFIs) are important causes of morbi-mortality in neonatal units, particularly in premature and low birth weight newborns.. Benitz and Al have observed that MFIs are very different according to gestational age and are dominated by the group B streptococci with an incidence of 12% in 0.8% of infants less than 28 weeks of amenorrhea and 64.5% in 89.7% of term infants.. A French study states that the three main germs responsible are: group B streptococci (25% - 60%), Escherichia coli (20 - 40%), and listeria (<5%). Risk factors are divided into maternal and fetal risk factors. The most factors commonly implicated are prematurity, premature rupture of membranes, chorioamnionitis, maternal per-Partum fever, and maternal history of genital infection before and during pregnancy. All the studies agree to begin the management of suspected IMF in newborns with the following clinical signs: fever (T>37.5) or hypothermia (T<36), tachycardia (HR>160 beats), tachypnea (RR>60 cycles), jaundice, neurological signs (drowsiness, hypotonic, convulsion) and digestive signs (vomiting, in appetite). According to the French Society of Neonatology in the 2017 version of its recommendations, the care should be provided by:

- (a) A complete physical examination;
- (b) Probabilistic antibiotic therapy with beta-lactam antibiotics and aminoglycosides, but never Phenobarbital.

During our pediatric internship at the State University Hospital of Haiti (HUEH), we have noticed Phenobarbital is administered to newborns with MFIs. Should we question this or is there a relationship between MFIs and Phenobarbital? Our goal is to draw attention to the indications of Phenobarbital in newborns and the importance of discussing the new recommendations in management.

Case Study: This is a 3-day-old male, born at the term in a soiled environment with a birth weight of 2845 gr, of a 31-year-old mother, G3P3 including cesarean section. The pregnancy had been monitored from 5 months of age when she received two vaccinations and had two abdominal-pelvic ultrasounds without revealing in particular, - it should be noted that she has a history of genitourinary infection (GUI) -, the newborn was admitted to the emergency room of the neonatology unit of the HUEH for fever and jaundice.

The first evaluation reveals a tonic, febrile state with the following vital signs: HR: 128 beats/mn, RR: 40 cycles/mn, T° 37.7 and oxygen saturation of 98 %. Physical examination reveals a slight overlap of the sutures, ogival palate with a palpable mass and a skin recoloration time (TCR) of 2 seconds. Examination of the dander and skin reveals grade III jaundice and the malodorous umbilical stump. The clinical impression on admission room was MFI and management was done with Dextrose/Saline (D/S) 0.225 %, amoxicillin 142 mg, IV /8h, gentamicin 8 mg IV, vitamin K: 2 mg IM, Tetanus Serum : 750 IU subcutaneously and Phenobarbital 7 g IV. To confirm the diagnosis, a complete blood count, CRP, HIV, bilirubin level, blood glucose, ionogram, and urine test were ordered. Paraclinical data showed a hemoglobin level of 19.8 gr/dl, red blood cells: 4.87 million; white blood cell count 15,600, lymphocyte count 43%, neutrophil count 55%, eosinophilic count 2%, and platelets 190,000; total bilirubin count 3.2 mg, direct bilirubin 0.9 mg, and indirect bilirubin 2.3 mg, the germ involved was not yet revealed. The newborn was hospitalized and showed a marked improvement in his condition. The main drugs administered are presented in (Table 1).

Table 1 : Drugs used during hospitalization period (Administration day to the first days at Hospital)

	Ampicillin	Gentamicin	Phenobarbital	Vit K	SAT
Admission	142 mg/IV/q8h	8 mg/IV/24hr	7 mg/ IV/q12 hr	2 mg/ IM	750 UI/ Sc
J3	142 mg/IV/q8h	8 mg/IV/24hr			
J4	142 mg/IV/q8h	8 mg/IV/24hr	7 mg/ IV/q12 hr		
J5	142 mg/IV/q8h	8 mg/IV/24hr			
J7	142 mg/IV/q8h	8 mg/IV/24hr	7 mg/ IV/q12 hr		

(IV: Intravenous; IM: Intramuscular; Sc: Subcutaneous; IU: International unit)

Discussion: Phenobarbital or 5-phenyl-5-thiobarbituric acid is an anticonvulsant of the barbiturate family introduced in 1904, it is the drug first in cases of convulsions in newborns. Its mechanism is not very clear, but it appears that it acts mainly at the level of the neuron membrane, particularly through changes in the ion channels, namely sodium (Na+) and calcium (Ca++) (6), and is mainly metabolized by the enzyme CYP2C9, and to a lesser extent by CYP2C19 and CYP2E1. The three main indications of Phenobarbital in neonatology are:

- 1) Enzyme inducer: it facilitates the metabolism of certain drugs such as theophylline.
- 2) Intracranial hemorrhage (ICH): very common in premature newborns, it leads to hydrocephalus and a high risk of neurological disorders.

There are differences of opinion regarding the indication of Phenobarbital in ICH. Smith and I have studied 12 clinical trials involving 982 children with ICH and concluded that Phenobarbital is not recommended for use in neonates. Whitelaw, who examined 740 preterm newborns, reached the same conclusion. Movales and Koerten, on the other hand, have proved the contrary. In a case-control study, they compared 2 groups of neonates less than 32 weeks of age and obtained these results: the first group received 15-40Ug/ml of Phenobarbital and did not give the other group. 21% of cases in the first group had ICH compared to 47% in the untreated group ($P < 0.001$). For example, they concluded that Phenobarbital reduces the incidence of HIC. Phenobarbital is widely used for seizure control in neonates: it controls seizure attacks in 77% of neonates with a loading dose of 20 mg/kg IV and a maintenance dose of 3-4 mg/kg PO.

Other indications for Phenobarbital are noted in the literature such as severe asphyxia, hypoxic-ischemic encephalopathy. However, there is no indication of Phenobarbital in newborns in the case of MFIs. On the other hand, studies have shown that Phenobarbital can reduce jaundice in premature infants. Note that jaundice is one of the signs of MFIs, especially mixed bilirubin jaundice. There is no consensus among researchers about its role in cases of jaundice. Anwar and Al have shown that Phenobarbital has no relevant effect when combined with phototherapy. Chawla and Parmar in a meta-analysis reported that Phenobarbital in premature newborns with unconjugated hyperbilirubinemia decreased bilirubin levels, but phototherapy, and in some cases transfusion, was required to achieve physiological bilirubin levels.

Conclusion and recommendation: Our patient presented the so-called grade III jaundice and the tests showed mixed hyperbilirubinemia, but did this justify the choice of Phenobarbital which was administered at 7mg/dl only and without phototherapy or transfusion? However, in the literature, it is administered in cases of hyperbilirubinemia only at a dose of 20mg/kg in addition to phototherapy. What seems intriguing is the condition of the newborn during hospitalization which was greatly improved and after about 8 days; he had already recovered and was even given his exit. What was the actual effect of Phenobarbital in this case? Is it the enzyme-inducing effect or its action on bilirubin? There should be further comments to conclude from a possible indication of Phenobarbital in MFI cases.

Biography:

Axler Jean Paul is a finishing graduating medical student at the Faculty of Medicine and Pharmacy of the state University of Haiti. He has published more than 3 research papers and serves as reviewer for several scientific journal, like BMJ case report.

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