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NeuroToxicology



Delayed acquisition of neonatal reflexes in newborn primates receiving a thimerosal-containing Hepatitis B vaccine: Influence of gestational age and birth weight

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ABSTRACT

This study examined whether acquisition of neonatal reflexes and sensorimotor skills in newborn rhesus macaques (*Macaca mulatta*) is influenced by receipt of the single neonatal dose of Hepatitis B (HB) vaccine containing the preservative thimerosal (Th). HB vaccine containing a standardized weight-adjusted Th dose was administered to male macaques within 24 h of birth ($n = 13$). Unexposed animals received saline placebo ($n = 4$) or no injection ($n = 3$). Infants were raised identically and tested daily for acquisition of 9 survival, motor, and sensorimotor reflexes by a blinded observer. In exposed animals there was a significant delay in the acquisition of three survival reflexes: *root*, *snout* and *suck*, compared with unexposed animals. No neonatal responses were significantly delayed in unexposed animals compared with exposed. Gestational age (GA) and birth weight were not significantly correlated. Cox regression models were used to evaluate the main effects and interactions of exposure with birth weight and GA as independent predictors and time-invariant covariates. Significant main effects remained for exposure on *root* and *suck* when controlling for GA and birth weight such that exposed animals were relatively delayed in time-to-criterion. There was a significant effect of GA on *visual follow far* when controlling for exposure such that increasing GA was associated with shorter time-to-criterion. Interaction models indicated that while there were no main effects of GA or birth weight on *root*, *suck* or *snout* reflexes there were various interactions between exposure, GA, and birth weight such that inclusion of the relevant interaction terms significantly improved model fit. This, in turn, indicated important influences of birth weight and/or GA on the effect of exposure which, in general, operated in a way that lower birth weight and/or lower GA exacerbated the detrimental effect of vaccine exposure. This primate model provides a possible means of assessing adverse neurodevelopmental outcomes from neonatal Th-containing HB vaccine exposure, particularly in infants of lower GA or low birth weight. The mechanism of these effects and the requirements for Th is not known and requires further study.

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1. Introduction

The Hepatitis B (HB) vaccine was introduced into the US childhood immunization schedule in 1991 (Anon., 1991). This schedule recommended that all infants irrespective of gestational

age (GA) and birth weight born to HB-negative mothers be immunized with a HB vaccine within 12 h of birth (i.e. before hospital discharge (Anon., 1991, 1992)). We were unable to identify pre-clinical or prospective neurotoxicity studies that assessed the safety of this policy.

The two formulations of HB vaccine manufactured during the 1990s contained the preservative thimerosal (Th), an antibacterial and fungistatic agent composed of ethyl mercury and thiosalicylate. The HB vaccine contained 12.5 μg ethyl mercury, given to neonates unadjusted for GA or birth weight. Following safety concerns, particularly in respect of the potential for neurotoxicity, a Congressionally mandated Food and Drug Administration (FDA)

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