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**VITAMIN K DEFICIENCY BLEEDING (VKDB)**

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**Abstract**

Vitamin K Deficiency Bleeding (VKDB) is rare; it can cause severe handicap or death but is preventable by the appropriate use of either oral or intramuscular vitamin K (VK) prophylaxis together with surveillance for liver disease. Konakion Neonatal, the product most commonly used for IM prophylaxis, has now been withdrawn. With exceedingly-rare exceptions, a single 1mg dose of this preparation IM at birth is known to protect against VKDB for several months. Konakion MM, the only licensed IM preparation now available, has a very different formulation conferring enhanced bioavailability when given orally but there are few data about long-term protection after a single IM dose. This BPSU study will provide that data.

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**Background**

VKDB has been the subject of 3 previous BPSU studies which, combined with information from contemporaneous surveys of prophylaxis, have shown a significant fall in the incidence of VKDB and allowed comparison between various prophylactic regimens in use. These data have undoubtedly influenced practice; the principle of VK prophylaxis is now accepted by all UK units<sup>1</sup> (although the route of administration remains controversial) and there is far greater awareness of the importance of investigating any 'warning bleed' or prolonged jaundice.

The third BPSU study (2000-02) found the rate of VKDB in the UK to be at its lowest recorded, comparing favourably with published rates from other countries, with no mortality or long-term morbidity.<sup>2,3</sup> At the time of this study the cremophore preparation of VK (Konakion Neonatal) was used by most of the 60% of units recommending IM prophylaxis.<sup>1</sup> A 1mg IM dose at birth of this preparation is known to provide virtually complete protection against VKDB for several months.<sup>4</sup> The reason is not entirely clear; perhaps the excipient forms an 'intramuscular depot' from which the VK is only slowly released.<sup>5</sup> Konakion Neonatal has now been withdrawn leaving only Konakion MM licensed for IM use.

Konakion MM's novel formulation enhances bioavailability after oral administration; however there are few data about long term serum levels after a single IM dose (we understand a small number of infants underwent formal pharmacokinetic evaluation with blood levels but as far as we are aware the data are not published) and its efficacy in providing long-term protection in large populations is unproven by epidemiological or survey data. The Medicines and Healthcare Product Regulatory Agency have advised a surveillance study to

monitor the effects of withdrawal of the cremophore preparation. This fourth BPSU study of VKDB, together with a contemporaneous survey of VK prophylaxis policies in the same population, will provide the efficacy data required and not available elsewhere.

<b>Coverage</b>	United Kingdom and the Republic of Ireland.
<b>Duration</b>	October 2006 - October 2008
<b>Objectives</b>	To determine the: <ul style="list-style-type: none"><li>• incidence of VKDB and associated outcomes (death, intracranial bleed, significant sequelae)</li><li>• VK prophylaxis given in each case of VKDB and reason if not given</li><li>• presence of risk factors - breast fed, jaundice, liver disease, failure to thrive</li><li>• clinical presentation – timing, site of bleed, warning bleeds</li><li>• treatment given to correct bleeding and its effectiveness</li></ul>
<b>Case definition</b>	Any infant under six months of age with spontaneous bruising, bleeding or intracranial haemorrhage associated with prolonged clotting times (prothrombin time at least twice control value) and normal or raised platelet count, NOT due to an inherited coagulopathy or disseminated intravascular coagulation. This is the same case definition as used in the 3 previous BPSU studies of VKDB, to allow comparison.
<b>Reporting Instructions</b>	Please report any infant presenting with a bleeding disorder in the first six months of life where no alternative firm diagnosis (e.g. haemophilia, septicaemia with DIC) has been established. If there is serious suspicion of VKDB, please report the case and allow us to decide.
<b>Methods</b>	Paediatricians will be asked on a monthly basis, via the orange card system, to report all cases meeting the case definition. Notifying paediatricians will be asked to complete a questionnaire and provide copies of anonymised relevant letters and discharge summary. No specimens are required. A contemporaneous national survey of VK prophylaxis policies, including the annual delivery rate in each unit, will be undertaken to provide the denominator data.
<b>Ethics Approval</b>	This study has been approved by the Cornwall Research Ethics Committee, reference 06/Q2101/74 and is exempt from site-specific assessment. The ethics approval requires that the R&D Departments at NHS organisations contributing data are provided with a copy of the REC application, the REC approval letter and the study protocol. Copies of these items will be sent to each notifying paediatrician with a request to kindly forward them to their R&D Department.
<b>Funding</b>	Funding has been obtained from Roche Products Ltd.
<b>References</b>	<ol style="list-style-type: none"><li>1. Busfield A, McNinch A and Tripp J. Neonatal vitamin K prophylaxis in the Great Britain and Ireland: the impact of perceived risk and product licensing on effectiveness. (submitted ADC 2006)</li><li>2. McNinch A, Busfield A and Tripp J. Vitamin K Deficiency Bleeding in the Great Britain and Ireland; British Paediatric Surveillance Unit Surveys, 1993 – 94 and 2001 – 02. (submitted ADC 2006)</li><li>3. McNinch A W, Tripp J H. Haemorrhagic disease of the newborn in the British Isles: two year prospective study. <i>BMJ</i> 1991;303:1105 – 1109</li><li>4. Cornelissen M, von Kries R, Loughnan P, Schubiger G. Prevention of Vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. <i>Eur J Paediatr</i> 1997 Feb;156: 126 – 130</li><li>5. Loughnan pm, Mcdougall PN. Does intramuscular vitamin K1 act as an unintended depot preparation? <i>J Paediatr Child Health</i>. 1996 jun;32(3):251-4.</li></ol>