Reviewer 1

Procaine Benzylpenicillin in Neonates

Frequently used clinical compendia in the U.S. (American Academy of Pediatrics Redbook, 2006; Pediatric Dosage Handbook, Taketomo CK, Hodding JH and Kraus DM (eds.), 14th edition, Lexi-Comp, American Pharmacists Association, 2008) recommend this drug only for use in the management of congenital syphilis at a dose of 50,000 U/kg/day given intramuscularly (IM) for a period of 10 days. In contrast to recommendations given in the WHO Pocketbook of Hospital Care for Children (2005), there are no data to support the use of procaine benzylpenicillin for the treatment of neonatal infections where crystalline penicillin G is considered to be the drug of choice. This would include treatment of bacterial meningitis where the amount of drug available to the central nervous system following single daily IM injections of procaine benzylpenicillin would be predicted to be far lower than those achieved with currently recommended meningitic dose regimens for crystalline penicillin G and thus, potentially sub-therapeutic.

While the systemic adverse effect profile of penicillin might be expected to be comparable between procaine benzylpenicillin and crystalline penicillin (e.g., hypersensitivity reactions), the formulation containing procaine is associated with specific adverse effects. For example, transverse myelitis with permanent paralysis and gangrene of extremities proximal to the injection site have been associated with the inadvertent intravascular administration (including inadvertent direct intra-arterial injection or injection immediately adjacent to
arteries) of procaine benzylpenicillin. Sterile abscess formation with necrosis and sloughing of the injection site have been reported following IM injection of this formulation into both the thigh and buttocks. Quadriceps femoris fibrosis and atrophy have also been reported following repeated IM administration of procaine benzylpenicillin into the anterolateral thigh (http://www.medsafe.govt.nz/profs/datasheet/c/Cilicaineinj.htm accessed 26 August 2008). For these reasons, the monograph contained in the Pediatric Dosage Handbook (2008) recommends avoiding the use of the formulation in neonates who weigh ≤ 1,200 grams. Finally, it should be noted that the incidence of all of the aforementioned adverse effects associated with procaine benzylpenicillin occur more frequently in neonates than in older patients (Pediatric Dosage Handbook, 2008); an association that likely has a developmental basis given the reduced muscle mass in both preterm and term neonates (contributing to less area for diffusion of the drug bolus injected into the muscle) and altered muscular blood flow (contributing to slower uptake of the formulation into the systemic circulation and increased residence time of the drug in the muscle bed).

Recommendations: 1). That procaine benzylpenicillin be maintained in the EMLc; 2) that its therapeutic use in neonates be restricted to infants weighing > 1,200 grams who have a diagnosis of congenital syphilis and where treatment with crystalline penicillin G (the first line agent) is not possible. The dose for this indication should be 50,000 U/kg/day for a 10 day treatment period; 3) as possible, the site for drug administration should be rotated in accordance with acceptable clinical practices for IM drug injection in neonates.
Caution should be taken to minimize the chance of intravascular injection and 4) the site(s) of administration should be carefully monitored throughout the course of treatment for any signs of vascular compromise and/or tissue injury.