

## CAFFEINE CITRATE - Commercial formulations

### Launch of a commercial formulation in the UK in May 2008

Those responsible for the care of the neonate in the UK and, indeed, in much of Europe, have long been frustrated by the fact that no commercial formulation of caffeine citrate has been available. Luckily it has not been difficult to get something suitable prepared 'in house'. However the Medicines and Healthcare products Regulatory Agency (MHRA) did decide in May 2008 to approve a marketing submission first made in 2003 for one product made in the UK by Viridian Pharma Ltd, a small commercial company based in Newport Gwent, [PL20346/0002] and distributed by Cardinal Health, in Brentwood, Essex [info@martindalepharma.co.uk]. A parallel product, Cafcit<sup>®</sup>, had become available in America in 1999 on the strength of a single small, commercially backed, trial involving 85 babies of 28–32 weeks gestation (Erenberg *et al.*, 2000).

**Caffeine base vs caffeine citrate:** Unfortunately the MHRA have insisted that Viridian label the UK product primarily in terms of the amount of caffeine *base* that it contains (5 mg/ml) rather than the amount of caffeine *citrate* present (10 mg/ml) and, since it has long been the tradition across most of the UK to prescribe the drug by specifying the amount of caffeine citrate the child was to receive, this could well cause some babies to be given twice as much as was intended. It is difficult to know why the MHRA imposed this requirement on the company – the logic is, of course, that it is the caffeine base that is therapeutically active. However, given that this is not how the drug has been prescribed across most of the UK (and in most of the rest of the world too) for the past thirty years, this decision could be hazardous. The company will do what it can to minimise the risk by placing both statements on the label, but the MHRA have insisted that it is the amount of base that should be given prominence. The only advice that can be given to all clinicians is that the drug must, in future, **always** be prescribed either in terms of the amount of caffeine base, or caffeine citrate, but never simply as the amount of 'caffeine' to be given. The current (sixth) edition of this *Formulary* makes this quite explicit.

**SPC restrictions:** Problems do not end here however. The British National Formulary for Children (*BNFC*), like this *Formulary*, states that one primary indication for use is not just the treatment of apnoea but also as an "adjunct to extubation in preterm infants." Unfortunately Viridian's license says, very clearly, that their product should only be used in infants "of sufficient respiratory maturity not to require positive pressure ventilation." Given what was reported at the annual meeting of the American Pediatric Societies in Hawaii in May 2008 this is particularly perverse and unhelpful, and means that the primary indication for using this drug in babies will still remain, in the UK, "off label". Decisions of this sort only serve to discredit, once again, the way the drugs regulatory agency currently operates in the UK.

**Unsupported warnings:** Users of the product marketed by Viridian are warned that use may be unwise "in neonates born to mothers who have ingested large quantities of caffeine prior to delivery, and neonates previously treated with theophylline as they may have pre-existing caffeine in their blood." They are also warned to exercise care "if there have been any unusual rhythm disturbances on a CTG trace before the baby is born, in neonates suffering gastro-oesophageal reflux and those with cardiac disease," and that there is a "potential for interaction with phenytoin or phenobarbitone [sic] if used during pregnancy." In fact there is very little published evidence that any of these things cause a problem, although it is clearly not appropriate to give a first loading dose of caffeine to a baby who has been receiving theophylline (a drug that is now very seldom used in most neonatal units). There are additional warnings about the risk of hypoglycaemia, hyperglycaemia, and hypertension, and a warning that use may cause "gastro-oesophageal reflux, induce stasis and increased enteral secretion and gastric aspirations". The basis for most of these warnings is far from clear.

**Excessive price:** The new product from Viridian comes in 1 ml ampoules that cost £5 and contain 10 mg/ml of caffeine citrate. The same product is advertised as suitable for either IV or oral use and the MHRA has intimated that, because a commercial product is now available, the continued preparation of products 'in house' would only be appropriate if it can be shown that they are 'materially' different. In fact extemporaneous products are in widespread use elsewhere in the world, and have been for thirty years. A 20 mg/ml IV preparation of caffeine citrate can be made by adding 10 g of anhydrous caffeine, and 10.94 g of citric acid to enough bacteriostatic water for injection to bring the resultant solution to 1000 ml (Nahata & Roberts 1987). Barnes *et al.* have described a 10 mg/ml oral product containing potassium sorbate as a preservative with a shelf life of at least a year that can be used for a month once open. It contains 0.1 mmol/ml of sodium (as sodium citrate) added to sustain the stability of the product's pH.

The FDA is well aware that, because the 3 ml vials of Cafcit designed both for IV and for oral use cost \$15 each, most large hospitals in America there currently make their own oral products 'in house'. Indeed quite a number still make their own sterile products. Product availability in the UK is currently in a state of some flux. While most hospital Trusts are now using the sterile product that has recently become commercially available, several are continuing to make an oral product 'in house', or purchasing supplies from a Trust that is, in the belief that it is very much safer to use a product that requires the minimum of handling before administration, and a product with which staff are already fully familiar. The cost of oral administration would also rise almost 30-fold if UK hospitals are not allowed the same latitude in this regard as those in the US.

The IV product that was made by Sandoz for the international neonatal caffeine (CAP) trial is still the product in use in Canada even though it still has no formal licence, This contains 20 mg of caffeine citrate and 15 mg of

sodium citrate made up to 1 ml with sterile water for injection, after adding enough citric acid to adjust the pH. It comes in 5 ml vials and costs about half what Cafcit costs in the United States of America.

## References

- Eisenberg MG, Kang N. Stability of citrated caffeine solutions for injectable and enteral use. *Am J Hosp Pharm* 1984;**41**:2405–6.  
 Nahata MC, Roberts DL. Formulation of caffeine injections for I.V. administration. *Am J Hosp Pharm* 1987;**44**:1308 and 1312.  
 Barnes AR, Hebron BS, Smith J. Stability of caffeine oral formulations in neonatal use. *J Clin Pharm Ther* 1994;**19**:391–6.  
 Erenberg A, Leff RD, Haack DG et al. Caffeine citrate for the treatment of apnea of prematurity: a double-blind placebo-controlled study. *Pharmacotherapy* 2000;**20**:644–52. [RCT]

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### Abstract of the paper presented in Hawaii in May 2008

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#### Caffeine for Apnea of Prematurity (CAP) Trial: Benefits may vary in subgroups.

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**Background:** Caffeine therapy reduces BPD and improves survival without neurodevelopmental disability in VLBW infants. It is uncertain if these effects are consistent across clinically relevant subgroups.

**Objective:** To determine in 2006 CAP trial participants if the benefits of caffeine vary according to 1) the indication for study drug 2) respiratory support and 30 age at randomization.

**Design/Methods:** Post hoc subgroup analyses were performed on:

- 1) indication: treat apnea, prevent apnea or facilitate extubation,
- 2) Positive pressure ventilation (PPV) at randomization: endotracheal tube (ETT), non-invasive or none,
- 3) Start of study drug: early or late ( $\leq 3$  vs  $> 3$  days).

Outcomes assessed were those showing treatment effects in the original analysis. We investigated the consistency of caffeine effects using regression models that incorporated treatment/subgroup factor interactions and report p values for the statistical tests of interaction.

#### Results:

- 1) There was little evidence of a differential treatment effect of caffeine over subgroups defined by the clinical indication for starting study drug.
- 2) The size and direction of the caffeine effect on death or disability differed depending on PPV at randomization ( $p = 0.032$ ). ORs (95% CI) were: no support 1.32 (0.81, 2.14); non-invasive support 0.73 (0.52, 1.03); ETT 0.73 (0.57, 0.94). Adjustment for baseline factors strengthened the effect ( $p = 0.017$ ).
- 3) Starting study drug early resulted in larger reductions in days of respiratory support. Postmenstrual age at time of discontinuing positive pressure ventilation was shorter with earlier treatment ( $p = 0.014$ ). Mean differences (95% CI) were: early 1.35 (0.90, 1.81) weeks; late 0.55 (-0.11, 0.99) weeks. Adjustment for baseline factors weakened this effect ( $p = 0.032$ ).

**Conclusions:** There is evidence of variable beneficial effects of caffeine. Infants receiving respiratory support appeared to derive more neurodevelopmental benefits from caffeine than unsupported infants. Infants who started caffeine early had a greater reduction in time on ventilation.

#### See:

- Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;**354**:2112-21. [RCT]  
 Schmidt B, Roberts RS, Davis P, et al. The long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;**357**:1893–1902. [RCT] (See also 1967–8.)