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Perspective

Is Caffeine Really a Magic Bullet for Neonatologists?

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Apnoea of prematurity (AOP) is a common developmental disorder with an incidence that increases with decreasing gestational age. Observational studies have demonstrated associations between AOP and deficits in cerebral oxygenation, increased risk for retinopathy of prematurity, and death or disability [1].

Caffeine, a drug with pleotropic organ effects, is effective for the treatment of AOP. Caffeine inhibits adenosine receptors (mainly in the heart and brain), increases respiratory drive, metabolic rate, diaphragm function, and diuresis among other effects. Apnoea events are frequently associated with bradycardias and desaturations which result in short term interventions such as increased ventilatory support, increased oxygen exposure, increased stimulation. The benefits of caffeine may result from prevention of interventions generally suspected of adverse long-term neurodevelopmental effects. Although the major clinical concern for infants put on caffeine was the potential toxicity on brain development, randomised studies found improved lung function and improved motor function at 11 years of age (yet with impaired growth of the corpus callosum) in patients receiving caffeine compared with those receiving placebo [2-4].

Timing

Caffeine therapy is commonly started by day 3 of life (even at admission at many Centres) based on the results of randomised and observational studies. However, some authors found increased prevalence of neurological complications when the drug is administered at high doses on day 1 in infants born < 30 weeks of gestation [5].

Discontinuation

The general recommendation is to discontinue therapy at a time point following AOP resolution, after which an infant would be apnoea free for 5 - 7 days prior to discharge. There may also be some benefit for extending the duration of caffeine therapy. A randomised trial in which preterm infants on caffeine therapy had either an extended course until 40 weeks postmenstrual age (PMA) or stopped therapy following AOP resolution between 34 and 37 weeks PMA reported that prolonged therapy resulted in fewer episodes of intermittent hypoxia and more time spent at goal saturation [6]. However, there is lack of data on the relationship between the cumulative dose of caffeine and subsequent outcomes.

Dose

Currently, there is no clear evidence about the optimal caffeine dose. Higher doses of caffeine compared with lower doses may reduce extubation failure, but high doses early after birth may result in cerebellar injury, although the trials of later use of high-dose caffeine show potential reduction in adverse neurodevelopmental and other important outcomes. There is uncertainty on the target plasma concentration and its correlation with efficacy, as clinically effective plasma concentrations vary over a wide range of 5 to 50 mg/L [7]. In the subgroup of infants who do not show a clinical response to standard doses of caffeine, higher plasma levels may be targeted, and monitoring

of plasma levels may be prudent. Salivary sampling may be an easy, non-invasive method proposed for a reliable measurement of caffeine concentrations [8].

Safety

The main adverse effects of caffeine are tachycardia, hypoglycaemia, slower weight gain and increased risk of seizures [9]. A potential association between the administration of caffeine and the development of necrotising enterocolitis in premature infants have been reported [10]. In a retrospective study, the cumulative dose and duration of therapy of caffeine, as well as steroids, were associated with osteopenia of prematurity [11]. More data are needed in order to rule out long-term consequences on central nervous system and sleep patterns among patients treated with caffeine (particularly at high doses).

In conclusion, caffeine is a very effective therapy for the prevention/treatment of AOP and post-extubation failure in newborns. Although it is usually well tolerated even in extremely preterm infants, further studies are needed to shed light on optimal time and discontinuation, target blood levels and long-term safety.

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