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Caffeine use in the neonatal intensive care unit

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A B S T R A C T

Caffeine is the most frequently used medication in the neonatal intensive care unit. It is used for the prevention and treatment of apnea, although this has been associated with lower incidence of bronchopulmonary dysplasia (BPD) and patent ductus arteriosus as well as intact survival at 18–21 months of life. Although neurodevelopmental advantage was no longer statistically significant at age 5 years, caffeine was associated with sustained improvement in co-ordination and less gross motor impairment than placebo. The mechanism of action of caffeine on prevention of apnea and activation of breathing seems to be through central inhibition of adenosine receptors. However, its impact on BPD and neurodevelopmental outcomes might be induced through its effects as anti-inflammatory mediator, protection of white matter, and induction of surfactant protein B. Whereas long-term studies have documented the safety of caffeine as used in current practice, further studies are clearly needed to identify optimum dosing, and time of starting and discontinuing caffeine.

1. Introduction

Over the last 40 years neonatology has experienced a multitude of changes in practice. Survival has improved markedly as has the number of neurodevelopmentally intact survivors. This may be attributed to many advances, including our enhanced understanding of both respiratory and central nervous system maturation. Respiratory control provides a key link between the immature lung and brain. It is, therefore, not surprising that xanthine therapy has found a prominent place in the management of high-risk neonates. Nonetheless, greater understanding of its mechanism of action and fine tuning of clinical practice are needed, as addressed in this review.

2. Historical perspective

2.1. Introduction into neonatology

There has been recognition since the 1930s and 1940s that both caffeine and aminophylline act as respiratory stimulants, presumably by increasing sensitivity to CO_2. In 1973 a report from the UK in 10 preterm infants demonstrated that apneic attacks were reduced or eliminated with aminophylline suppositories [1]. This set the stage for a series of studies in North America beginning in the mid-1970s that apnea could be reduced with theophylline and caffeine therapy [2,3]. Although concerns about safety were expressed, the response was so beneficial that a randomized clinical trial was considered inappropriate and did not occur for several decades.

2.2. Safety

Concerns about safety included the known side-effects, such as tachycardia and possible diuresis, but were focused primarily on the effects of xanthine therapy on behavioral state and metabolic rate. Despite the obvious stimulant effect of caffeine in later life, sleep organization did not appear to be affected in preterm infants, given the limits of available monitoring techniques; this impression persists to this day. Not surprisingly, increased respiratory drive might be associated with an increase in metabolic rate [4]. This has been confirmed in the CAP Trial [5] by a lag in weight gain in caffeine-vs placebo-exposed infants. However, this lower weight trajectory was not sustained and the benefits of caffeine appeared to supervene. Historically this concern led to a desire to maintain xanthine concentrations as low as possible. A final concern has been a potential effect on cerebral blood flow; numerous studies obviously employing non-invasive techniques in neonates have given inconsistent results with no clear detrimental effect on outcome.

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3. Theophylline versus caffeine

Although not universally available, caffeine is now the most widely used xanthine therapy, constituting 96% of all methylxanthines used in clinical practice. This is the result of many comparative studies done over several decades. Bairam et al. documented in a double-blind study that whereas both theophylline and caffeine were effective, the former tended to have more side-effects, and the latter exhibited greater pharmacologic stability, allowing for single maintenance daily dosing [6]. This has led to the broad consensus that therapeutic drug-monitoring of caffeine, when used for apnea of prematurity, is generally unhelpful and unnecessary [7]. Interestingly, theophylline can be methylated to caffeine in the neonate [8]. This may contribute to its efficacy, raising questions whether plasma concentrations of both xanthines should be measured in theophylline-treated infants.

4. Mechanism of action

4.1. Physiologic/biologic mechanisms

4.1.1. Enhanced respiratory control

There is little doubt that respiratory neural output is increased by xanthines, and it appears that it is particularly prominent in the neonatal period [9] (Fig. 1). The prominent effect on respiratory control in the neonate may relate to, as-yet poorly understood, neurodevelopmental maturational differences and/or the relatively high circulating concentrations of caffeine we deliver to preterm infants. Both central and peripheral mechanisms have been implicated. The former includes reversal of adenosinergic inhibition (as discussed later) of inspiratory neurons in the brainstem, enhanced CO_2 responsiveness, and possibly decreased hypoxic depression of breathing [10,11]. An effect of xanthines on peripheral chemosensitivity has also been implicated in animal models [12,13]. Peripheral chemoreceptors need to be intact for caffeine or aminophylline to increase ventilation and reverse hypoxic respiratory depression.

4.1.2. Improved diaphragmatic contractility and airway function

In recent years the concept of diaphragmatic fatigue appears to have received less attention as a cause of respiratory failure. Previous studies in adult patients with chronic obstructive pulmonary diseases demonstrated that theophylline enhanced transdiaphragmatic pressures via an effect on cellular calcium metabolism, as shown in a mature rodent model [14,15]. Whereas neonatal data were unable to confirm an effect of aminophylline on diaphragm contraction in a quietly breathing piglet [16], Parikka et al. reported an increase in diaphragmatic electrical activity in extremely low birth weight infants 30 min after a caffeine-loading dose [17].

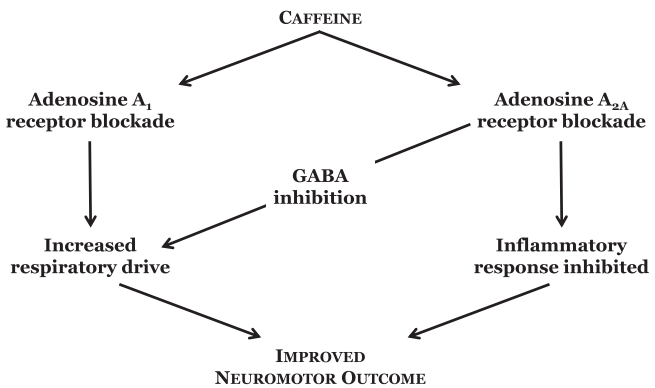

Fig. 1. Proposed pathways by which neonatal caffeine therapy results in improved longer-term outcomes. Other pathways, such as white matter protection and enhanced surfactant production, have been proposed.

Whereas increased airway reactivity is a major longer-term problem in former preterm infants, the benefits of bronchodilator therapy in the neonatal intensive care unit (NICU) are mixed. Xanthines can serve a bronchodilator function and a group of infants with bronchopulmonary dysplasia (BPD) did demonstrate improved respiratory function after caffeine administration [18]. Nonetheless, it is doubtful that this is a major physiologic mechanism for the beneficial effects of caffeine in preterm infants.

4.1.3. CNS white matter protection

Neonatal animal data support the concept that chronic hypoxia induces periventricular white matter injury via adenosine receptor activation (see below). This raises the possibility that caffeine may provide a protective effect via adenosine receptor blockade. In neonatal mice caffeine reversed hypoxia-induced abnormal oligodendrocyte maturation [19]. However, since adenosine release induced by hypoxia may, in theory, also have a neuroprotective effect, it is questionable whether caffeine, as is used in preterm infants, directly elicits white matter protection [20].

4.1.4. Anti-inflammatory effect

Apart from enhancement of respiratory neural output, inhibition of inflammation is possibly the most likely mechanism whereby caffeine exerts its benefit in neonates. Three recent studies in neonatal animal models support this concept. In one study, hyperoxia-induced pulmonary inflammation, which is a well-established neonatal model, and the resultant cellular inflammatory response were reversed by caffeine in infant rats [21]. In another study employing preterm rabbits, caffeine additionally reversed the functional and structural lung injury induced by hyperoxic exposure [22]. We have studied cytokine expression and respiratory function in rat pups in which proinflammatory lung pathophysiology was induced by injecting lipopolysaccharide into the amniotic sac prior to delivery. Postnatal caffeine significantly reduced proinflammatory cytokine expression in the lung and improved postnatal respiratory system resistance in the pups [23]. Given the immunomodulatory potential of caffeine, drug and cytokine concentrations have been correlated together in preterm infants. Available data suggest that whereas caffeine, at therapeutic concentrations, may inhibit activation of a proinflammatory cascade, and its adverse clinical consequences, these benefits may be diminished when caffeine concentrations exceed the therapeutic range [24].

4.1.5. Induction of surfactant protein B transcription

Caffeine has been shown to induce the transcription of various surfactant protein B transcription factors through a c-AMP-dependent pathway [25]. Furthermore, there was a synergistic action between various steroids and caffeine in induction of endogenous surfactant protein production, indicating the ability of caffeine to amplify the signaling pathways of glucocorticoids.

4.1.6. Potentially adverse biologic effects

Whereas human infant data clearly demonstrate benefit for caffeine therapy, questions have been raised about potential safety concerns and adverse effects. Much of this concern is derived from rodent data. In contrast to the anti-inflammatory effect described above, lung inflammation and alveolar apoptosis were increased after caffeine exposure in hyperoxic mouse pups, but this may relate to a relatively high caffeine dosage [26]. In the brain of developing mice, a dose-dependent effect of caffeine was observed in decreasing astrocytogenesis [27]. Furthermore, early caffeine

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