The Use of Caffeine for Apnoea Associated with Trisomy 13 and Trisomy 18

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Apnoea is a major complication and a leading cause of death for infants with trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) In recent years, the question of safety and potential merits of caffeine use to mitigate apnoea associated with these conditions has been prompted by parents.

The phenotype of Patau syndrome includes features of cleft lip and palate, anophthalmia/microphthalmia, postaxial polydactyly, scalp defects, ear abnormalities, cardiac anomalies, omphalocele, central apnoea, holoprosencephaly, seizures and neurodevelopmental delay. Edwards syndrome is associated with characteristic craniofacial features, cleft palate, overriding fingers, clenched fists, rocker bottom feet, syndactyly, hypotonia, central apnoea, neurodevelopmental delay, seizures, cardiac anomalies, omphalocele and kidney anomalies. The prevalence of live born infants with trisomy 18 and trisomy 13 is estimated as 1/6,000-1/8,000 and 1/10,000-1/20,000 respectively¹,². A 2019 study across 18 countries reported the median mortality for trisomy 13 and trisomy 18 in the first week of life was 48% and 42% respectively, half of which occurred on the first day after delivery³. Mortality in the first year of life was 87% for infants with trisomy 13 and 88% for infants with trisomy 18, therefore approximately 10% of infants may survive to 1 year of age³. A 2015 study of 36 infants born with trisomy 18 reported the most common cause of death in both preterm and term infants before 30 days of age was respiratory failure or apnoea, whereas babies who survived longer than 30 days of age died primarily from heart failure⁴.

Apnoea associated with these syndromes can be central, obstructive, or epileptic in origin. Central apnoea is due to temporary failure of the pontomedullary pacemaker to stimulate the normal breathing rhythm. It may be caused by a variety of neurological, neuromuscular, brainstem or craniofacial abnormalities. There is considerable overlap in the clinical presentation of central and obstructive apnoea. Obstructive apnoea is secondary to obstruction of the airways and ongoing central stimulation of the respiratory system is present.
These infants are at increased risk of development of obstructive apnoea due to associated craniofacial features, hypotonia, laryngomalacia and tracheomalacia and adenoid and lingual tonsil hypertrophy. Apnoea secondary to epileptic seizures is increasingly recognised in infants with trisomy 18. A 2015 study of 16 such infants identified three with electroencephalogram (EEG) confirmed seizures, two of whom suffered apnoea corresponding with ictal discharges. Antiepileptic medication was successful in treating the epileptic apnoea identified in these three infants. Kumada et al also reported a case of an infant with Edwards syndrome who developed epileptic apnoea at 10 months of age whose epilepsy was successfully managed with zonisamide. Both reports stress the critical differentiation of epileptic apnoea from central apnoea since medications, such as theophylline and caffeine, which may be considered to ameliorate central apnoea, can be harmful to individuals with epileptic apnoea.

Management of apnoea for infants with trisomy 13 and trisomy 18 will depend on whether the apnoea is central, obstructive or epileptic in nature, associated medical issues, and parental wishes. Potential therapeutic strategies include medication, non-invasive ventilation, surgery, conservative management or acceptance. Medications including acetazolamide, theophylline and progesterone have been theorized as potentially beneficial in the management of apnoea and sleep disordered breathing in the general population. However, trials evaluating their safety and efficacy are lacking and there are no reports at present of their use in trisomy 13 or trisomy 18 patients.

The therapeutic evidence base for caffeine has been most thoroughly established within the premature population. Caffeine reduces the severity of apnoea of prematurity through stimulation of the respiratory centre in the medulla, increased minute ventilation, increased sensitivity to carbon dioxide, improved contraction of the diaphragm, enhanced skeletal muscle tone and modulation of neurotransmitters, and peripheral chemoreceptor activity. Numerous studies have demonstrated that caffeine use in the premature population reduces the frequency of apnoea, promotes independence from mechanical ventilation, decreases intermittent hypoxemia and reduces the likelihood of developing bronchopulmonary dysplasia. Therapeutic use of caffeine outside of the premature population is not commonplace in clinical practice nor documented in the available literature. No literature currently exists documenting the use of therapeutic caffeine for amelioration of apnoea associated with trisomy 13 or trisomy 18 patients.

While caffeine has a proven safety profile and known benefits in the premature population it would be remiss to assume that such characteristics could be directly applicable to the Patau and Edwards syndrome populations. There is no evidence base for its use in this context. Babies with trisomy 13 and trisomy 18 may suffer a myriad of anomalies which may affect the pharmacokinetic and pharmacodynamic profiles of the drug. There is no commonly adopted standardised protocol for the optimal timing and dosing of caffeine therapy outside of respiratory management of premature infants, and there are potential serious consequences of caffeine overdose. The use of caffeine for infants and children with trisomy 13 and trisomy 18 poses other practical questions including how to best measure its therapeutic effect, how to dose adjust appropriately, how to monitor for toxicity and when to stop administering the medication.
As apnoea is a leading cause of death in the first days and weeks of age for infants with trisomy 13 and trisomy 18 ethical concerns of administering a medication which may interrupt a natural death must be duly considered.

Clinicians must consider the origin of apnoea, suitable investigations and management holistically. Physicians must be prepared for balanced conversations with families, aware of the current evidence base for therapeutic interventions and have fully considered the ethical implications posed by the individual case. Whilst interest in the use of caffeine in this situation for management of apnoea is understandable, the authors of this article contend that there is not currently sufficient evidence to justify or recommend widespread unselected use. As described, in some circumstances it may indeed be harmful and cause unnecessary distress. Performing a sufficiently powered and controlled study is unlikely to be possible and clinicians should continue to act in a clinically informed case by case basis.

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