Pediatrics and Neonatology (2017) xx, 1–7

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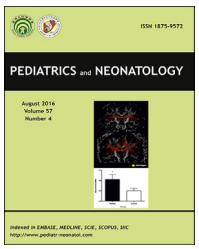

REVIEW ARTICLE

Caffeine citrate — Is it a silver bullet in neonatology?

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Received Jul 27, 2016; received in revised form Sep 22, 2016; accepted Oct 19, 2016
Available online ■ ■ ■

Key Words
caffeine;
apnea;
preterm;
ventilation;
extubation

Caffeine citrate is one of the most prescribed drug in the present day NICU for apnea. Its efficacy, tolerability, wide therapeutic index and safety margin has made it the drug of choice among the methylxanthines. Its therapeutic uses in apnea of prematurity, mechanical ventilation, bronchopulmonary dysplasia has made it a "silver bullet" in neonatology. However, there are still controversies surrounding this drug. This review is aimed to update the reader about the basic pharmacology, current therapeutic uses, adverse effects, controversies as well as present and future research of caffeine.

1. Introduction

Caffeine citrate is presently one of the most prescribed medicines in neonatal units for apnea of prematurity. It is the first choice among all methylxanthines because of its efficacy, better tolerability and wider therapeutic index as well as longer half-life.[1] Although the use of methylxanthines has been present for more than 40 years, it has gained wider acceptability in the last decade only. The Caffeine for apnea of prematurity [CAP] trial has substantiated the efficacy, safety and tolerability of caffeine in preterm infants. There were other trials before the CAP trial, but all were smaller and focused on short-term use only.[2] With wider use after the CAP trial, caffeine has now become one of the most preferred drugs for apnea among neonatologists worldwide and has been named a "Silver" or "Magic" bullet.[3,4] Despite this, there are controversies surrounding this drug which future research may resolve. This review is intended to discuss brief history, updated pharmacology, therapeutic uses, adverse effects and controversies as well as the future research of this drug.

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http://dx.doi.org/10.1016/j.pedneo.2016.10.003

Please cite this article in press as: Shrestha B, Jawa G, Caffeine citrate — Is it a silver bullet in neonatology?, Pediatrics and Neonatology (2017), http://dx.doi.org/10.1016/j.pedneo.2016.10.003

2. Brief history

Coffee has been in use since the 15th Century as a rejuvenating drink. It was in the early 19th Century that pure caffeine was extracted from Arabian mocha coffee beans by the young physician, Friedlieb Ferdinand Runge.[5] In 1973, Kuzemko and Paala first published their landmark paper on the successful treatment of apnea in 10 preterm babies using aminophylline.[6] Further studies confirmed the efficacy of aminophylline in the prevention of apnea.[7,8] It was not until 1977 that Aranda JV et al first used caffeine as a therapy against apnea of prematurity successfully.[9] After many years of research, the CAP trial substantiated caffeine as the ultimate drug for apnea of prematurity.

3. Physiochemical properties

In its pure form, caffeine is a white odorless powder with melting point around 235° C.[10] Caffeine is slightly basic in nature with pKa value of around 0.6.[11] The chemical structure of caffeine is represented in Figure 1. Caffeine is classified under an achiral molecule which may be synthesized from dimethylurea and malonic acid.[12,13] However, as caffeine is easily obtained as a by-product of decaffeination, it is rarely synthesized.[14]

4. Pharmacokinetics

Caffeine is rapidly and completely absorbed orally with almost no first pass metabolism. It is metabolized by the enzymes in liver whose maturity progresses with increasing gestational age. Hence, the metabolism of caffeine in preterm neonates is much slower than in children and adults.[1] Microsomal cytochrome P450 mono-oxygenase and enzyme xanthine oxidase are the enzymes responsible for its metabolism. In preterm neonates, the predominant process of caffeine metabolism is N7 demethylation, which increases exponentially with postnatal age.[15] The half-life of caffeine in preterm neonates is very long, ranging from 65 h to 102 h. This is maintained even up to 38 weeks until the maturity of hepatic biotransformation.[15] The rate of metabolism of caffeine is found to be higher in female than male preterm neonates.[16]

Peak plasma concentration with both oral and intravenous route is almost the same and is reached within thirty minutes to two hours. The clearance increases non-linearly with increasing post-natal age, reaching a plateau at 120 days, and volume of distribution increases linearly with increasing weight.[1,17] The bioavailability of oral dose is not disturbed by concomitant feeds. Renal route is the main route of excretion in neonates, where almost 86% of the drug is passed unchanged in urine, whereas in adults only 4% is excreted via renal route. The elimination half-life starts to decrease from birth and reaches the adult values at 60 weeks' post-conception age.[17]

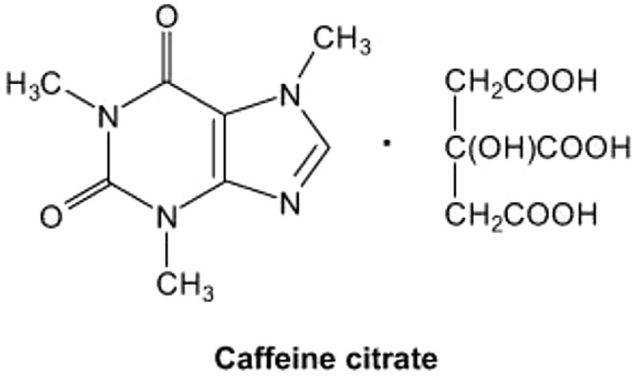

Figure 1 The chemical structure of caffeine.
Adapted from Comer AM, Perry CM, Figgitt DP. Caffeine citrate: a review of its use in apnea of prematurity. *Pediatric Drugs* 2001;**1**:61–79.

5. Pharmacodynamics

5.1. Mechanisms of action

Three underlying mechanisms constitute the basis of caffeine's pharmaceutical effects. Firstly, it is the adenosine receptor antagonist, secondly, it is a phosphodiesterase inhibitor, and thirdly, it is an active intracellular calcium mobilizer.[17] Figure 2 represents the proposed mechanisms of actions of caffeine citrate.

Adenosine is a purine nucleoside present in the brain whose level rises with inflammation. It has four known receptors — A1 and A2a, A2b and A3. These receptors, with their effects upon adenylate cyclase, lead to numerous effects such as central respiratory depression, sedation, anti-diuresis and decreased GFR, smooth muscles constriction and dilation, locomotor activity, etc. Caffeine, a trimethylxanthine, is a known specific inhibitor of at least two of these receptors—A1 and A2a. By blocking these receptors, caffeine manifests the most important pharmacological effects in preterm neonates.[2,17]

Caffeine is also an inhibitor of phosphodiesterase and prevents breakdown of cyclic adenosine monophosphate [cAMP]. Increased level of cAMP leads to stimulation of the central nervous system. However, being a weak inhibitor, a much higher concentration of caffeine is required and at therapeutic doses caffeine is unlikely to mediate this effect.[17,18]

Caffeine also binds to calcium channels and releases calcium from intracellular sites. It also inhibits voltage-

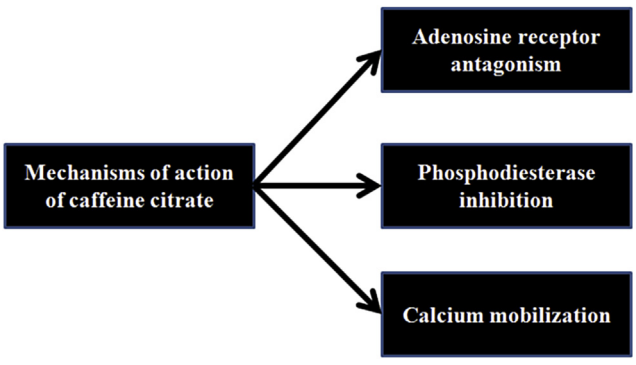

Figure 2 Mechanisms of action of caffeine citrate.

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