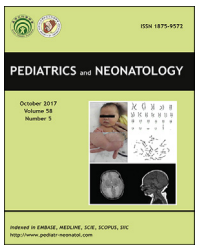
Pediatrics and Neonatology (2017) 58, 391–397

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



Review Article

Caffeine citrate — Is it a silver bullet in neonatology?

Bikash Shrestha [a,*], Gaurav Jawa [b]

[a] Department of Paediatrics, Nepalese Army Institute of Health Sciences, Bhandarkhal, Sanobharyang, Kathmandu, Nepal
[b] Department of Neonatology, Fortis La Femme Hospital, New Delhi, India

Received Jul 27, 2016; received in revised form Sep 22, 2016; accepted Oct 19, 2016
Available online 27 March 2017

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.

* Corresponding author. Department of Paediatrics, Nepalese Army Institute of Health Sciences, Bhandarkhal, Sanobharyang, GPO Box-10160, Kathmandu, Nepal. Fax: +977 1 4881263.
E-mail address: kalmaan@yahoo.com (B. Shrestha).

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]

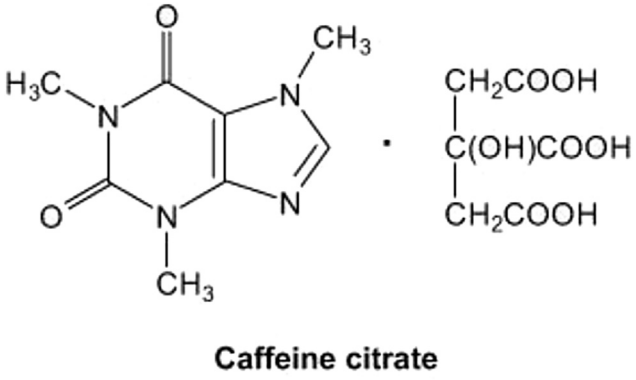


Figure 1 The chemical structure of caffeine.
Adapted from Comer AM, Perry CM, Figgitt DP. Caffeine citrate: a review of its use in apnea of prematurity. *Pediatric Drugs* 2001;**1**:61–79.

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-

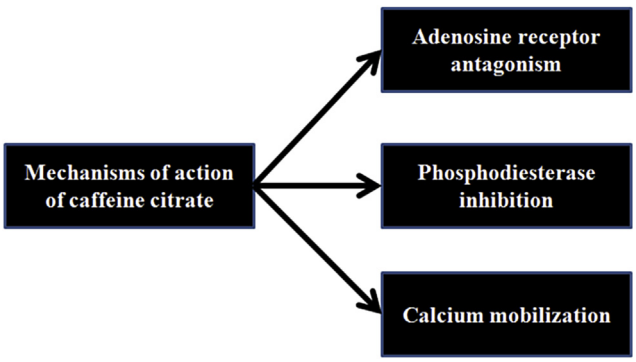


Figure 2 Mechanisms of action of caffeine citrate.

sensitive calcium channels and may inhibit neurotransmission. However, the dose required for these effects may be in toxic levels.[18] On the other hand, considering the wide therapeutic index, its actions of phosphodiesterase inhibition and calcium metabolism might be relevant. Further research is warranted into these aspects of mechanism of action of caffeine.

5.2. Pharmacologic actions

Caffeine stimulates the respiratory center, sensitizing it to hypercapnia. This leads to increase in mean respiratory rate and tidal volume, improved pulmonary blood flow, better carbon dioxide sensitivity and enhanced diaphragmatic function and breathing pattern.[1,17] It also acts as a central stimulant as well as a somnolytic agent. The adenosine blocking action of caffeine is also known to secondarily affect several other neurotransmitters in the brain like dopamine, serotonin, noradrenaline, acetylcholine, gamma-aminobutyric acid [GABA], etc.[17] Caffeine stimulates the myocardium and increases heart rate, cardiac output, stroke volume as well as mean arterial blood pressure. In kidneys, caffeine increases glomerular filtration rate and produces diuresis. This is primarily mediated via its adenosine antagonistic activity in the kidneys. Caffeine also increases basal metabolic rate, enhances catecholamine secretion and alters glucose homeostasis.[15]

5.3. Dosing and route

Caffeine is available as caffeine citrate, which is available in both oral and injectable formulations. Earlier, caffeine was also available as an intramuscular injection of caffeine benzoate. However, in view of bilirubin displacement from the albumin binding sites in the neonates, this formulation has gone out of favor.[19] The dose of caffeine base is half that of caffeine citrate. The most popular dosing of caffeine citrate is 20 mg/kg loading and 5 mg/kg of maintenance dose OD, given either as slow intravenous infusion over twenty to thirty minutes or as oral formulation. This standard dosing is known to achieve therapeutic level of eight to 20 mg/L in more than 70% of neonates.[15] However, many studies have shown higher doses of caffeine to be more effective with negligible adverse effects.[20–23] Loading dose of up to 50 mg/kg and maintenance dose of up to 20 mg/kg has been shown to be more effective in reducing apneic episodes and facilitating extubation in comparison to standard dose. Table 1 shows the two possible doses for caffeine in preterm neonates. However, no consensus has been reached regarding this new, higher therapeutic dose of caffeine and future studies are awaited on this subject.

5.4. Drug interactions

The dependency of caffeine upon cytochrome P450 monooxygenase makes it susceptible to interact with those drugs which are a substrate for, or inhibit or induce, this hepatic enzyme. Drugs like ketoconazole and cimetidine inhibit caffeine metabolism and hence lower doses of caffeine may be required while these drugs are being used concomitantly. Anti-convulsant drugs like phenytoin and phenobarbitone, on the other hand, potentiate caffeine metabolism and may necessitate higher doses of caffeine when used together.[15,17]

5.5. Drug level

The caffeine level can be measured in blood, plasma, serum or urine. The plasma caffeine level in regular coffee drinkers is around two to ten mg/L.[24] The therapeutic range of caffeine for apnea in preterm neonates is eight to 20 mg/L. It is a drug with wide therapeutic index and has been shown to be safe even at higher levels of 50 to 84 mg/L.[1,15,17] The caffeine level in acute overdose may be above 40—400 mg/L. In sports, urinary concentration above 15 mg/L is taken as abuse level.[24] Considering a wide safe margin and minimal adverse effects, regular monitoring of serum level may not be required, unless there is suspicion of toxicity or lack of clinical effects.[25–27]

6. Therapeutic uses

6.1. Apnea

The most important therapeutic value of caffeine has been in reducing apnea of prematurity. Henderson-Smart and De Paoli concluded methylxanthines to be effective in reducing the frequency of apnea of prematurity and the use

Table 1 The regular and alternate doses of caffeine citrate.

Age (PMA)	Usual dose[a]	Optional dose/ alternate dose[a]
Birth to 34 weeks	Loading — 20 mg/kg Maintenance — 5—10 mg/kg (Start at 5—8 mg/kg and increase to 10 mg/kg) once daily	Loading — up to 80 mg/kg Maintenance — up to 20 mg/kg
More than 34 weeks	Not established	Not studied

[a] The doses refer to caffeine citrate dose. The caffeine base dose is half of caffeine citrate dose. The dose is same for both oral and injectable solutions.

Adapted from Dobson NR, Hunt CE. Pharmacology review: Caffeine use in neonates: Indications, pharmacokinetics, clinical effects, outcomes. *Neoreviews* 2013;**14**:e540.

of mechanical ventilation in two to seven days after starting treatment.[28] Among the methylxanthines, caffeine has been the choice of drug over theophylline because of its efficacy and better safety profile. A systematic review of three trials of comparative study between caffeine and theophylline found equal efficacy of caffeine with lesser adverse effects.[29] The post hoc analysis of the CAP trial also showed that infants treated with caffeine had better clinical outcomes.[30–32] Considering the improved outcomes and better safety profile of caffeine, the reviewers concluded caffeine to be the "preferred drug" for the treatment of apnea of prematurity. Although caffeine has been effective for treatment, Henderson-Smart and De Paoli found that there is not enough evidence at present to determine the prophylactic role of caffeine.[33] However, considering the various positive clinical effects as shown in the CAP trial with minimal adverse effects, early caffeine therapy may be justified in the premature infants. Besides apnea of prematurity, caffeine was also found to be effective in other causes of apnea like post-operative apnea, general anesthesia-related apnea, viral infection-related apneas, and apneas associated with apparent life-threatening events.[1]

6.2. Ventilation

The systematic review of methylxanthines prophylaxis for weaning and facilitating extubation in mechanically ventilated preterm infants has concluded that there is significant reduction of extubation failure within 1 week (RR 0.48, 95% CI 0.32–0.71).[34] Several trials provided the evidence that high dose caffeine in the periextubation period reduced extubation failure as well as duration of mechanical ventilation with negligible side effects.[20,21,23] The CAP trial mentioned that caffeine helped in reducing the days of oxygen use, positive pressure ventilation and endotracheal intubation but did not substantiate the extubation rate directly.[30] The exact mechanism by which caffeine facilitates extubation is not known but it may be related to the effect of caffeine which leads to improved respiratory muscle strength.[35]

6.3. Bronchopulmonary dysplasia

Caffeine has been shown to reduce the incidence of bronchopulmonary dysplasia in preterm infants. Besides vitamin A, caffeine is the only drug with high quality evidence to support routine use for prevention of bronchopulmonary dysplasia in preterms.[36] Studies have suggested that early initiation of caffeine has been associated with significantly reduced rates of bronchopulmonary dysplasia.[32,37,38] This action of caffeine may be indirectly related to its strengthening of the chest muscles or lesser use of oxygen or both. The exact dose, timing and role of early caffeine therapy have not yet been delineated, but it is expected that further research will justify this assertion.

6.4. Intermittent hypoxia

Intermittent hypoxia is a common occurrence among premature infants but its clinical significance is not well elicited. However, studies have shown that it may be correlated with severity of retinopathy of prematurity along with adverse neurodevelopmental outcomes.[1] Caffeine has been shown to significantly reduce the number of intermittent hypoxic episodes at postmenstrual age [PMA] of 35–36 weeks.[39] Future studies should perhaps clarify whether caffeine use and intermittent hypoxia episodes were correlated with long-term neurodevelopmental outcomes.

6.5. Patent ductus arteriosus [PDA]

Caffeine use has been associated with PDA closure. The CAP study analysis showed that the group with caffeine use required less intervention for PDA closure in comparison to placebo (29% vs. 38% with p value < 0.001 and adjusted odds ratio 0.67). The requirement of PDA ligation in caffeine group was 4.5%, whereas it was 12.6% in the placebo group with a statistically significant p value and adjusted odds ratio of 0.32.[30] Other studies also showed that early caffeine use within 3 days was associated with less intervention for PDA in comparison to later caffeine use.[37,38] The beneficial effect of caffeine on PDA may be correlated with its diuretic and anti-prostaglandin effects.[15]

6.6. Neurodevelopmental outcome

Prolonged caffeine intake may have a neuroprotective effect, presumably by up regulating adenosine A1 receptors.[40] The CAP trial showed reduced likelihood of death, clinical disability and neurocognitive impairment at 18 months PMA in infants weighing less than 1250 g when caffeine was used from day 3 until 34 weeks PMA (40.2% vs. 46.2% infants with p value 0.008 and odds ratio 0.77).[31] Subsequent follow up of CAP trial at five years did not show any difference in the composite outcome of death or severe impairment. However, the same study revealed statistically significant improvement in visual perception and motor coordination.[41] The exact mechanism by which caffeine has positive effects on CNS is unknown but it may be related to its ability to reduce intermittent hypoxia and perhaps its direct neuroprotective effects.[1]

6.7. Retinopathy of prematurity

The CAP trial showed reduced incidence of severe retinopathy of prematurity in caffeine group when compared to placebo (5.1% vs. 7.9% with adjusted odds ratio 0.61).[31] This effect would perhaps be explained by reduced oxygen and ventilation days and reduced incidence of intermittent hypoxia with caffeine group.[1]

7. Possible effects

7.1. Renal effect

Caffeine induces diuresis by enhancing renal blood flow as well as glomerular filtration rate. It also increases creatinine clearance and urinary calcium excretion; however, it

does not induce any changes in serum sodium, potassium, phosphorus or calcium concentration.[15] Future studies may perhaps clarify how significant the renal effects of caffeine are.

7.2. Effect on growth

It has been shown that caffeine increases oxygen consumption and energy expenditure, leading to less weight gain.[15] It was also shown in the CAP study that early weight gain was lower with caffeine use but subsequent study showed that the difference was insignificant at 18–21 months.[30,31] Hence, at present, the effects of caffeine upon growth, although minor, seem only temporary.

7.3. GI effects

Caffeine has been known to induce gastroesophageal reflux. This is mediated by increased gastric secretions and reduced lower esophageal sphincter tone.[15] Preterm infants are known to have reflux and thus it is difficult to correlate the effects of caffeine over gastroesophageal reflux.[1] It has also been shown that caffeine reduces splanchnic blood flow.[15] One study documented a higher tendency of necrotizing enterocolitis with the use of caffeine although it was not statistically significant.[42] However, further studies, including the CAP trial, were unable to substantiate this association.[21,30] In view of GI effects of caffeine, along with its role in inflammation, there appears to be a potential for considerable research upon this topic.

7.4. Inflammatory role

Caffeine modulates immune cell functions by adenosine receptor antagonism as adenosine receptors are expressed on immune cells.[43] A recent study elucidated the interactive role of caffeine over inflammation. At therapeutic dose, caffeine had an anti-inflammatory role via reduction of cytokines like interleukin-6 and tumor necrosis factor-alpha and increment of interleukin-10. At higher therapeutic doses, it mediated the pro-inflammatory role.[44] The inflammatory role of caffeine may perhaps explain the mechanism of beneficial effects it has upon bronchopulmonary dysplasia. However, future studies may explain the exact nature of the effect which caffeine has upon inflammation.

8. Adverse effects

Caffeine is generally a very safe drug. It has known side effects that are comparatively minor. The CAP trial substantiated that it does not have any apparent short or long-term adverse effects upon the neonates.[30,31]

The common transient side effects attributed to caffeine include tachycardia, hypertension, tremors, vomiting and rarely opisthotonus, hyperglycemia, hypokalemia, etc.[23,45] Acute overdose may result in jitteriness, seizures, hypertonia, hypercalcemia, etc.[1] However, in view of its wide therapeutic index, the adverse effects are relatively minor and the risk-benefit ratio appears extremely negligible.

9. Controversies

One of the significant controversies surrounding caffeine has been the dose. The standard dose of caffeine (20 mg/kg loading and five mg/kg OD maintenance) may have been an under-dose as many studies have suggested that a higher dose is more efficacious.[20,21,23] Considering the wide therapeutic index and safety margin, the present dose may perhaps be under-represented. Besides the dose, there has been no consensus regarding whether early caffeine or late caffeine is preferable or if there is any role of prophylactic caffeine therapy.

The fact that the CAP trial and other studies have shown a reduction in apnea frequency between two to seven days after starting caffeine also leaves us with the query of how long to continue administration. As apnea of prematurity is known to occur until 34 weeks, is it worthwhile and effective to continue caffeine in extreme preterms for so long?

Caffeine has also been implicated as a risk factor for spontaneous abortion. Some studies showed that daily intake of high doses of caffeine before pregnancy led to spontaneous abortions.[46–48] Other studies did not show such association.[49–51] Despite its association with fetal loss, use of caffeine in neonates would perhaps not be contraindicated as the dose used in neonates is relatively much smaller than the amount of caffeine consumption in the study. [52]

10. Future research

In view of the various therapeutic roles of caffeine in neonates, there is no doubt that this is the most used and preferred drug among neonatologists worldwide. However, there is requirement of extensive research on this drug, especially with regard to its dose, timing, duration, consideration of prophylaxis, possible effects in various systems, its role in inflammation, and questions over long-term adverse effects. In view of ongoing research, it is expected that future will address these issues.

11. Summary and conclusions

Caffeine citrate is one of the most important medicines in use in NICU. Its efficacy, tolerability, wide therapeutic index, safety and its use in apnea, mechanical ventilation as well as bronchopulmonary dysplasia has made it the "Silver bullet" in neonatology. However, there is a requirement for further research on this drug regarding extensive possible effects, the most effective dose and long-term safety profile.

Conflicts of interest statement

The authors have no conflicts of interest relevant to this article.

References

1. Dobson NR, Hunt CE. Pharmacology review: caffeine use in neonates: indications, pharmacokinetics, clinical effects, outcomes. *Neoreviews* 2013;**14**:e540—50.
2. Kreutzer K, Bassler D. Caffeine for apnea of prematurity: a neonatal success story. *Neonatology* 2014;**105**:332—6.
3. Aranda JV, Beharry K, Valencia GB, Natarajan G, Davis J. Caffeine impact on neonatal morbidities. *J Matern Fetal Neonatal Med* 2010;**23**:S20—3.
4. Bancalari E. Current management of apnea in premature infants: is caffeine the magic bullet? *Early Hum Dev* 2014;**90**: S1—2.
5. Weinberg BA, Bealer BK, editors. *The world of caffeine: the science and culture of the world's most popular drug*. London: Routledge; 2002.
6. Kuzemko JA, Paala J. Apnoeic attacks in the newborn treated with aminophylline. *Arch Dis Child* 1973 May;**48**:404—6.
7. Shannon DC, Gotay F, Stein IM, Rogers MC, Todres ID, Moylan FM. Prevention of apnea and bradycardia in low-birthweight infants. *Pediatrics* 1975;**55**:589—94.
8. Uauy R, Shapiro DL, Smith B, Warshaw JB. Treatment of severe apnea in prematures with orally administered theophylline. *Pediatrics* 1975;**55**:595—8.
9. Aranda JV, Gorman W, Bergsteinsson H, Gunn T. Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. *J Pediatr* 1977;**90**:467—72.
10. "Caffeine". ChemSpider. Royal Society of Chemistry. Available at http://www.chemspider.com/Chemical-Structure.2424.html?rid=0bb094c4-a76d-44a1-b5f1-79947af47782S. Accessed October 16, 2014.
11. Harry GB, Richard JP. *Profiles of drug substance, excipients and related methodology. Critical compilation of pKa values for pharmaceutical substances*. 1st ed, vol. 33. London: Academic Press; 2007. p. 635.
12. Vallombroso T. *Organic chemistry pearls of wisdom*. 1st ed. Boston Publishing Corp; 2001. p. 43.
13. Temple NJ, Wilson T. *Beverages in nutrition and health*. Totowa, NJ: Humana Press; 2003. p. 172.
14. Simon T. "Crystalline caffeine". Bristol University. Available at http://www.chm.bris.ac.uk/webprojects2001/tilling/synthesis.htm. Accessed August 3, 2009.
15. Natarajan G, Lulic-Botica M, Aranda JV. Clinical pharmacology of caffeine in the newborn. *Neoreviews* 2007;**8**:e214—21.
16. Al-Alaiyan S, Al Rawathi S, Raines D, Yusuf A, Legayada E, Shoukri MM, et al. Caffeine metabolism in the premature infants. *J Clinical Pharmacol* 2001;**41**:620—7.
17. Comer AM, Perry CM, Figgitt DP. Caffeine citrate: a review of its use in apnoea of prematurity. *Pediatr Drugs* 2001;**3**:61—79.
18. Myers JP, Johnson DA, McVey DE. Caffeine in the modulation of brain function. In: Gupta BS, Gupta U, editors. *Caffeine and behavior: current views and research trends*. Boca Raton (FL): CRC Press LLC; 1999. p. 17—30.
19. Cattarossi L, Colacino V, Janes A, LoGreco P, Rubini S, Zilli M, et al. Oral versus intramuscular loading of caffeine in idiopathic apnoea of prematurity. *Eur J Pediatr* 1988;**148**:262—3.
20. Steer PA, Flenady VJ, Shearman A, Lee TC, Tudehope DI, Charles BG. Periextubation caffeine in preterm neonates: a randomized dose response trial. *J Paediatr Child Health* 2003; **39**:511—5.
21. Steer PA, Flenady VJ, Shearman A, Charles B, Gray PH, Henderson-Smart D, et al. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F499—503.
22. Gray PH, Fenaldy VJ, Charles BG, Steer PA, Caffeine Collaborative Study Group. Caffeine citrate for very preterm infants: effects on development, temperament and behaviour. *J Paediatr Child Health* 2011;**47**:167—72.
23. Mohammed S, Nour I, Shabaan AE, Shouman B, Abdel-Hady H, Nasef N. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. *Eur J Pediatr* 2015;**174**: 949—56.
24. Baselt R. *Disposition of toxic drug and chemicals in man*. 9th ed. Seal Beach, CA: Biomedical Publications; 2011. p. 236—9.
25. Natarajan G, Botica ML, Thomas R, Aranda JV. Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007;**119**:936—40.
26. Leon AE, Michienzi K, Ma CX, Hutchison AA. Serum caffeine concentration in preterm neonates. *Am J Perinatol* 2007;**24**: 39—47.
27. Pesce AJ, Rashkin M, Kotagal U. Standards of laboratory practice: theophylline and caffeine monitoring. National Academy of Clinical Biochemistry. *Clin Chem* 1998;**44**: 1124—8.
28. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. *Cochrane Database Syst Rev* 2010;(12):CD000140.
29. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev* 2010;(1):CD000273.
30. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;**354**:2112—21.
31. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;**357**:1893—902.
32. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, et al. Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr* 2010;**156**:382—7.
33. Henderson-Smart DJ, De Paoli AG. Prophylactic methylxanthine for prevention of apnoea in preterm infants. *Cochrane Database Syst Rev* 2010;(12):CD000432.
34. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. *Cochrane Database Syst Rev* 2010;(12):CD000139.
35. Kassim Z, Greenough A, Rafferty GF. Effect of caffeine on respiratory muscle strength and lung function in prematurely born, ventilated infants. *Eur J Pediatr* 2009;**168**:1491—5.
36. Jensen EA, Foglia EE, Schmidt B. Evidence based pharmacologic therapies for prevention of bronchopulmonary dysplasia: application of the grading of recommendations assessment, development, and evaluation methodology. *Clin Perinatal* 2015;**42**:755—79.
37. Dobson NR, Patel RM, Smith PB, Kuehn DR, Clark J, Vyas-Read S, et al. Trends in caffeine use and association between clinical outcomes and timing of therapy in very low birth weight infants. *J Pediatr* 2014;**164**:992—8.
38. Patel RM, Leong T, Carlton DP, Vyas-Read S. Early caffeine therapy and clinical outcomes in extremely preterm infants. *J Perinatol* 2013;**33**:134—40.
39. Rhein LM, Dobson NR, Darnall RA, Corwin MJ, Heeren TC, Poets CF, et al. Effects of caffeine on intermittent hypoxia in infants born prematurely: a randomized clinical trial. *JAMA Pediatr* 2014;**168**:250—7.
40. Gaytan SP, Pasaro R. Neonatal caffeine treatment up-regulates adenosine receptors in brainstem and hypothalamic cardiorespiratory related nuclei of rat pups. *Exp Neurol* 2012;**237**: 247—59.
41. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012;**307**:275—82.

42. Erenberg A, Leff RD, Haack DG, Mosdell KW, Hicks GM, Wynne BA. Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo controlled study. *Pharmacotherapy* 2000;**20**:644—52.
43. Chavez-Valdez R, Wills-Karp M, Ahlawat R, Cristofalo EA, Nathan A, Gauda EB. Caffeine modulates TNF-alpha production by cord blood monocytes: the role of adenosine receptors. *Pediatr Res* 2009;**65**:203—8.
44. Chavez-Valdez R, Ahlawat R, Wills-Karp M, Nathan A, Ezell T, Gauda EB. Correlation between serum caffeine levels and changes in cytokine profile in a cohort of preterm infants. *J Pediatr* 2011;**158**:57—64.
45. Picone S, Bedetta M, Paolillo P. Caffeine citrate: when and for how long. A literature review. *J Matern Fetal Neonatal Med* 2012;**25**:S11—4.
46. Tolstrup JS, Kjaer SK, Munk C, Madsen LB, Ottesen B, Bergholt T, et al. Does caffeine and alcohol intake before pregnancy predict the occurrence of spontaneous abortion? *Hum Reprod* 2003;**18**:2704—10.
47. Axelsson G, Rylander R, Molin I. Outcome of pregnancy in relation to irregular and inconvenient work schedules. *Br J Ind Med* 1989;**46**:393—8.
48. Fenster L, Hubbard AE, Swan SH, Windham GC, Waller K, Hiatt RA, et al. Caffeinated beverages, decaffeinated coffee, and spontaneous abortion. *Epidemiology* 1997;**8**:515—23.
49. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract* 1993;**43**:245—8.
50. Cnattingius S, Signorello LB, Annerén G, Clausson B, Ekbom A, Ljunger E, et al. Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med* 2000;**343**:1839—45.
51. Lawson CC, LeMasters GK, Wilson KA. Changes in caffeine consumption as a signal of pregnancy. *Reprod Toxicol* 2004;**18**:625—33.
52. Lassi ZS, Imam AM, Dean SV, Bhutta ZA. Preconception care: caffeine, smoking, alcohol, drugs and other environmental chemical/radiation exposure. *Reprod Health* 2014;**11**:S6.