

CAFFEINE CITRATE (Commentary)

Dietary intake during pregnancy and lactation

Pregnancy

Many papers have appeared in the last 40 years saying that those who drink more than modest amounts of coffee (and other caffeine-containing drinks) are more likely to suffer infertility, fetal birth defects, miscarriage, stillbirth, premature birth, fetal growth restriction and cot death. And each such paper has then spawned a flurry of further papers reporting a failure to find any such association. The problem is that women who drink more coffee than most nearly always differ from other would-be mothers in other ways too. They smoke more for one thing, which makes deciding what is causing what immensely difficult. The US Food and Drug Administration has been advising women to 'avoid or limit' their intake of caffeine in pregnancy since 1980, and the UK Food Standards Agency issued slightly more nuanced advice in 1984, which it updated in October 2001 and again in November 2008. Estimating fetal exposure is much more difficult than is generally supposed because cup size, and the way drink is prepared, varies widely. The caffeine content of different brands of tea and coffee varies greatly (Bracken *et al.*, 2002), and these drinks are not the only significant dietary sources of caffeine (see box). The speed with which caffeine is cleared by the liver also varies more than is generally realised, is increased in smokers, and is affected by a range of genetic polymorphisms affecting the liver enzyme cytochrome P450 1A2.

Common drinks and their typical caffeine content

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|--------------------------------------|----------------------------|
| Cola and other 'energy' drinks | 12–60 mg per 300 ml can |
| Bottled iced tea | 15–25 mg per 300 ml bottle |
| Brewed tea (non-herbal) [†] | 20–50 mg/cup* |
| Mate | 30–60 mg/cup |
| Decaffeinated coffee | 4–8 mg/cup |
| Instant coffee | 40–140 mg/cup |
| Brewed coffee | 60–200 mg/cup |
| Chocolate | 5–35 mg per 50 g bar |

[†] Twenty percent more than this for tea brewed for more than 3 minutes

* Taken to be a 300 ml (~10 oz) cup

Teratogenicity: Caffeine crosses the placenta easily, and the speed with which it is then metabolised declines during pregnancy. However fetal deformity has only been seen in animals given bolus doses that were ten times higher than would ever be achieved by any form of dietary intake.

Fertility: A widely quoted paper in the *Lancet* in 1988 suggested that "women who consumed more than the equivalent of one cup of coffee per day were half as likely to become pregnant per cycle as women who drank less", but the nine studies that have looked into this finding since then found little evidence to support this conclusion once other influences such as maternal age, smoking and parity were taken into account.

Miscarriage: This is certainly rather more common in women who drink substantial amounts of coffee in early pregnancy. It is not clear whether continuing high consumption has put the fetus at risk, or whether sustained consumption is simply a marker for a pregnancy that is already doomed, because an increased aversion to coffee is, along with nausea and vomiting, a consistent early feature of healthy pregnancy, but one recent study (Weng *et al.*, 2008) suggests there could be a causal relationship. The report of a dose-dependent relationship between intake **before** pregnancy and the risk of miscarriage does suggest that a very high pre-pregnancy intake may be unwise, but the adjusted odds ratio when the 186 women taking less than 75 mg a day were compared with the 230 taking more than 900 mg a day was only just significant (1.72; 95% CI 1.00 and 2.96). The association was only seen in one of the three prospective studies done to date, but the other two had few women with an intake this high (Tostrup *et al.*, 2003).

Low birth weight: While caffeine consumption does not make preterm birth more likely, more than a dozen observational studies have suggested that babies born to these mothers weigh less at birth. A randomised controlled trial (Bech *et al.*, 2007) in which more than 500 women were randomised to use a decaffeinated brand of instant coffee throughout the second half of pregnancy failed to detect any such effect, but it could be argued, and is being argued, that this was because randomisation was only used to modify caffeine intake during the second half of pregnancy. That certainly is the conclusion reached by those who undertook a further large observational study funded by the UK Food Standards Agency (FSA) published in late 2008 (CARE Study Group 2008).

The press release that the FSA put out about this study said: "Pregnant women are being advised to limit their daily caffeine intake, ideally keeping this below 200 mg a day. This is roughly two mugs of coffee a

day although caffeine is also present in tea, chocolate, some soft drinks and certain medicines. Too much caffeine might result in a baby having a lower birth weight than it should, which can increase the risk of some health conditions for the baby in later life, or could possibly result in spontaneous miscarriage.” What this did *not* bring out, but is clear from the original paper, is that almost two thirds of the caffeine ingested by these women during pregnancy came from **tea** and only 14% came from coffee! The English were always known to be great tea drinkers, and we have now had this scientifically confirmed.

Unfortunately the media, taking their lead from the FSAs press release, came out with the over simple message that “Coffee harms your baby”. Nobody noticed that ‘soft’ cola drinks accounted for almost as much of the caffeine as coffee (with chocolate a close runner up). And nobody noted that, if you followed the FSA’s advice diligently, and only ingested 150 mg, instead of 250 mg, of caffeine a day throughout pregnancy, this would probably only increase the weight of the baby by about 30 grams (a conclusion similar to that reached by Bracken *et al.* in 2002). And nobody has yet produced any evidence to show that such a difference in birth weight actually matters. The idea that babies “should” be a certain weight at birth is, of course, all of a piece with the idea that they “should” grow at some pre-specified rate after birth (an idea that causes endless maternal anxiety and ignores all concept of individuality). Obstetricians already fret that some babies are dangerously overweight, urging women to consider Caesarean delivery for ‘fetal macrosomia’. Note also the element of scaremongering implicit in the statement that “too much caffeine ... *might* cause miscarriage” without any helpful cross reference to the only studies (see above) that give some idea of how “much” might be “too much”.

The message that the media came away with was that every good mother who “wants the best for their baby” (as Professor Cade put it in the FSA’s press release), should probably stick to water and avoid any caffeine as well as any alcohol from the moment they think they might want to become pregnant! The CARE Study Group authors certainly said that they “could find no level of intake at which there was no association with fetal growth restriction”. Oddly these effects were most marked in the women who metabolised caffeine most quickly, suggesting that it is not caffeine but some metabolite that actually affects fetal growth. Many will probably simply conclude that there is wisdom in the old adage “moderation in all things”.

Stillbirth: A paper in 2003 (Wisborg *et al.*) reported an excess of fetal death in the second half of pregnancy after adjustment for smoking status in women attending one maternity unit in Denmark who said, at booking, that they drank 8 or more cups of coffee a day. So too did a later replication using information from the Danish National Birth Cohort for women saying they drank 4 or more cups a day. A recent study in Uruguay (which did not fully adjust for smoking status) came to similar conclusions. It will take a randomised trial to show that this association is ‘causal’, but the prudent conclusion, for the moment, has to be that high caffeine intake in pregnancy is unwise.

Cot death: There is one report of high consumption in late pregnancy being associated with an increased incidence of cot-death – a finding that further studies were unable to replicate.

Christian MS, Brent RL. Teratogen update: evaluation of the reproductive and developmental risk of caffeine. *Teratology* 2001;64:51–78

Leviton A, Cowan L. A review of the literature relating caffeine consumption by women to their risk of reproductive hazards. *Food Chem Toxicol* 2002;40:1271–310.

Bracken MB, Triche E, Grosso L, Hellenbrand K, Belanger K, Leaderer BP. Heterogeneity in assessing self-reports of caffeine exposure: implications for studies of health effects. *Epidemiology* 2002;13:165–71.

Tostrup JS, Kjær 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.

Wisborg K, Kesmodel U, Bech BH, Hedegaard M, Henriksen TB. Maternal consumption of coffee during pregnancy and infant death in first year of life. *BMJ* 2003;326:420–3. (See also 1268–9.)

Signorello LB, McLaughlin JK. Maternal caffeine consumption and spontaneous abortion. A review of the epidemiologic evidence. *Epidemiology* 2004;15:229–39.

Lawson CC, LeMasters GK, Wilson KA. Changes to caffeine consumption as a signal of pregnancy. *Reprod Toxicol* 2004;18:625–33.

Bech BH, Nohr EA, Vaeth M, Henriksen TB, Olsen J. Coffee and fetal death: a cohort study with prospective data. *Am J Epidemiol* 2005;162:983–90.

Grosso LM, Bracken MB. Caffeine metabolism, genetics, and perinatal outcomes: a review of exposure assessment considerations in pregnancy. *Ann Epidemiol* 2005;15:460–6

Chiapparino F, Parazzini F, Chatenoud L, Ricci E, Tozzi L, Chiantera V, *et al.* Coffee drinking and risk of preterm birth. *Eur J Clin Nutr* 2006;60:610–13.

Matijasevich A, Barros FC, Santos IS, Yemini A. Maternal caffeine consumption and fetal death: a case-control study in Uruguay. *Paediatr Perinat Epidemiol* 2006;20:100–9.

Bech BH, Obel C, Henriksen TB, *et al.* Effect of reducing caffeine intake on birth weight and length of gestation: randomised controlled trial. *BMJ* 2007;334:409–12. [RCT] (See also 377–8.)

Weng X, Odouli R, Li D-K. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. *Am J Obstet Gynecol* 2008;198:e1-279.e8.

CARE Study Group. Maternal caffeine intake during pregnancy and risk of growth restriction: a large prospective observational study. *BMJ* 2008;337:1334–8. (See also 1305–6.) [Cite as *BMJ* 2008;337:a2332 and a2207]

Lactation

A breast fed baby only ingests, on a weight-for-weight basis, 5 to 15% of the mother's caffeine intake but, because the half life is so long, a high maternal intake could conceivably produce symptoms of mild toxicity in a young baby. There is, nevertheless, only a single clinical report (unsupported by any plasma levels) to suggest that 'jitteriness' or any other sign of early toxicity has ever occurred in practice. However, mothers should be reminded that there are significant quantities of caffeine in tea, coffee, cola and chocolate (see above table). They should also be reminded that caffeine is a significant constituent of many 'over the counter' pain-relief remedies, and that there is no evidence that the caffeine content of these preparations is of more than minimal analgesic value (Zhang, 1996).

Tyrala EE, Dodson WE. Caffeine secretion into breast milk. *Arch Dis Child* 1979;**54**:787–800.

Bailey DN, Welbert RT, Naylor AJ. A study of salicylate and caffeine excretion in the breast milk of two nursing mothers. *J Anal Toxicol* 1982;**6**:64–8.

Sagraves R, Bradley JM, Delgado MJM, *et al.* Pharmacokinetics of caffeine in human breast milk after a single oral dose of caffeine. [Abstract] *Drug Intell Clin Pharm* 1984;**18**:507.

Berlin CM, Denson HM, Daniel CH, *et al.* Disposition and dietary caffeine in milk, saliva, and plasma of lactating women. *Pediatrics* 1984;**73**:59–63.

Ryu JE. Caffeine in human milk and in serum in breast-fed infants. *Dev Pharmacol Ther* 1985;**8**:329–37.

Ryu JE. Effect of maternal caffeine consumption on heart rate and sleep time of breast-fed infants. *Dev Pharmacol Ther* 1985;**8**:355–63.

Stavchansky S, Combs A, Sagraves R, *et al.* Pharmacokinetics of caffeine in breast milk and plasma after single oral administration of caffeine to lactating mothers. *Biopharm Drug Dis* 1988;**9**:285–99.

Blanchard J, Weber CW, Shearer L-E. Methylxanthine levels in breast milk in lactating women of different ethnic and socioeconomic classes. *Biopharm Drug Dis* 1992;**13**:187–96.

Nehlig A, Derby G. Consequences on the newborn of chronic consumption of coffee during gestation and lactation: a review. *J Am Coll Nutr* 1994;**13**:6–21.

Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain – a meta-analysis. *J Clin Pharm Ther* 1996;**21**:261–82. [SR]

Neonatal use of caffeine

Early history: The English paediatrician Jan Kuzemko, and his registrar in Peterborough, Josy Paala, were the first to show, in 1973, that rectal aminophylline could reduce the incidence of neonatal apnoea. Dr Kuzemko had been using aminopylline suppositories in the management of toddlers with severe episodic asthma, and had been able to show "that using 10–20 mg/(kg.day) rectally was therapeutically useful, produced blood levels of 10–20 g/ml, and did not generate any significant side effects". Faced with a baby with repeated apnoea in his nursery, he speculated that it might be of help in this infant "because of its action on the respiratory centre". The result was sufficiently encouraging for Douglas Gairdner to try the same approach on two babies in Cambridge. When the nursing staff found this successful he encouraged the Peterborough clinicians to launch a prospective study of ten consecutive babies – the study that finally generated the first published paper three years later.

Early replication of this study in the three separate centres in America over the next couple of years led the paediatric pharmacologist Jacob Aranda and his colleagues in Montreal to undertake a very thorough study of the pharmacokinetics of both theophylline and caffeine in the late 1970s. As a result, oral treatment with theophylline (or IV treatment with aminophylline) soon came into widespread use in north America, although it took more than a decade for the same strategy to become common in the UK. It took even longer for caffeine to become the more widely used product, largely because no commercial product was available. A licensed product of the latter did eventually become commercially available in the USA in 2000, but use to speed extubation in the very preterm baby still remains an "off label" use of this product. No firm has shown any interest in making any such product available in Europe as yet, and no government agency has shown any interest in filling the therapeutic void that this causes. This lack of commercial interest is presumably because the market is small and the raw material so cheap that it could be difficult to make any profit from its sale, but this reflects badly on the industries' claim to be motivated by anything other than shareholder profit.

Kuzemko JA, Paala J. Apneic attacks in the newborn treated with aminophylline. *Arch Dis Child* 1973;**48**:404–6.

Shannon DC, Gotay F, Stein IM, *et al.* Prevention of apnoea and bradycardia in low-birth-weight infants. *Pediatrics* 1975;**55**:589–94.

Uauy R, Shapiro D, Smith B, *et al.* Effect of theophylline on severe primary apnea of prematurity. A preliminary report. *Pediatrics* 1975;**55**:595–8.

Bednarek FJ, Roloff DW. Treatment of apnea of prematurity with aminophylline. *Pediatrics* 1976;**58**:335–9.

Aranda JV, Gorman W, Bersteinsson H, *et al.* Efficacy of caffeine in treatment of apnea in the low birth weight infant. *J Pediatr* 1977;**90**:467–72.

Aranda JC, Collinge JM, Zinman R, *et al.* Maturation of caffeine elimination in infancy. *Arch Dis Child* 1979;**54**:96–9.

Aranda JV, Grondin D, Sasniuk BI. Pharmacologic considerations in the therapy of neonatal apnea. *Pediatr Clin North Amer* 1981;**28**:113–33.

Aranda JV, Lopes JM, Blanchars P, *et al.* Treatment of neonatal apnoea. In: Rylance G, Harvey D, Aranda JV, eds. *Neonatal pharmacology and therapeutics*. Chapter 8. Oxford: Butterworths, 1991:95–115.

Pharmacokinetics: Caffeine (1,3,7-trimethylxanthine) is well absorbed by mouth, and IV treatment is seldom necessary. It has long been known to have many advantages over theophylline (1,3-dimethylxanthine) in the management of neonatal apnoea. The gap between the optimum therapeutic blood level and the blood level at which toxic symptoms first appear is much wider and, because of the prolonged half life, blood levels do not normally need to be monitored and the drug does usually need to be given more than once a day. Caffeine is mostly excreted, unchanged, in the urine in the period immediately after birth, but clearance gradually becomes more rapid as a result of increased liver metabolism and, in infants more than four months old, caffeine is normally eliminated as rapidly as it is in adult life. As a result, the half life at birth (60–140 hours) is almost 16 times as long as it is in an adult.

- Gorodischer R, Karplus M. Pharmacokinetic aspects caffeine in premature infants with apnoea. *Eur J Clin Pharmacol* 1982;**22**:47–52.
- Le Guennec J-C, Billon B, Paré C. Maturational changes of caffeine concentrations and disposition in infancy during maintenance therapy for apnea of prematurity: influence of gestational age hepatic disease, and breast-feeding. *Pediatrics* 1985;**76**:834–40
- Pons G, Carrier O, Richard M-O, *et al.* Developmental changes of caffeine elimination in infancy. *Dev Pharmacol Ther* 1988;**11**:258–64.
- Pearlman SA, Duran CS, Wood MA, *et al.* Caffeine pharmacokinetics in preterm infants older than 2 weeks. *Dev Pharmacol Ther* 1989;**12**:65–9.
- Goacoiá GP, Jungbluth GL, Jusko WJ. Effect of formula feeding on oral absorption of caffeine in premature infants. *Dev Pharmacol Ther* 1989;**12**:205–10.
- De Carolis MP, Romagnoli C, Muzii U, *et al.* Pharmacokinetic aspects of caffeine in premature infants. *Dev Pharmacol Ther* 1991;**16**:117–22.
- Thomson AH, Kerr S, Wright S. Population pharmacokinetics of caffeine in neonates and young infants. *Ther Drug Monit* 1996;**18**:245–53.
- Falcão AC, Fernández de Gatta MM, Delgado Iribarnegaray MF, *et al.* Population pharmacokinetics of caffeine in premature neonates. *Eur J Clin Pharmacol* 1997;**52**:211–7.
- Lee TC, Charles B, Steer B, *et al.* Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity. *Clin Pharmacol Ther* 1997;**61**:628–40.
- Al-Alaiyan S, Al-Rawithi S, Yusuf A, *et al.* Caffeine metabolism in premature infants. *J Clin Pharmacol* 2001;**41**:620–7.
- Lee, HS, Chirino-Barcelo Y, Tan KL, *et al.* Caffeine in apnoeic Asian neonates: a sparse data analysis. *Br J Clin Pharmacol* 2002;**54**:31–7.
- Concha Leon AE, Michienzi K, Ma C-X, *et al.* Serum caffeine concentrations in preterm neonates. *Am J Perinatol* 2007;**24**:39–47.
- Natarajan G, Botica M-L, Thomas R, *et al.* Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007;**119**:936–40.

Metabolic effects: Four of the five studies that have looked into the metabolic effect of methylxanthine administration in infancy have suggested that use causes a marked and sustained rise in metabolic rate, and the recent international CAP trial has shown that this does indeed have a small but detectable impact on early neonatal growth. There was, however, absolutely no impact on long term measures of growth, and even a non-significant tendency for head circumference to be higher at 18 months in those treated with caffeine.

- Gerhardt T, McCarthy J, Bancalari E. Effect of aminophylline on respiratory centre activity and metabolic rate in premature infants with idiopathic apnea. *Pediatrics* 1979;**63**:537–42.
- Milsap RL, Krauss AN, Auld PAM. Oxygen consumption in apneic premature infants after low-dose theophylline. *Clin Pharmacol Ther* 1980;**28**:536–40.
- Fjeld CR, Cole FS, Bier DM. Energy expenditure, lipolysis, and glucose production in preterm infants treated with theophylline. *Pediatr Res* 1992;**32**:693–8.
- Carielli VP, Verlato G, Benini F, *et al.* Metabolic and respiratory effects of theophylline in the preterm infant. *Arch Dis Child* 2000;**83**:F39–43.
- Bauer J, Maier K, Linderkamp O, *et al.* Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnea. *Pediatrics* 2001;**107**:660–3.

Toxicity: Toxicity is uncommon and is it seldom necessary to measure plasma levels (see the report by Pesce *et al.*, 1998 for technical details), but a ten fold overdose can make a baby extremely ill. Tachycardia, agitation and hypertonia are the first signs. A really severe overdose can also cause metabolic acidosis and hyperglycaemia (Anderson *et al.*, 1999) while a diuresis can also occasionally cause transient hyponatraemia and hypokalaemia. The symptoms of an overdose of theophylline are very similar (Lowry *et al.*, 2001). Text book suggestions that seizures are one complication of neonatal toxicity, though widely quoted, seem to have been influenced by the rigidity and opisthotonic posturing described in some early reports (Banner and Czajka, 1980; van den Anker *et al.*, 1992). No seizures were seen in the baby reported as having received a ten fold overdose IV by Anderson *et al.* (1999), or in one baby who received a single oral dose that was a *hundred times* higher than was intended (Ergenekon *et al.*, 2001), and both these babies are reported to have made a complete recovery after supportive treatment. Indeed, while accidental ingestion and deliberate administration are known to have killed at least three young children (Rivenes *et al.*, 1997) recovery seems to have been complete in all the neonatal cases reported to date. What emerges from all these reports is the ease with which ten fold dosing errors can occur when an appropriate licensed preparation is not available.

- Kulkarni PB, Dorand RD. Caffeine toxicity in a neonate. *Pediatrics* 1979;**64**:254–5.
- Banner W, Czajka PA. Caffeine overdose in the neonate. *Am J Dis Child* 1980;**134**:495–8.
- Perrin C, Debruyne D, Lacotte J, *et al.* Treatment of caffeine intoxication by exchange transfusion in a newborn. *Acta Paediatr Scand* 1987;**76**:679–81.
- Deitrich AM, Mortensen ME. Presentation and management of an acute caffeine overdose. *Pediatr Emerg Care* 1990;**6**:296–8.
- van den Anker JN, Jongejan HTM, Sauer PJJ. Severe caffeine intoxication in a preterm neonate [letter]. *Eur J Pediatr* 1992;**151**:466–8.

- Rivenes SM, Bakerman PR, Miller MB. Intentional caffeine poisoning in an infant. *Pediatrics* 1997;**99**:736–8
- Pesce AJ, Rashkin M, Kotagal U. Standards of laboratory practice: theophylline and caffeine monitoring. *Clin Chemistry* 1998;**44**:1124–8.
- Anderson BJ, Gunn TR, Holford NHG, *et al.* Caffeine overdose in a premature infant: clinical course and pharmacokinetics. *Anesth Intensive Care* 1999;**27**:307–11.
- Ergenekon E, Dalgiç N, Aksoy E, *et al.* Caffeine intoxication in a premature neonate. *Paediatr Anaesth* 2001;**11**:737–9.
- Lowry JA, Jarrett RV, Wasserman G. Theophylline toxicokinetics in premature newborns. *Arch Pediatr Adolesc Med* 2001;**155**:934–9.

Use in the management of apnoea: Apnoea has many causes and, as with any other condition, diagnosis should normally precede treatment. Reactive bradycardia is common, but often occurs without the baby becoming hypoxic. Brief central apnoea (periodic breathing) is very common, but longer episodes can lead to upper airway closure, and airway obstruction can trigger central apnoea (so-called 'mixed' apnoea). Continuous positive airway pressure (CPAP) will prevent most obstructive and mixed apnoea. Caffeine is more helpful in managing central apnoea. Reflux can cause apnoea, and many suspect that prolonged apnoea can also trigger secondary reflux. Attention of optimising the position in which a baby is nursed can certainly reduce the number of apnoeic episodes, but treating reflux seldom does much to reduce the incidence of apnoea. Mattress pads and impedance monitors will not identify obstructive apnoea. Apnoea gets commoner after the first few days of life, and often remains a problem for many weeks in the very preterm baby.

Early studies (Tudehope *et al.*, 1986) failed to show any link between such episodes and the likelihood of later disability. More recent studies, however, that have focused on the incidence of bradycardia (< 80 bpm) and, more particularly, hypoxic bradycardia, have shown that developmental delay is quite common in babies who have many such episodes (Janvier *et al.* 2004), especially if some of the episodes are severe. The risk of developmental delay is particularly high if the episodes do not stop before the baby reaches a postmenstrual age of 37 weeks (Pillekamp *et al.*, 2007). Such problems are particularly common in babies who already have existing ultrasound evidence of cerebral damage. However, the fact that the international caffeine (CAP) trial has now shown, quite unexpectedly, that treatment with a standard dose of caffeine can actually **reduce** the incidence of cerebral palsy and cognitive delay in surviving babies weighing ≤ 1250 g at birth, may be an indication that serious bradycardic apnoea can sometimes cause further progressive cerebral damage and is not just a sign that the baby has already suffered an unmodifiable cerebral insult.

However, although the large CAP trial tells us that giving caffeine to the preterm baby, and giving it *early* (three quarters of all the children in the trial were started on caffeine within five days of birth), is beneficial, it does not tell us *why* it is beneficial. It was considered impractical to try and record the amount of hypoxic bradycardia that occurred to babies in this trial (and routine documentation of such events is known to be unreliable), so we do not know whether caffeine reduced the frequency with which this happened. In so far as caffeine resulted in the endotracheal tube being removed and to all CPAP being stopped a week earlier, this could have made such events more common. What is clear is that the babies who received caffeine stopped being given oxygen ten days earlier, that fewer were judged to still be oxygen dependent at 36 weeks and labelled, therefore, as having 'bronchopulmonary dysplasia' (36.3 v. 46.9%) and that fewer developed severe retinopathy, as defined by the need for surgery or the development of stage 4 or stage 5 disease (5.1 v. 7.9%). We already know that too much oxygen is toxic to the eye, and that it may be toxic to the lung. Is this study telling us that too much oxygen could also be toxic to the developing neonatal brain?

There have been observational studies suggesting the caffeine may make necrotising enterocolitis more common, but there was no evidence of this in the CAP trial (6.4 v. 6.7%). Treatment with caffeine more than halved the number of babies judged to need duct ligation (4.5 v. 12.6%), and it is fairly clear that this is not an unexpected effect of the drug on ductal muscle (Clyman and Roman, 2008). Such a difference was not a pre-defined secondary trial outcome, so the finding needs to be treated with some caution. Nevertheless, the difference seems to be much too large to have simply occurred by chance. There has been much debate recently as to how often persisting ductal patency in the ventilator-dependent preterm baby really needs treatment (Bose and Laughon, 2007). There is no agreed way of classifying the seriousness of persisting patency at present (McNamara and Sehgal, 2007), and there must be a lingering suspicion that some ducts end up getting tied simply because they are 'there', especially when staff seem to be finding it difficult to wean a baby from respiratory support in the belief that continued patency is what is making extubation difficult. Few doubt that this is sometimes true, but how often it is true is far less clear.

- Aranda JV, Turmen T. Methylxanthines in apnea of prematurity. *Clin Perinatol* 1979;**6**:87–108.
- Romagnoli C, De Carolis MP, Muzii E, *et al.* Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. *Therapeutic Drug Monitoring* 1992;**14**:14–19.
- Scanlon JEM, Chin KC, Morgan MEI, *et al.* Caffeine or theophylline for neonatal apnoea. *Arch Dis Child* 1992;**67**:425–8. [RCT]
- Romagnoli C, De Carolis MP, Muzii U, *et al.* Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. *Ther Drug Monit* 1992;**14**:14–9. [RCT]
- Larsen PB, Brendstrup L, Skov L, *et al.* Aminophylline versus caffeine for apnea and bradycardia prophylaxis in premature neonates. *Acta Paediatr* 1995;**84**:360–4.
- Laubscher B, Greenough A, Dimitriou G. Comparative effects of theophylline and caffeine on respiratory function of prematurely born infants. *Early Hum Dev* 1998;**50**:185–92.

- Tobias JD. Caffeine in the treatment of apnea associated with respiratory syncytial virus infection in neonates and infants. *South Med J* 2000;**93**:294–6.
- Erenberg A, Leff RD, Haack DG, *et al.* Caffeine citrate for the treatment of apnea of prematurity: a double-blind placebo-controlled trial. *Pharmacotherapy* 2000;**20**:644–52. [RCT]
- Comer AM, Perry CM. Caffeine citrate. A review of its use in apnoea of prematurity. *Paediatr Drugs* 2001;**1**:61–9.
- Bhatt-Mehta V, Schumacher RE. Treatment of apnea of prematurity. *Pediatr Drugs* 2003;**5**:195–210.
- Martin RJ, ed. Exploring neonatal apnoea: the journey continues. [Symposium] *Semin Neonatol* 2004;**9**:167–244.
- Janvier A, Khairy M, Kokkotis A, *et al.* Apnea is associated with neurodevelopmental impairment in very low birthweight babies. *J Perinatol* 2004;**24**:763–8.
- Schmidt B, Roberts RS, David P, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;**354**:2112–21. [RCT]
- Pillekamp F, Hermann C, Keller T, *et al.* Factors influencing apnea and bradycardia of prematurity – implications for neurodevelopment. *Neonatology* 2007;**91**:155–61.
- Schmidt B, Roberts RS, Davis P, *et al.* Long term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;**357**:1893–1902. [RCT] (See also 1967–8.)
- McNamara PL, Seghal A. Towards rational management of patent ductus arteriosus: the need for disease staging. *Arch Dis Child* 2007;**92**:F424–7.
- Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. *Arch Dis Child* 2007;**92**:F498–502.
- Clyman RI, Roman C. The effects of caffeine on the preterm sheep ductus arteriosus. *Pediatr Res* 2008;**62**:167–9.

Weaning neonates from respiratory support: That caffeine and theophylline can facilitate extubation in the very preterm baby as well as reduce the number of apnoeic attacks, is already well established (as the existing, now dated, Cochrane reviews make clear). Extubation can be particularly difficult to achieve in the very preterm baby, and there is one trial suggesting that very high dose treatment can halve the risk of extubation failure. The dose of caffeine used in this trial (Steer *et al.*, 2004) was four times higher than the dose generally recommended. This generates very high plasma caffeine levels, and such high doses will need to be used with great care – and for as short a time as possible – until more is known about the long term effect of such a strategy. Enthusiasm also needs to be tempered by a realisation that, though high dose use halved the number of babies in whom extubation initially proved unsuccessful, it only shortened the total time they spent on a ventilator by a day and a half (7.4 v 9.0 days).

Steer P, Flenady V, Shearman A, *et al.* Preextubation caffeine in preterm neonates with apnoea of prematurity: a randomised dose response trial. *J Paediatr Child Health* 2003;**39**:511–5. [RCT]

Steer P, Flenady V, Shearman A, *et al.* High dose caffeine for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child* 2004;**89**:F400–503. [RCT]

Potential adverse effects: Whether there are any countervailing adverse effects remains less well established. Caffeine is a mild diuretic and sustained use increases urinary calcium loss (Zanardo *et al.*, 1995). We also know that methylxanthine use reduces early weight gain, presumably because of the drug's effect on metabolic rate, but we also know now that this has no long term impact on later growth. Changes in gut blood flow and gastric emptying have been documented, but we now know that the reduction in splanchnic blood flow (Lee *et al.*, 1999) is not associated with any increased risk of necrotising enterocolitis, as was once feared. A loading dose more than twice as high as the one recommended here causes a measurable fall in cerebral blood flow (Hoecker *et al.*, 2002; 2006), but it is not known whether this is of any long term significance. Caffeine is a direct myocardial stimulant and use in the preterm infant causes an increase in ventricular output, stroke volume and mean arterial blood pressure (Walther *et al.*, 1990) – effects that were generally assumed to be beneficial rather than potentially adverse consequences of treatment.

In one important follow-up study (Davis *et al.*, 2000) the incidence of cerebral palsy was higher in those babies who were treated with theophylline, but this just shows that the information provided by any observational study is never as reliable, or as informative, as the information provided by a controlled trial. In hindsight, now that the outcome of the CAP trial is known, it is clear that theophylline use was almost certainly not the cause of the cerebral palsy seen in this well conducted study (a conclusion the authors were careful *not* to draw). A much more likely explanation is that non-routine use was triggered in this study by some early manifestation of the problem that later developed into cerebral palsy. With chickens and eggs it is always very difficult to know whether the chicken really came before the egg.

Walther FJ, Erikson R, Sims ME. Cardiovascular effects of Caffeine therapy in preterm infants. *Am J Dis Child* 1990;**144**:1164–6.

Zanardo V, Dani C, Trevisanuto D, *et al.* Methylxanthines increase renal calcium excretion in preterm infants. *Biol Neonate* 1995;**68**:169–74.

Lane AJP, Coombs RC, Evans DH, *et al.* Effect of caffeine on neonatal splanchnic blood flow. *Arch Dis Child* 1999;**80**:F128–9.

Dani C, Bertini G, Reali MF, *et al.* Brain haemodynamic changes in preterm infants after maintenance dose caffeine and aminophylline treatment. *Biol Neonate* 2000;**78**:27–32.

Daviis PG, Doyle LW, Rickards AL, *et al.* Methylxanthines and sensorineural outcome at 14 years in children < 1501 birthweight. *J Paediatr Child Health* 2000;**36**:47–50.

Sreenan C, Etches PC, Demianczuk N, *et al.* Isolated developmental delay in very low birth weight infants: association with prolonged doxapram therapy of apnea. *J Pediatr* 2001;**139**:832–7. (See also 2002;**141**:296–7.)

Hoecker C, Nelle M, Poeschl J, *et al.* Vaffeine impairs cerebral and intestinal blood flow velocity in preterm infants. *Pediatrics* 2002;**109**:784–7. (See also **112**:1000.)

Gounaris A, Kokori P, Varchalama L, *et al.* Theophylline and gastric emptying in very low birthweight neonates: a randomised controlled trial. *Arch Dis Child* 2004;**89**:F297–9. [RCT]

Hoescker C, Nelle M, Beedgen B, *et al.* Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. *Arch Dis Child* 2006;**91**:F61–4.

Status as a 'licensed' drug: Roxane Laboratories put a preparation suitable for IV use on the market on America with FDA approval in 2000, but the only indication for use currently cited by the manufacturer is the "short term treatment of apnea of prematurity in infants of between 28 and <33 weeks' gestational age". The company has not sought permission to market the product outside America and, despite almost thirty years of increasingly widespread use, no other commercial preparation has yet come onto the market. There is little doubt that the lack of a commercial product in a dilution suitable for neonatal use has been the factor responsible for all the iatrogenic cases of drug toxicity reported to date (see above).

One last thought :

"Caffeine is the only addictive psychoactive substance to have overcome world wide resistance and disapproval to the extent that it is freely available almost everywhere, unregulated, sold without license, offered over the counter in tablet and capsule form, and even added to beverages intended for children."

Weinberg BA, Bealer BK. *The world of caffeine: the science and culture of the world's most popular drug.* London: Routledge, Taylor & Francis Group; 2002.

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