

CAFFEINE CITRATE (Comment) [1]

Recent news from the CAP trial collaborators

Patience and tenacity sometimes bring unexpected rewards, but none of those who backed the Caffeine for Apnoea of Prematurity (CAP) Trial when it opened in January 2000 can have thought that this study would come up with the findings that were announced for the first time at the American Pediatric Academic Societies' annual meeting in Toronto in May 2007. Indeed the result of the follow up assessment of the two thousand and six children recruited into this trial at 18–21 months was still not complete at the end of 2006 so the summary of the findings could not be included in the main programme, and had to be submitted as a 'Late Breaking' abstract at the last minute. The full paper summarizing those findings appeared in the *New England Journal of Medicine* six months later (Schmidt *et al.*, 2007). A further subgroup analysis has now been undertaken and presented, yet again, as a late breaking abstract for the meeting in Hawaii in May this year. It shows that treatment delivers most benefit is started early (within 3 days of birth), and in those who are ventilator dependent at the time treatment is started.

Background: Caffeine first came into use in the late 1970s soon after an enterprising British paediatrician showed that theophylline could be used to reduce the incidence of apnoea in the preterm baby (Kuzemko and Paala, 1973) and, over the next thirty years, sustained high dose treatment came to be very widely used in many countries, even though no study had yet been done to show that such use was safe (Schmidt, 1999). Indeed observational studies had shown that babies so treated tended to do less well at follow up, although it was impossible to know whether it was the apnoea (or what was causing the apnoea) that was responsible for the poor outcome, or the drug that was being given to control that apnoea (Davis *et al.*, 2000). The same seemed to be true when doxapram was used as a respiratory stimulant (Sreenan *et al.*, 2001). As a result, the aim of the randomized double-blind CAP trial when it was launched was to "to determine whether survival without developmental disability at a corrected age of 18 months is improved if apnea of prematurity is managed **without** methylxanthines (caffeine) in infants weighing 500–1250 grams at birth."

The trial took a year longer than expected because recruitment from centers in Europe was poorer than had been pledged, but it was achieved after five years. Recruitment in the UK was particularly poor, and less than a fifth of what had been hoped for. Regulatory delays caused several UK units to pull out of the trial, and recruitment was further damaged by the fact that the Northern and Yorkshire multicentre research ethics committee insisted that parents had to be told that caffeine could cause fits. That this was something that had only been seen after a ten fold overdose, and that such an overdose was much more likely to happen with an extemporaneously prepared product (there being no licensed preparation available in the UK) than with the centrally prepared trial drug, failed to sway the committee and, as a result, many parents, on reading the relevant four page information leaflet said, in some confusion, that they did not want to join the trial but did want their baby to have caffeine !

Power calculations showed that, if 25% of children in the control group (the caffeine treated group) died after recruitment or were disabled at follow up, 2000 babies would need to be recruited to be 80% certain that avoiding such treatment detected a 25% relative risk reduction (two-tailed alpha = 0.05). Getting this number of babies posed quite a challenge because only half of one per cent of all babies weigh 1250 grams or less at birth. Indeed, it required international collaboration, and the Canadian Institutes of Health Research (with commendable foresight) accepted the need for this. In the end half the babies came from Canada, a quarter from Australia, and a quarter from Europe (but only 50 from the UK).

Some have expressed surprise that the trial was not stopped early because it must have become clear quite early on that babies receiving the active drug were coming off the ventilator significantly sooner than babies in the placebo group. Had confirmation of this significant (but already suspected) short term outcome caused the trial to close, as has happened to several other trials recently, the extremely important long term findings that have now emerged would have never come to light. As it was, by the time the trial *did* close to recruitment, it had also become clear that early extubation was also reducing the length of time that babies on caffeine needed oxygen after extubation (Schmidt *et al.*, 2006), and we now know that, when use is initiated in the first ten days of life, this significantly improves the likelihood of disability-free long-term survival (Schmidt *et al.*, 2007).

So what lessons can we draw from this study ? *First*, trials need to look at outcomes that matter to patients. Trials that only look at short term outcomes tell us nothing about what treatment does for long term survival, and for the quality of life enjoyed by the survivors. *Second*, trials have to be large to acquire this sort of evidence, and this often requires international collaboration. *Third*, trials must not

be closed early because of some favourable short term outcome in one treatment group before the long term outcomes are known. *Fourth*, ethics committees need to accept that their concern to ensure that parents are told about every conceivable risk can leave parents so confused that recruitment is damaged. Had that happened in this study the UK committee that did this would have almost certainly been responsible for depriving neonatal medicine of the only treatment strategy that has yet been identified for reducing disability following very preterm birth (because there is very little chance that another study would have ever been funded had the CAP trial had to close early before reaching its planned target). Research ethics committees need to take more seriously the possibility that their requirements can do more harm than good to the very people they are purporting to protect.

Fifth, we have to admit that we do not have the faintest idea why treatment works. No animal study to date has delivered any great insight, and none of the many clinical studies into the drug's effect on metabolic rate, renal function or regional blood flow have been of much help. Was the difference in outcome in the CAP trial, where three quarters of the babies were started on treatment within five days of birth, due to the fact that babies in the active arm of the study were extubated one week earlier, came off CPAP support one week earlier, and were last judged to need oxygen ten days earlier? If so, should we be trying harder to withdraw these forms of support? Did the number of babies judged to need medical treatment for patent ductus (38% in the placebo group and 28% in the caffeine group) or the number coming to surgery because of a patent duct (12.6% versus 4.5%) have an impact? We know that caffeine has no pharmacological effect on the duct (Clyman and Roman, 2008), that units vary widely in the frequency with which they judge continued patency serious enough to require intervention, and that there is a tendency for outcome to be worse in those judged to need surgery (Kabra *et al.*, 2007). Should we be trying harder to avoid surgical intervention? Was it because the babies suffered less apnoea after coming off respiratory support even though benefit was only seen in those on support at randomization (see abstract below)? Most babies in the CAP trial remained on treatment for six weeks, but the incidence of apnoea was not monitored, and there was no evidence that treatment with caffeine reduced the number of episodes of hypoxaemia in the trial that Bucher and Duc did in 1988. The CAP trial has finally provided clinicians with a few clear answers but, as with most productive clinical research, it has also generated a host of further questions – questions that, in their turn, point to the need for further clinical trials. Clinicians will await with enhanced interest what Professor Barbara Schmidt and her colleagues find when all these children are seen again when they are five years old.

Applied clinical research can be as valuable as 'basic' research: Professor Jacob Aranda published his first paper on the use of caffeine to control neonatal apnoea in 1977 but, thirty years later, we still do not understand how this achieves the good it seems to achieve. Many claim that it is advances in basic science that deliver most of the major advances in medicine, but that is not always true, even though that is where much of the money and most of the kudos currently goes. None of the many clinicians who helped enroll babies into the CAP trial are likely to gain any recognition for the contribution they made to this study. We can not thank the pharmaceutical industry for its help and support either. Indeed the world still lacks a commercial preparation for oral use. Governments believe that market forces can be relied upon to provide a product if there is a need for it, but caffeine is so cheap that industry can't be bothered to provide it. The regulatory authorities, for their part, have still not got round to approving neonatal use even though several Cochrane reviews demonstrating efficacy have been in existence for a decade, because they continue to wait passively for industry to come to them with the evidence. And the voluntarily sustained systematic Cochrane reviews are themselves now seriously out of date. The outcomes of the neonatal use of theophylline and caffeine are currently scattered across seven different reviews, and there is probably a need for a new review that synthesizes all the information now becoming available, comparable to the recent revision of the Cochrane review of antenatal steroid use by Roberts and Danziel.

Conclusion: We are left with something of an enigma, because there is still much concern that exposure to caffeine during pregnancy can be hazardous (as the web site commentary associated with this monograph reviews). Women are advised that it may be unwise to drink more than three cups of strong coffee a day when pregnant or contemplating pregnancy, but this is what we are now giving their babies after birth even though, because clearance is very low in the first few months of life, this produces a sustained blood level that is ten times higher than would be expected in an adult consuming the same amount of caffeine a day. So where do we go from here? Drugs do not generally get a license until the manufacturer has done the studies needed to show the most appropriate dose to use. It does not look as though any study of optimum neonatal dosing will ever be done, but clinicians should not assume that, because a loading dose of 20 mg/kg followed by an oral maintenance dose of 5 mg/kg once a day worked so well in the CAP trial, an even higher dose would necessarily be equally safe (although there is one randomized controlled trial suggesting that brief high dose treatment can speed extubation (Steer *et al.*, 2004)..

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