Intravenous bolus administration of caffeine citrate in premature babies

The study presented here demonstrates that the administration of caffeine citrate (Peyona) as an intravenous bolus is safe and well tolerated by preterm infants. The rationale and advantages of bolus use in daily clinical practice are discussed.

Olayinka Ejiwumi
BSc, MBChB, DCH
Associate Specialist

Stamatina Leontiadi
MRCPCH
Neonatal Grid Registrar

Deborah Hopper
MRPharmS
Paediatric Pharmacist

Peter Reynolds
MBBS, MSc, PhD
Consultant Neonatologist
peter.reynolds@asph.nhs.uk

Neonatal Intensive Care Unit, St. Peter's Hospital, Chertsey, Surrey

Keywords

caffeine citrate; intravenous; undiluted bolus; premature

Key points

Ejiwumi O., Leontiadi S., Hopper D., Reynolds P. Intravenous bolus administration of caffeine citrate in premature babies. *Infant* 2016; 12(6): 219-21.

1. Caffeine citrate (Peyona) can be administered as an intravenous bolus, rather than by infusion, to preterm infants without significant physiological changes.
2. Complications such as skin erythema, pain and cardiac arrhythmia were not seen in this audit and are rare.
3. Bolus administration saves nursing time and drug wastage, and remains normal practice at St. Peter's Hospital.

The use of caffeine citrate to treat and/or prevent apnoea of prematurity in preterm infants is well established and its safety was confirmed in the Caffeine for Apnea of Prematurity study, a large randomised controlled trial in 2,006 infants.[1] The 2013 European Consensus Guidelines state: "Caffeine should be part of routine care for very preterm babies with respiratory distress syndrome to facilitate extubation and reduce broncho-pulmonary dysplasia."[2]

In 2003, orphan designation (EU/3/03/132) was granted by the European Commission to Combino Pharm, S.L., Spain, for caffeine citrate to be used in the treatment of primary apnoea of prematurity and in 2007 this was transferred to Chiesi Farmaceutici S.P.A., Italy. Peyona (caffeine citrate) was licensed for use in preterm infants in 2009.[3]

Prior to this, the neonatal intensive care unit (NICU) at St. Peter's Hospital and many others were using a different, licenced preparation of caffeine citrate (Martindale/Viridian). The acidic nature (pH2-3) and higher osmolarity (296mOsm/L) of this preparation had led us to administer it as a diluted bolus dose rather than an infusion, as we found this to be less painful for the infant and was, in our experience, less likely to cause erythema or an extravasation injury. We speculated that the reason for this improvement with bolus dosing was that the prolonged contact of the solution with the vein when infused slowly seemed to be more harmful and painful.

The pH and osmolarity of Peyona are different (pH4.7, osmolarity 153-155mOsm/L), which might make it better tolerated intravenously. Due to a pricing advantage, the NICU switched to Peyona. It was decided at the time of changeover that it would be in our infants' best interests to continue to administer it as a

FIGURE 1 Drawing up caffeine citrate for the administration of intravenous loading and maintenance doses.

bolus as this was the normal practice, although we were aware that this was not the manufacturer's recommendation. We also decided, because of the improved pH and osmolarity, that dilution would not be necessary. We therefore decided to carry out a prospective audit of adverse physiological changes, evidence of pain or extravasation injury, and any reported adverse incidents arising from bolus administration.

Normal indications for caffeine citrate

Our current practice is that Peyona is prescribed routinely for all infants born at less than 30 weeks' gestation. For infants born at 30-32 weeks' gestation, a 'wait and see' approach is often adopted. Our NICU has a strong ethos of non-invasive ventilation based around the use of nasal high flow in all gestations for stabilisation and ongoing respiratory care.

An intravenous loading dose of 20mg/kg caffeine citrate is given once, followed after 24 hours by a daily intravenous maintenance dose of 10mg/kg (**FIGURES 1 and 2**). Occasionally the maintenance dose is subsequently increased to 15mg/kg daily. Both are given as an undiluted bolus over one to five minutes. When the infant is tolerating more than 50% of total fluids as enteral feeds, the caffeine citrate is then administered by naso/orogastric tube.

Audit of caffeine administration

Over a nine-month period during 2015 we prospectively audited the routine observations (heart rate, respiratory rate, oxygen saturations and blood pressure) prior to the administration of intravenous loading and maintenance doses of Peyona. We also asked the nursing staff to record the duration of administration. Five minutes after the dose, a further set of observations were recorded.

Any signs of discomfort or evidence of irritation/extravasation at the intravenous catheter site were also recorded. Nurses were expected to report any concerns (such as arrhythmia or tachycardia) which were not detected by the observations, and to submit clinical incident forms (Datix) as per normal practice.

No parental consent was sought as this was an observational audit of routine practice, and no intervention or patient identifiers were required.

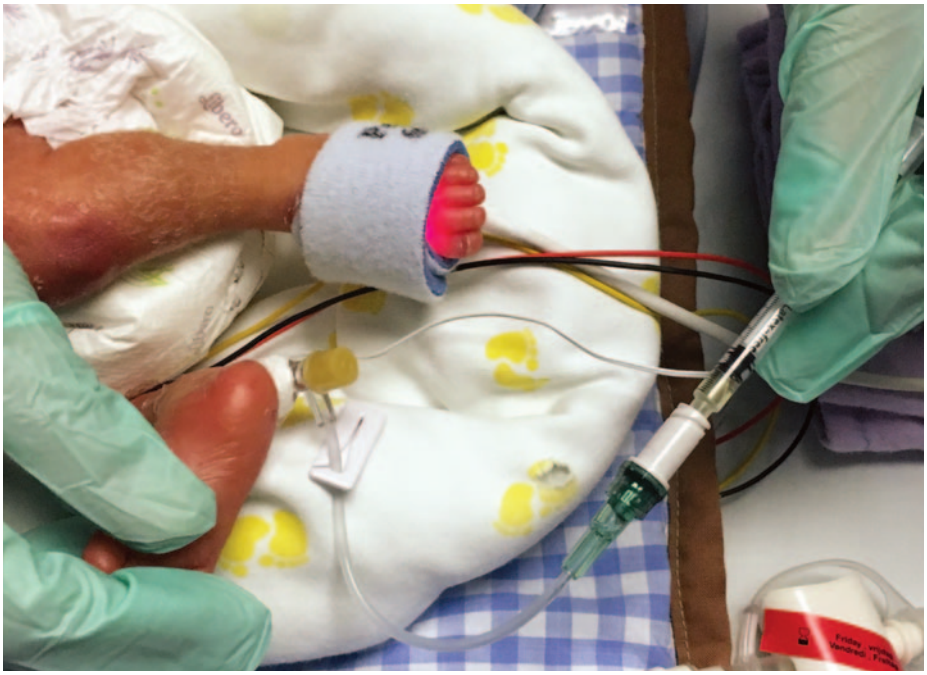

FIGURE 2 Intravenous bolus administration of caffeine citrate in a preterm infant.

Results

We collected data from a total of 92 infants (out of 105 admitted during the period). Gestations ranged from 22^{+0} to 31^{+6} weeks (mean 27^{+3} weeks). Not all infants admitted had data recorded, and some data were incomplete. Twenty-two infants did not have observations recorded for the loading doses; of these 54% (12/22) were delivered in other hospitals and stabilised prior to transfer into St. Peter's NICU. Data on the first maintenance dose was missing in 11 infants admitted during the audit period. No incident reporting forms were submitted during the audit period concerning the administration of intravenous caffeine citrate.

Data for the loading dose of caffeine citrate were recorded in 65 infants ranging from 22^{+0} to 31^{+6} weeks, (mean gestational age = 27^{+2} weeks). The mean birth weight was 978g (range = 425-1826g). Loading doses, based on 20mg/kg of caffeine citrate, ranged from 8.5-37mg (mean = 20mg). These were administered over 30 seconds to five minutes (mean and mode values = two minutes). Mean change in heart rate was +2 beats/min, mean change in respiratory rate was +4 breaths/min, mean change in oxygen saturation (recorded completely in 64 infants) was +1% and mean change in blood pressure (recorded completely in 59 infants) was 0mmHg. None of these were significant changes using a two-sample Student's t-test, with significance at a p value of <0.05 (**TABLE 1**).

Data for the first maintenance dose of caffeine citrate were recorded in 82 infants (including the 65 infants for whom loading doses were recorded) ranging from 22^{+0} to 31^{+6} weeks (mean gestational age = 27^{+3} weeks. The mean birth weight for this group was 987g (range = 425-1930g). The first maintenance dose, based on 10mg/kg of caffeine citrate, ranged from 8.5-37mg (mean = 10mg). These were administered over 30 seconds to five minutes (mean and mode values = two minutes). Mean change in heart rate was +1 beats/min, mean change in respiratory rate was +3 breaths/min, mean change in oxygen saturation was 0% and mean change in blood pressure (recorded completely in 72 infants) was 0mmHg. None of these were statistically significant changes, also using the Student's t-test (**TABLE 1**).

Further data were obtained for subsequent maintenance doses. One hundred and eleven complete sets of data were recorded in the same population of 81 infants. There were no important changes in heart rate, respiratory rate, oxygen saturations or blood pressure.

Discussion

This audit has demonstrated that the undiluted bolus administration of licensed caffeine citrate (Peyona) is safe, and does not cause pain, venous damage or important differences in routinely measured physiological parameters. The authors have seen no evidence of cardiac arrhythmias caused by bolus administration.

Practice varies considerably with caffeine

administration. A discussion on the Neonatal Paediatric Pharmacists Group discussion board raised concerns about wastage and time set against whether bolus administration might cause blood pressure instability; some units divide doses into two boluses rather than infusing.

The strength of this audit is that it is based on the unit's normal practice (both before and after the audit); any alterations in practice by the nursing staff are unlikely. Routine, non-invasive observations that are available in any neonatal unit were collected; the results are not only transferable but can also be easily replicated if desired.

The weakness of this work is that these observations have not been compared to any other preparation of caffeine citrate; the results should only be applied to a single brand (Peyona). However, while use of the Martindale preparation was not audited, the authors were not aware of any problems with bolus administration and the only reason for switching brands was that Peyona was cheaper. It may be that the estimations of duration of bolus are imprecise; the bolus is frequently given somewhat faster than the time stated on the audit form. In 22 infants, the loading dose observations were missing (due to a combination of infants being born elsewhere and subsequently transferred into the unit, as well as missed observations due to pressure on nursing staff time). However, the authors do not believe that this would have changed the results.

During the nine-month audit period no clinical incidents were recorded resulting from caffeine administration, therefore it is highly unlikely that a particularly stable or resilient population of preterm infants were unwittingly audited. Due to the size of this audit, rare complications such as arrhythmia may not have been detected; however arrhythmias related to caffeine administration have not been seen in the unit either before or since the audit. The authors do not believe that the second set of observations have missed a transient effect; they would advise others who wish to change to their practice to conduct an observational audit to provide additional reassurance.

	Mean pre-dose	Mean post-dose	Number of samples	*p*-value
Loading dose				
Heart rate (beats/min)	150	152	65	0.719
Respiratory rate (breaths/min)	53	57	65	0.129
Oxygen saturation (%)	94	94	64	0.883
Blood pressure (mmHg)	36	36	59	0.875
Maintenance dose				
Heart rate (beats/min)	153	153	82	0.652
Respiratory rate (breaths/min)	57	60	82	0.192
Oxygen saturation (%)	94	94	82	0.75
Blood pressure (mmHg)	36	36	72	0.654

TABLE 1 The analysis of pre- and post-dose observations associated with the administration of an intravenous bolus of caffeine citrate. Mean sample values (rounded) with *p*-values for both loading and maintenance dosing observations conducted prior to, and after, administration. No observations were significantly different after intravenous caffeine citrate was given.

Some infants do develop tachycardia while on maintenance caffeine and may require the drug to be reduced or stopped. However this is seen in infants on oral doses as well as intravenous doses and does not appear to be related to the mode of administration; it is more commonly seen after several doses have been given and is likely to be due to drug accumulation.

Conclusion

In summary, caffeine citrate (Peyona) can be administered as an undiluted bolus in preterm babies for the treatment and prevention of apnoea of prematurity without adverse effects, for both the intravenous loading and intravenous maintenance doses. This reduces drug wastage, reduces the time spent preparing and administering infusions and continues to be normal practice at St. Peter's Hospital.

Declaration

PR has received financial support from Chiesi Limited to speak at and attend scientific meetings.

Acknowledgement

The authors wish to thank all neonatal nurses at St. Peter's Hospital for their willingness to complete the audit forms.

References

1. **Schmidt B., Roberts R.S., Davis P. et al.** Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;354:2112-21.
2. **Sweet D.G. Carnielli V, Greisen G. et al.** European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants: 2013 update. *Neonatology* 2013;103: 353-68.
3. **European Medicines Agency.** *Public Summary of Opinion on Orphan Designation Caffeine Citrate for the Treatment of Primary Apnoea of Premature Newborns.* [Online] 2011. Available at: www.ema.europa.eu/docs/en_GB/document_library/orphan_designation/2009/10/WC500005920.pdf [Accessed 23 May 2016].