Transcutaneous electromyography of the diaphragm

Monitoring breathing and the effect of respiratory support in preterm infants

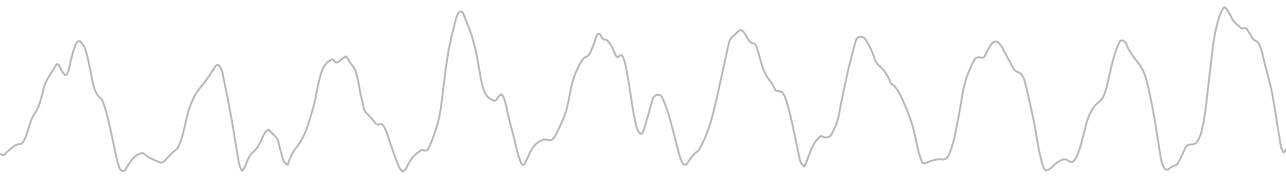
de Waal, C.G.

Chapter 4

Doxapram treatment and diaphragmatic activity in preterm infants

C.G. de Waal
G.J. Hutten
J.V. Kraaijenga
F.H. de Jongh
A.H. van Kaam

Submitted



Abstract

Background

Doxapram is a treatment option for severe apnea of prematurity. However, the effect of doxapram on the diaphragm, the main respiratory muscle, is not known.

Objectives

To investigate the effect of doxapram on diaphragmatic activity measured with transcutaneous electromyography of the diaphragm (dEMG).

Methods

A pilot study was conducted in a tertiary neonatal intensive care unit. Diaphragmatic activity was measured from 30 minutes before up to three hours after the start of doxapram treatment. dEMG parameters were compared to baseline (5 minutes before doxapram treatment) at 15, 60, 120 and 180 minutes after the start of doxapram infusion.

Results

Eleven preterm infants were included with a mean gestational age of 25.5 ± 1.2 weeks and birth weight of 831 ± 129 gram. The $amplitude_{dEMG}$, $peak_{dEMG}$ and $tonic_{dEMG}$ values did not change in the three hours after start of doxapram infusion compared to baseline. Clinically, the number of apnea in the 24 hours after doxapram treatment decreased significantly.

Conclusion

Doxapram infusion does not alter diaphragmatic activity measured with transcutaneous dEMG in preterm infants with AOP, indicating that its working mechanism is primarily on respiratory drive and not on respiratory muscle activity.

Introduction

Apnea of prematurity (AOP) is common in preterm infants and can be treated with pharmacological interventions and respiratory support.[1,2] First line therapy consists of methylxanthines, i.e. caffeine, and nasal continuous positive airway pressure. When this treatment is not sufficient, doxapram could be considered.[2] Doxapram is an analeptic drug that stimulates peripheral chemoreceptors in the carotid bodies as well as the central chemoreceptors in the respiratory center in the brainstem.[3] Previous research has shown that infusion of doxapram is effective in reducing apneic events and preventing respiratory insufficiency requiring intubation and invasive mechanical ventilation.[4] Furthermore, some small physiological studies have shown an increase in minute ventilation and tidal volume after infusion of doxapram, but only if dosed > 1 mg/kg/hour.[5,6]

Recently, it has been shown that caffeine administration in preterm infants suffering from AOP leads to an increase in diaphragmatic activity.[7] However, the effect of doxapram on the diaphragm, the main respiratory muscle, is not known. Therefore, a pilot study was conducted to investigate the effect of doxapram on diaphragmatic activity measured with transcutaneous electromyography of the diaphragm (dEMG).

Methods

A prospective observational pilot study was conducted in the neonatal intensive care unit of the Academic Medical Center Amsterdam, the Netherlands. Preterm infants born at a gestational age (GA) less than 32 weeks with AOP unresponsive to caffeine treatment and non-invasive respiratory support were included when starting treatment with doxapram infusion. The decision to start doxapram was made by the attending physician. The study protocol was approved by the local Medical Ethics Committee and both parents provided written informed consent.

Study procedure

Recording of diaphragmatic activity was initiated 30 minutes before the start of doxapram treatment and was continued for three hours after the infusion started. Transcutaneous dEMG was obtained from three skin electrodes (disposable Kendall H59P Electrodes; Covidien, Mansfield, Massachusetts, USA), two placed on the left and right frontal diaphragm and one common electrode placed on the sternum. The electrodes were connected to a portable 16-channel physiological amplifier (Dipha-16, Demcon, Son, The Netherlands), which wirelessly sent the measured raw dEMG data to a bedside computer. The software package Polybench (Applied Biosignals, Weener, Germany) was used to process the raw signal to an averaged dEMG signal, which was used for data analyses. Further information on data processing has been published previously.[8]

According to our unit protocol, doxapram infusion started with a loading dose of 2.5 mg/kg in 15 minutes and was thereafter continued with an infusion rate of 0.5 mg/kg/hour. Depending on the effect on apnea, the dose could be increased to a maximum of 2.0 mg/kg/hour. Failure of doxapram treatment was defined as respiratory failure requiring intubation and invasive mechanical ventilation within 48 hours after doxapram was started.

Data collection and analysis

Demographic and clinical data were collected of all included infants. Data on respiratory support was collected up to 48 hours after the start of doxapram. The number of apnea, associated with desaturation (SpO_2 < 80%) and/or bradycardia (heart rate < 100 beats per minute), was registered in the 24 hours before and 24 hours after the start of doxapram infusion. Diaphragmatic activity was measured as $amplitude_{dEMG}$, $peak_{dEMG}$ and $tonic_{dEMG}$ values of the dEMG signal over 30 seconds of stable recording at baseline (5 minutes before doxapram treatment) and at 15, 60, 120 and 180 minutes after the start of doxapram infusion. A percentage change in dEMG derived parameters was measured at each time point compared to baseline. Furthermore, the inspiratory time, expiratory time, respiratory rate and heart rate were collected from the dEMG signal at all time points.

Statistical analysis

SPSS version 24 (IBM, Armonk, New York, USA) was used for statistical analysis. Depending on their distribution, data were expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)). Numerical data were expressed as number and percentage.

Repeated measurement analysis was done by using the Friedman test and post-hoc Dunn's test to describe dEMG and clinical parameters over time. The number of apnea in the 24 hours before and 24 hours after the start of doxapram were compared with the Wilcoxon signed rank test. A p-value of < 0.05 was defined as statistically significant.

Results

Study population

Eleven preterm infants with a mean GA of 25.5 ± 1.2 weeks and birth weight of 831 ± 129 gram were measured with dEMG when doxapram infusion was started (median postnatal age: 15 (11 – 22) days). All infants were treated with caffeine base (5 mg/kg/day) and nasal intermittent positive pressure ventilation at the time doxapram was started. 82% of the infants had been mechanically ventilated before doxapram treatment.

Table 1. The effect of doxapram infusion on parameters measured with transcutaneous dEMG

	Baseline	***15 minutes***	***60 minutes***	***120 minutes***	***180 minutes***	
	n = 11	**n = 11**	**n = 11**	**n = 10**	**n = 10**	
dEMG parameters						
Δ $Amplitude_{dEMG}$ (%)	0 (0 - 0)	-0.7 (-17.8 - 31.7)	-5.0 (-21.6 - 0.5)	-13.5 (-27.7 - 17.2)	9.1 (-19.9 - 25.1)	p=0.948
Δ $Peak_{dEMG}$ (%)	0 (0 - 0)	1.1 (-10.8 - 20.7)	-5.4 (-28.05 - 2.8)	-9.1 (-27.8 - 3.9)	-6.6 (-18.0 - 27.4)	p=0.811
Δ $Tonic_{dEMG}$ (%)	0 (0 - 0)	2.7 (-12.0 - 17.6)	-6.4 (-19.4 - 28.7)	-5.8 (-24.7 - 4.2)	14.7 (-23.2 - 32.8)	p=0.293
Inspiratory time (s)	0.5 (0.4 - 0.5)	0.5 (0.4 - 0.5)	0.5 (0.4 - 0.5)	0.5 (0.4 - 0.5)	0.5 (0.4 - 0.5)	p=0.988
Expiratory time (s)	0.6 (0.4 - 0.6)	0.6 (0.5 - 0.6)	0.5 (0.5 - 0.6)	0.6 (0.5 - 0.7)	0.5 (0.5 - 0.6)	p=0.993
Respiratory rate (breaths/min)	56 (53 - 77)	58 (53 - 64)	61 (57 - 67)	58 (52 - 64)	61 (54 - 67)	p=0.949
Heart rate (beats/min)	156 (148 - 162)	150 (140 - 164)	154 (132 - 164)	156 (111 - 162)	156 (113 - 173)	p=0.051

$Amplitude_{dEMG}$, $peak_{dEMG}$ and $tonic_{dEMG}$ are expressed as percentage change compared to baseline, median (IQR). P-values based on the Friedman's test for repeated measurements. dEMG, electromyography of the diaphragm

The effect of doxapram

The amplitude$_{dEMG}$, peak$_{dEMG}$ and tonic$_{dEMG}$ values did not change in the three hours after start of doxapram infusion compared to baseline (Table 1). Furthermore, no change was seen in inspiratory time, expiratory time, respiratory rate and heart rate in this time window.

Four (36%) infants failed doxapram treatment and needed invasive mechanical ventilation within 48 hours. Compared to infants successfully treated with doxapram, no difference was found in terms of diaphragmatic response.

Clinically, the treatment with doxapram led to a significant decrease in the number of apnea from 32 (24 - 51) in the 24 hours before to 23 (18 – 28) in the 24 hours after the start ($p = 0.012$). This reduction in apnea was most prominent in infants not requiring intubation and invasive mechanical ventilation in the 48 hours after starting doxapram treatment.

Discussion

In this pilot study on the effect of doxapram on diaphragmatic activity in preterm infants, no significant change in dEMG derived parameters was found in the first three hours after the start of doxapram treatment.

Doxapram is an increasingly used drug to treat infants with severe AOP resistant to caffeine therapy and maximal non-invasive respiratory support.[9] Previous studies have shown that doxapram reduces apnea frequency and the need for invasive mechanical ventilation.[4] However, its working mechanism is still poorly understood.

Our study confirms the positive effect of doxapram on apnea reduction, but adds important new knowledge that this beneficial effect is probably not mediated through an increase in diaphragmatic activity measured in stable transcutaneous dEMG recordings. This suggests that the primary effect of doxapram is to regulate respiratory drive and not respiratory muscle activity. This in contrast to caffeine, which results in a direct and persistent increase in diaphragmatic activity in preterm infants.[7] It is unlikely that this different effect of doxapram and caffeine on diaphragmatic activity is dose related, as we administered a doxapram loading dose of 2.5 mg/kg in 15 minutes which is the maximal tested dose for treatment of AOP in preterm infants.[10] As doxapram is very rapidly metabolized and its clinical effect is often seen within minutes, extending the three-hour measurement would probably not have changed our findings. It is important to acknowledge that we only included eleven infants in this study. However, the absence of any signal indicating a doxapram mediated effect on diaphragmatic activity, makes it unlikely that we would have found a clinically relevant treatment effect on this outcome in a larger sample size.

In conclusion, doxapram infusion does not alter diaphragmatic activity measured with transcutaneous dEMG in preterm infants with AOP, indicating that its working mechanism is primarily on respiratory drive and not on respiratory muscle activity. This probably explains the additive effect of doxapram in caffeine treated preterm infants with persistent AOP.

References

1. Eichenwald EC. Apnea of Prematurity. Pediatrics. 2016;137(1):e20153757.
2. Hascoet JM, Hamon I, Boutroy MJ. Risks and benefits of therapies for apnoea in premature infants. Drug Saf. 2000;23(5):363–79.
3. Yost C. A new look at the respiratory stimulant doxapram. CNS Drug Rev. 2006;12(3–4):236–49.
4. Flint R, Halbmeijer N, Meesters N, van Rosmalen J, Reiss I, van Dijk M, et al. Retrospective study shows that doxapram therapy avoided the need for endotracheal intubation in most premature neonates. Acta Paediatr Int J Paediatr. 2017;106(5):733–9.
5. Barrington KJ, Finer NN, Peters KL, Barton J. Physiologic effects of doxapram in idiopathic apnea of prematurity. J Pediatr. 1986;108(1):124–9.
6. Bairam A, Faulon M, Monin P, Vert P. Doxapram for the initial treatment of idiopathic apnea of prematurity. Biol Neonate. 1992;61(4):209–13.
7. Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH. The Effect of Caffeine on Diaphragmatic Activity and Tidal Volume in Preterm Infants. J Pediatr. 2015;167(1):70–5.
8. O'Brien M, van Eykern L, Prechtl H. Monitoring respiratory activity in infants - a non-intrusive diaphragm EMG technique. Non-invasive physiological measurements. Londen: Academic Press Inc. 1983. p. 131–77.
9. Prins S, Pans S, van Weissenbruch M, Walther F, Simons S. Doxapram use for apnoea of prematurity in neonatal intensive care. Int J Pediatr. 2013;2013:1–5.
10. Barrington KJ, Finer NN, Torok-Both G, Jamali F, Coutts RT. Dose-response relationship of doxapram in the therapy for refractory idiopathic apnea of prematurity. Pediatrics. 1987;80(1):22–7.