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Respiratory Effects of 1-Propylxanthine on Neonatal Rats

by

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Thesis Director

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Abstract

Neonatal apnea is commonly treated by methylxanthines like caffeine or theophylline, but these drugs have the potential to create serious side effects. As an alternative, a new xanthine analog, 1-propylxanthine (1-PX), was recently synthesized at Eastern Illinois University. The respiratory effects of 1-PX were investigated in 4- to 7-day-old rats to determine if 1-PX could be a respiratory stimulant. Each rat was placed in a heated body plethysmograph, and its respiratory rate and volume were measured using a flow transducer, pneumotachograph, and Power Lab data acquisition system. After a 10-min control period, the rat was given a s.c. dose of 1-PX (10, 20, 40, or 80 mg/kg) or saline. Respiration was then recorded for one hour. Dose-related increases were observed in respiratory rate and minute ventilation, while there were highly variable changes in tidal volume and a small increase in mean inspiratory flow. The 80 mg/kg dose elicited a 32% increase in respiratory rate and an 8% increase in minute ventilation. A CO₂-response study was also conducted on a separate group of rats in order to determine if 1-PX increases the respiratory response to CO₂. In the CO₂-response study, each rat (4- to 7-days-old) was placed in a heated body plethysmograph, and its respiratory rate and volume along with the inspired CO₂ concentration were recorded by a flow transducer, pneumotachograph, Datex-252 airway gas monitor, and PowerLab data acquisition system. Respiration was recorded for 10 minutes while the rat was breathing room air (0% CO₂). The CO₂ concentration was then increased in 1% increments from 1-6%. After the initial CO₂-response test, each rat received a s.c. injection of 20, 40, or 80 mg/kg 1-PX or saline. The CO₂-response test was repeated at three 15-min intervals after drug administration. Dose-related increases were observed in both minute ventilation and tidal volume, while there were highly variable changes in respiratory rate and

mean inspiratory flow. The 80 mg/kg 1-PX dose elicited a 127% increase in minute ventilation and an 84% increase in tidal volume. The results indicate that 1-PX is slightly less potent than theophylline and approximately equal in potency to 1-methylxanthine as a respiratory stimulant.

Introduction

Pauses in breathing lasting from 6 to 10 seconds occur in all infants. These pauses are due to the immaturity of the respiratory system and are not necessarily harmful to the infant (1). If these pauses in breathing occur three or more times for more than three seconds with less than 20 seconds in respiration between pauses, the condition is termed apnea (1). Apnea is not significant until the respiratory pauses last 20 seconds or longer or is coupled with bradycardia, cyanosis, or pallor (1). Apnea and the resultant combination of bradycardia and desaturation often require the use of pharmacological intervention that can cause serious side effects (2).

Methylxanthines are respiratory stimulants administered to neonates with apnea and have been shown to affect the child's growth, neurological development, and behavior (3). In therapeutic ranges, theophylline, a methylxanthine, can cause side effects that include nausea, headache, diuresis, and occasionally cardiac arrhythmias and seizures (4). Theophylline (1,3-dimethylxanthine) has also caused tachycardia, vomiting, diarrhea, and abdominal distention at therapeutic concentrations (5). Caffeine, another methylxanthine, has also been shown to cause tachycardia at therapeutic levels and to affect the central nervous system causing nervousness or anxiety, restlessness, tremors, insomnia, and hyperesthesia (6).

Neonatal apnea is thought to be caused by adenosine accumulation in the brain caused by the dephosphorylation of adenosine triphosphate (ATP) during hypoxia. Methylxanthines block

this hypoxia-induced apnea, and their therapeutic effects have been suggested to be due to the antagonistic action on adenosine receptors (7). Methylxanthines are the most common type of drug used to combat recurrent apnea in neonates because of the stimulatory effect that it has on the respiratory center. The most important therapeutic action of methylxanthines in children and adults is their ability to relax bronchial smooth muscle in order to increase air flow in diseases such as asthma (6). Methylxanthines also appear to cause an increased sensitivity of the medullary respiratory centers to the presence of CO_2 which increases the respiratory minute volume in response to increased alveolar Pco_2 (6).

The 1-position of alkylxanthines is thought to be essential for adenosine antagonism while the 3-position of xanthines is essential for increased bronchodilation. Both the 1-position and 3-position of alkylxanthines may increase toxic potency. The 7-position of xanthines decreases bronchodilation and toxic potency (8). Caffeine and theophylline, the two most used xanthines, both have methyl groups at the 1 and 3 positions while caffeine also has a methyl group at the 7-position (6). Since the 7-position causes decreased bronchodilation and the 3-position has been shown to only enhance stimulation of respiration, the 1-position remains to be the cause of respiratory stimulation (9). In this experiment, the respiratory effects of the new drug, 1-propylxanthine (1-PX), were observed in neonatal rats with the hypothesis that 1-PX increases the ventilation and increases the respiratory response to CO_2 in neonatal rats.

Materials and Methods

Setting up the equipment for the procedure began with connecting the Power Lab to the ETH-255 Bridge/ Bio Amplifier with a BNC cable plugged into the channel 1 output of the

amplifier to the front channel 1 input of the Power Lab unit. Channel 1 controls were set as follows: Gain= X1, Low Pass= 50 Hz, and High Pass= DC. The power supply was then turned on to the water bath, pneumotachograph, Power Lab, amplifier, and computer. The Validyne model MC 1-3 pneumotachograph was attached to a Fleisch #0000 flow transducer and plugged into channel 1 of the amplifier. The chart program with approved settings was opened on the computer with channel 1 recording the flow, channel 2 recording the total volume, and channel 3 recording the number of breaths. The instruments were calibrated to eliminate drift in the volume recording. The chart calibration included opening the Computed Input Column for channel 2 and turning the channel 1 offset knob to zero. The drift was rechecked before each animal treatment. The volume calibration was performed by filling a 20 ml syringe with exactly 20 ml of air and inserting the syringe on the left end of the flow transducer that is connected to the pneumotachograph. The reset button located on the chart calibration screen was clicked and the 20 ml of air from the syringe was plunged into the flow transducer within 5 seconds. The reading on channel 2 should be 20 ml; if this was not the case, then the calibration was repeated. After the equipment was calibrated, the Computed Input screen was exited.

A newborn rat was randomly selected from a litter for a treatment. The rat was no less than 4 days old and no more than 7 days old. The rat's mass, sex, age, and litter number were recorded in an Excel spreadsheet. An appropriate diaphragm with a hole in the center was selected according to the size of the rat and was placed over the lubricated end of the plethysmograph with a small rubber band. The rat's head was forced through the hole in the diaphragm, and a plastic crosspiece was placed behind the rat to keep it from backing out. The end of the plethysmograph was plugged with a rubber stopper that contained a rubber tube that

would be attached to the flow transducer. Lubricant was applied around the neck of the rat to assure a tight seal. A small plastic cylinder was placed around the rat's head to allow the rat to rest its chin, and this cylinder was held in place with tape. The plethysmograph was placed in the center of a jacketed water bath and the plastic tube from the plethysmograph was attached to the flow transducer of the pneumotachograph.

Recording was started and continued for ten minutes. After the initial ten minutes, two control measurements were taken by highlighting a ten second region of the graph in channel 1. The chart data was then copied and pasted into an Excel spreadsheet. The injection was prepared by determining the dose of 1-PX or saline (10 mg/kg with a concentration of 2 mg/ml, 20 mg/kg with a concentration of 4 mg/ml, 40 mg/kg with a concentration of 8 mg/ml, 80 mg/kg with a concentration of 16 mg/ml, or 0.9% NaCl) required by multiplying the rat's mass by 5 microliters/ gram. The 80 mg/kg 1-PX dose was derived from the 8 mg/ml solution by doubling the amount of the 8 mg/ml solution because there were solubility problems with higher concentrations of 1-PX. The 1-PX was synthesized by Dr. Howard Black and Aaron Lineberry of the Eastern Illinois University Chemistry Department. The 100 μ l syringe was completely filled, the 26 gauge needle was attached, and the solution was pushed into the 26G needle until a drop of solution was ejected. The syringe was then filled completely to the determined amount, and the rat was injected under the scalp of the neck with a single subcutaneous dose of 1-PX (10, 20, 40, or 80 mg/kg) or saline (0.9% NaCl) without removing the rat from the plethysmograph.

The plethysmograph was placed back into the jacketed water bath and attached to the right side of the flow transducer of the pneumotachograph. Recording was started immediately

after injection and continued for 60 minutes with 10 second recordings highlighted and saved to the Excel spreadsheet every 5 minutes. Eight rats were tested at each dose, with a total of 40 rats used in the study.

The same procedure as above was followed in the 1-PX CO₂-response study with only a few differences. Again, 4- to 7-day-old rats were used in this experiment, but the treatments were reduced to saline, 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-PX. Setting up the equipment for the procedure began with connecting the Power Lab to the ETH-255 Bridge/ Bio Amplifier with a BNC cable plugged into the channel 1 output of the amplifier to the front channel 1 input of the Power Lab unit. Channel 1 controls were set as follows: Gain= X1, Low Pass= 50 Hz, and High Pass= DC. The power supply was then turned on to the water bath, pneumotachograph, Power Lab, amplifier, Datex-252 airway gas monitor, and computer. The Datex-252 airway gas monitor was plugged into channel 1 of the amplifier while the Validyne model MC 1-3 pneumotachograph was attached to a Fleisch #0000 flow transducer and plugged into channel 2 of the amplifier. The chart program with approved settings was opened on the computer with channel 1 recording the flow, channel 2 recording the total volume, channel 3 recording the number of breaths, and channel 4 recording the CO₂ concentration. The instruments were calibrated to eliminate drift in the volume recording. The chart calibration included opening the Computed Input Column for channel 2 and turning the channel 1 offset knob to zero. The drift was rechecked before each animal treatment. The volume calibration was performed by filling a 20 ml syringe with exactly 20 ml of air and inserting the syringe on the left end of the flow transducer that is connected to the pneumotachograph. The reset button located on the chart calibration screen was clicked and the 20 ml of air from the syringe was plunged into the

flow transducer in about 5 seconds. The reading on channel 2 should be 20 ml; if this was not the case, then the calibration was repeated. After the equipment was calibrated, the Computed Input screen was exited.

A newborn rat (4-to 7-days-old) was randomly selected from a litter for a treatment. The rat's mass, sex, age, and litter number were recorded in an Excel spreadsheet. An appropriate diaphragm with a hole in the center was selected according to the size of the rat and was placed over the lubricated end of the plethysmograph with a small rubber band. The rat's head was forced through the hole in the diaphragm, and a plastic crosspiece was placed behind the rat to keep it from backing out. The end of the plethysmograph was plugged with a rubber stopper that contained both a rubber tube that would be attached to the pneumotachograph and a rubber tube that was attached to the gas mixer, Anthoson. Lubricant was applied around the neck of the rat in order to assure a tight seal. A small plastic cylinder was placed around the rat's head to allow the rat to rest its chin, and this cylinder was held in place with tape. The plethysmograph was placed in the center of the jacketed water bath, and the plastic tube from the plethysmograph was attached to the flow transducer of the pneumotachograph. A rubber stopper plugged the other end of the jacketed water bath at the end closest to the rat's head, and a thin tube was inserted through this rubber stopper into the jacketed water bath from the Datex-252 airway gas monitor.

Recording was started and continued for ten minutes while the rat was breathing room air (0% CO₂). An air compressor generated this room air by sending room air to a gas mixer, Anthoson, that sent air into the jacketed water bath. The CO₂ concentration was then increased in 1% increments from 1 to 6% by mixing CO₂ from a concentrated gas tank and room air from the air compressor with the gas mixer, Anthoson. The Datex-252 airway gas monitor detected the

carbon dioxide level in the jacketed water bath and sent the signal to the PowerLab data acquisition system, which converted this signal into quantitative data.

After the initial CO₂-response test, the injection was prepared by determining the dose of 1-PX (20 mg/kg with a concentration of 4 mg/ml, 40 mg/kg with a concentration of 8 mg/ml, or 80 mg/kg with a concentration of 16 mg/ml) or 0.9% saline placebo required by multiplying the rat's mass by 5 microliters/ gram. The 80 mg/kg 1-PX dose was derived from the 8 mg/ml solution by doubling the amount of the 8 mg/ml solution because there were solubility problems with higher concentrations of 1-PX. The 1-PX was synthesized by Dr. Howard Black and Aaron Lineberry of the Eastern Illinois University Chemistry Department. The 100 µl or 150 µl syringe was completely filled, the 26 gauge needle was attached, and the solution was pushed into the 26G needle until a drop of solution was ejected. The syringe was then filled completely to the determined amount, and the rat was injected under the scalp with a single subcutaneous dose of 1-PX or saline without removing the rat from the plethysmograph.

The plethysmograph was placed back into the jacketed water bath and attached to the right side of the flow transducer of the pneumotachograph. The CO₂-response test was then repeated at 15, 30, and 45 minutes after drug administration. Minute ventilation (V_E), respiratory rate (f), tidal volume (V_T), and mean inspiratory flow (V_T/T_I) at the varying levels of inspired CO₂ concentrations were collected by the PowerLab.

Results

The rats given saline had an overall reduction in their mean percent change in f and V_E with time, while the rats given lower doses of 1-PX had a decrease in mean percent change in

V_E , but to a lesser extent than saline shown in Figure 1 and 2. There were dose-related increases in both mean percent change in f and V_E compared to saline during the first 30 minutes after administration of 1-PX (Fig. 1, 2). The f was significantly higher than the saline controls in the 20, 40, and 80 mg/kg 1-PX doses ($p < 0.01$). The rats given the 80 mg/kg dose of 1-PX had the greatest increase in mean percent change in f and in V_E as compared to the saline treatment. The 40 mg/kg 1-PX dose elicited a greater response in the rats' mean percent change in f and V_E than the 20 mg/kg dose and the 10 mg/kg dose as compared to the saline dose. For example, at 30 minutes the saline treatment elicited a 13% decrease in f and a 23% decrease in V_E , the 10 mg/kg 1-PX dose elicited a 7% decrease in f and a 13% decrease in V_E , the 20 mg/kg 1-PX dose caused a 15% increase in f ($p < 0.05$) and a 15% decrease in V_E , and the 40 mg/kg 1-PX dose caused an 11% increase in f ($p < 0.01$) and a 10% decrease in V_E , while the 80 mg/kg 1-PX dose elicited a 26% increase in f ($p < 0.01$) and an 8% increase in V_E .

Figure 3 shows that the mean percent change in V_T for the 10 mg/kg dose of 1-PX increased compared to the saline dose. Saline produced an 11% decrease in mean percent change in V_T at 20 minutes, while the 10 mg/kg dose of 1-PX elicited a 4% decrease in mean percent change in V_T at 20 minutes. The remaining doses of 20 mg/kg, 40 mg/kg, and 80 mg/kg 1-PX showed a decreased mean percent change in V_T as compared to saline with the 80 mg/kg dose of 1-PX causing the greatest decrease. The 20 mg/kg dose of 1-PX seems to decrease the mean percent change in V_T more than the 40 mg/kg dose. No discernable pattern was seen in mean percent change of V_T ; therefore, there seems to be no correlation between dose and effects on V_T . Mean percent change in V_T/T_I increased to a small extent by 1-PX shown in Figure 4.

The V_E , V_T , and V_T/T_I increase in neonatal rat respiration both in the saline control treatment and in the 1-PX doses in response to CO_2 ; however, the slopes of the 1-PX doses are steeper than the pre-injection control slopes. The f remains unchanged in neonatal rats in respiration response to CO_2 . Also, the pre- and post-injection CO_2 response curves are very similar for the saline rats.

Within the CO_2 -response study, both mean percent change in V_E and mean percent change in V_T exhibited dose-related increases as seen in Figures 5-9. The effects of 1-PX on mean percent change of V_E were clearly dose-related at 15 minutes post-injection as illustrated in Figure 5. The greatest increase in mean percent change in V_E occurred 30 minutes post-injection; however, in this case, the 20 mg/kg 1-PX dose produced a slightly greater increase than the 40 mg/kg 1-PX dose as depicted in Figures 6. At 15 minutes post-injection, 6% CO_2 caused a 65% increase in mean percent change in V_E for the saline dose (compared to a 54% increase pre-injection), a 70% increase for the 20 mg/kg 1-PX dose, 82% increase for the 40 mg/kg 1-PX dose, and 100% increase for the 80 mg/kg dose, while the mean percent change in V_E in response to 6% CO_2 30 minutes post-injection was 76% for the saline dose (compared to a 54% increase pre-injection), a 99% increase for the 20 mg/kg 1-PX dose, a 90% increase for the 40 mg/kg 1-PX dose, and a 127% increase for the 80 mg/kg 1-PX dose. Both Figures 6 and 7 depict dose-related effects in mean percent change in V_E at 30 and 45 minutes post-injection except that the 20 mg/kg and 40 mg/kg 1-PX doses were reversed with the 20 mg/kg dose of 1-PX having a greater increase in mean percent change in V_E than the 40 mg/kg dose of 1-PX.

The greatest dose-related effects in mean percent change of V_T occurred at 30 minutes post-injection while 15 minutes post-injection also showed dose-related effects but to a lesser extent than 30 minutes post-injection as illustrated in Figures 8 and 9. Mean percent change in V_T 45 minutes post-injection showed no discernable pattern as seen in Figure 10. Mean percent change in f at 15, 30, and 45 minutes post-injection also displayed no discernable pattern; however, a flat response to CO_2 was observed in the mean percent change in f , and this flat response was not altered by the drug treatment as depicted in Figures 11-13. Mean percent change in V_T/T_I at 30 and 45 minutes post-injection shows the 40 mg/kg 1-PX dose as the most effective dose while the other doses as well as the mean percent change in V_T/T_I at 15 minutes post-injection seems to illustrate no discernable pattern as shown in Figures 14-16.

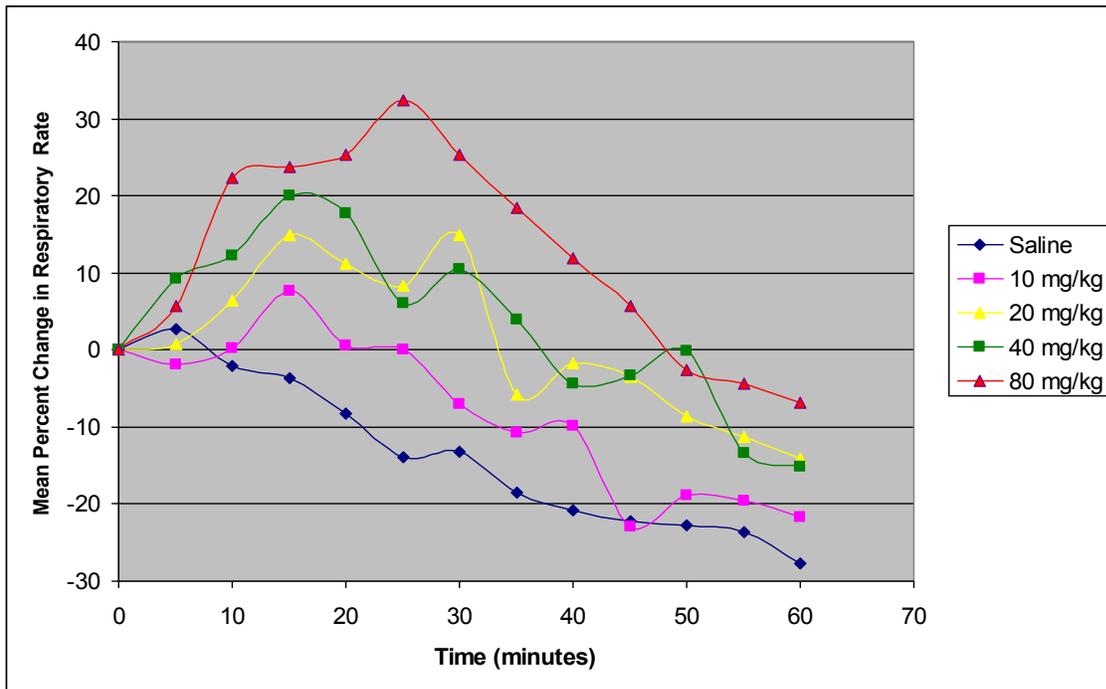


Fig. 1. Time (min) vs mean percent change in respiratory rate of 8 neonatal rats injected with doses of 10 mg/kg, 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

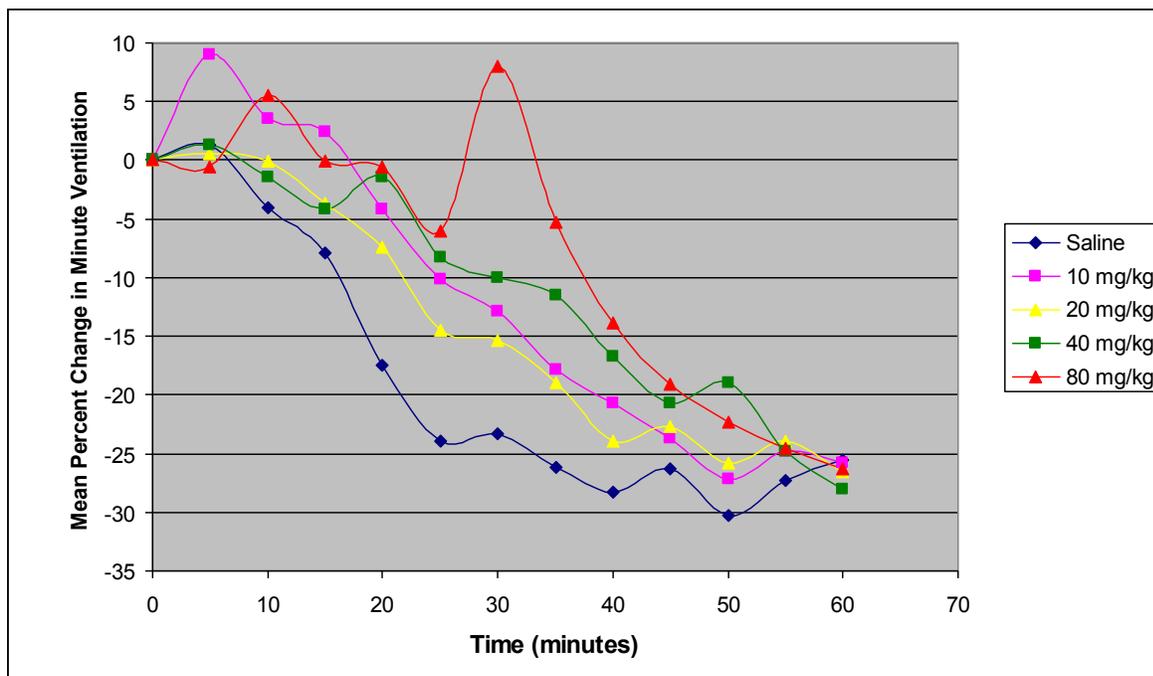


Fig. 2. Time (min) vs mean percent change in minute ventilation of 8 neonatal rats injected with doses of 10 mg/kg, 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

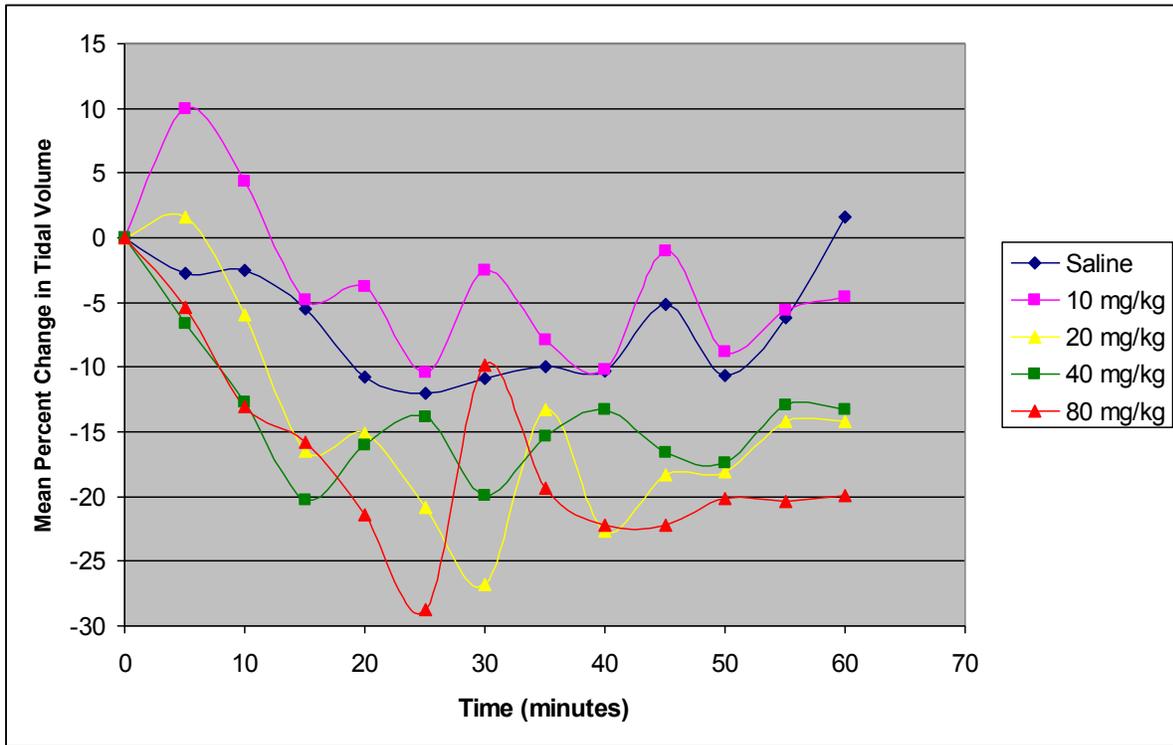


Fig. 3. Time (min) vs mean percent change in tidal volume of 8 neonatal rats injected with doses of 10 mg/kg, 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

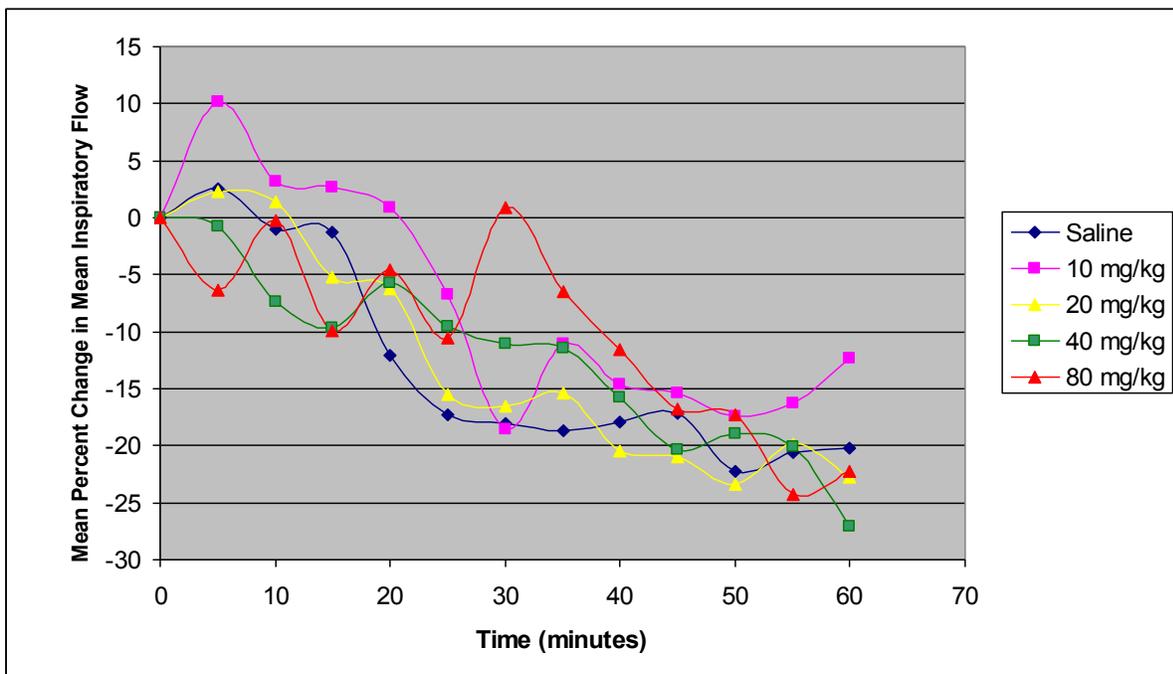


Fig. 4. Time (min) vs mean percent change in mean inspiratory flow of 8 neonatal rats injected with doses of 10 mg/kg, 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

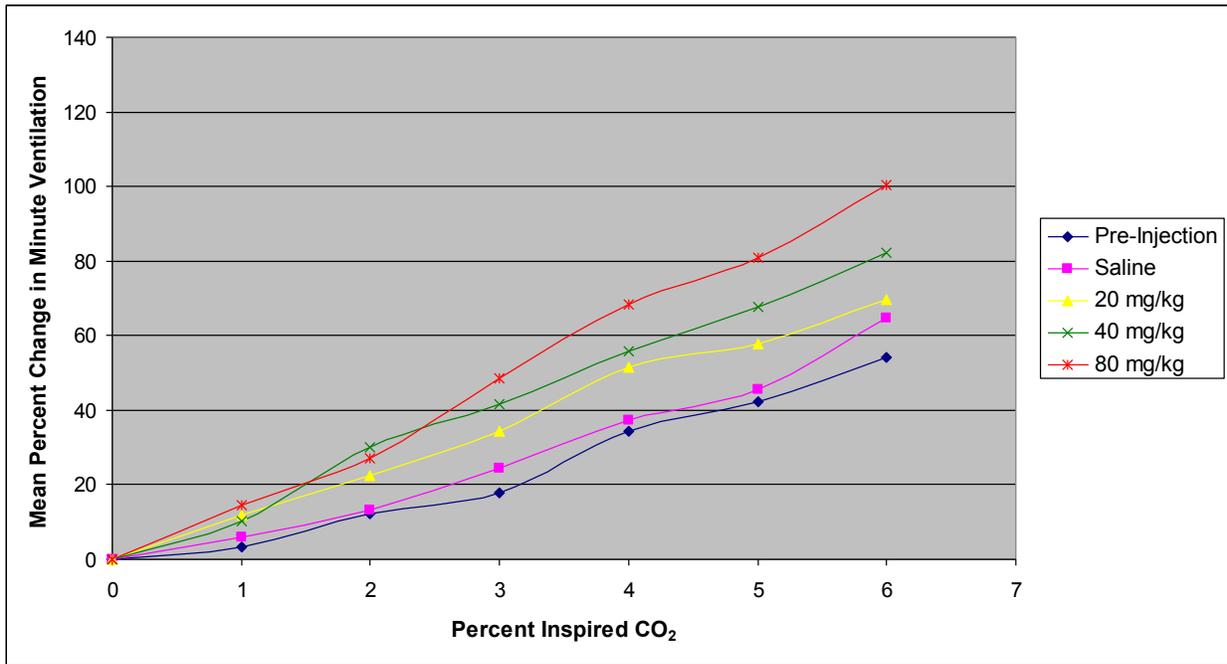


Fig. 5. Mean percent change from the 0% CO₂ measurement in minute ventilation of 8 neonatal rats 15 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

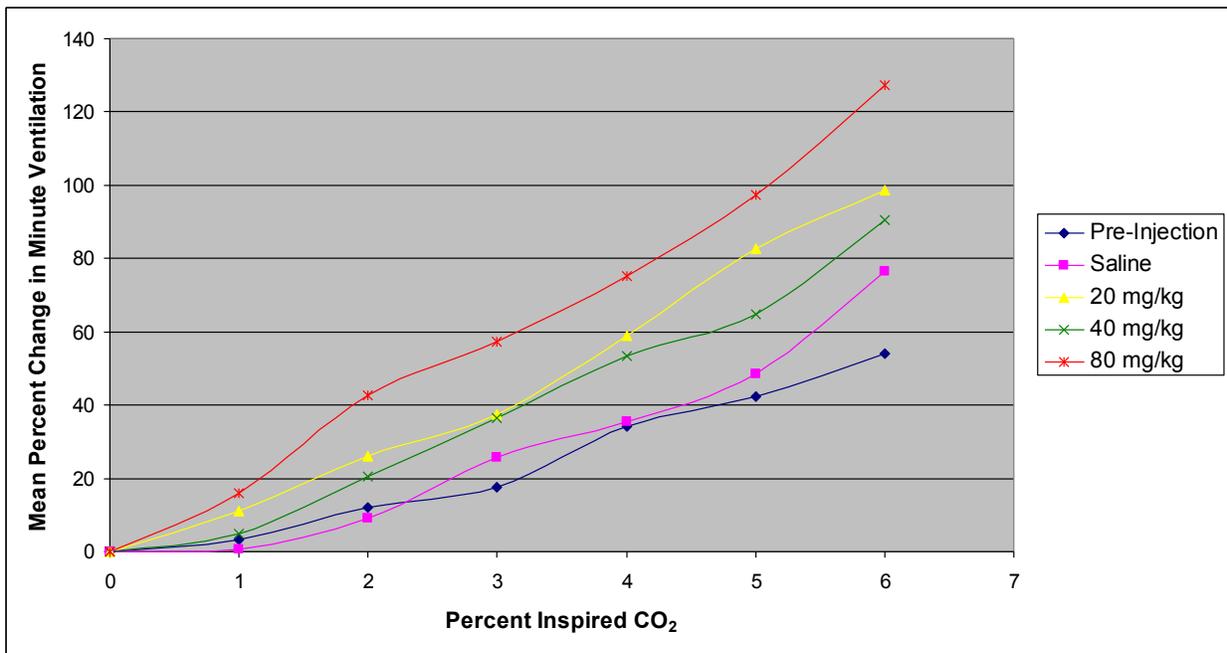


Fig. 6. Mean percent change from the 0% CO₂ measurement in minute ventilation of 8 neonatal rats 30 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

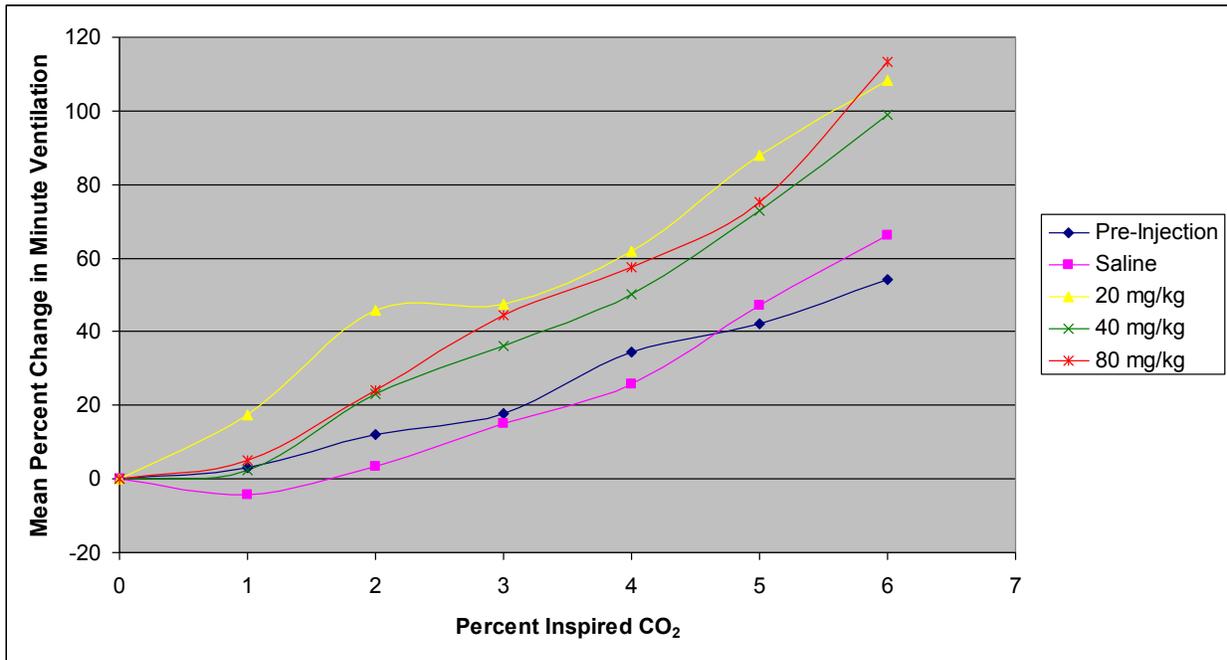


Fig. 7. Mean percent change from the 0% CO₂ measurement in minute ventilation of 8 neonatal rats 45 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

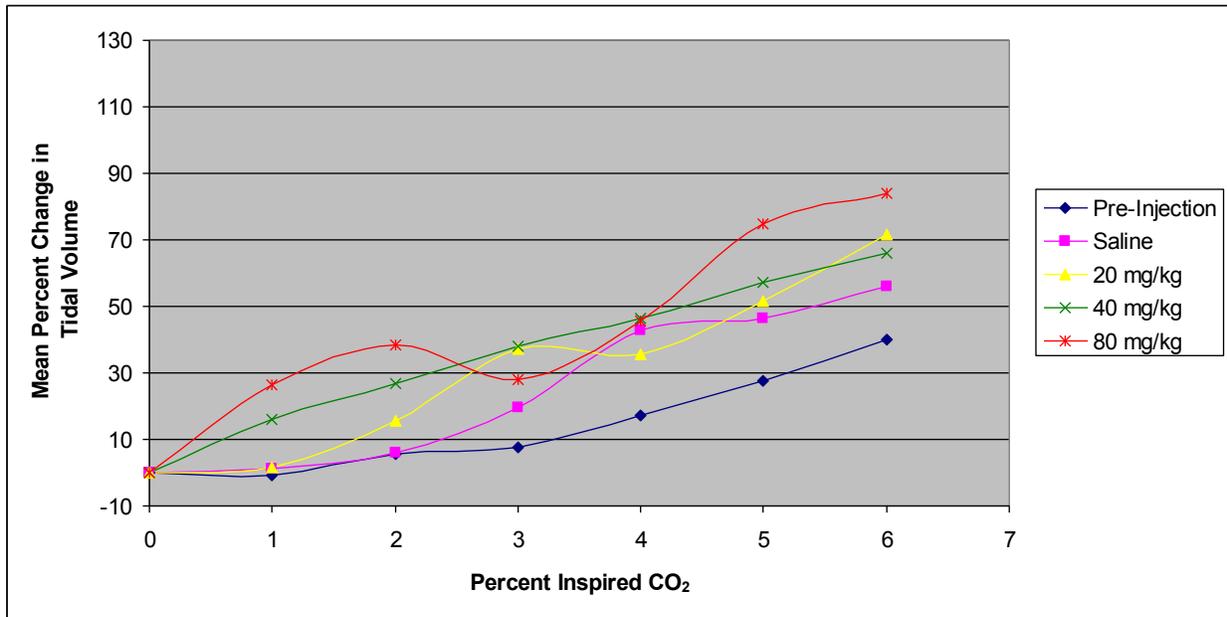


Fig. 8. Mean percent change from the 0% CO₂ measurement in tidal volume of 8 neonatal rats 15 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

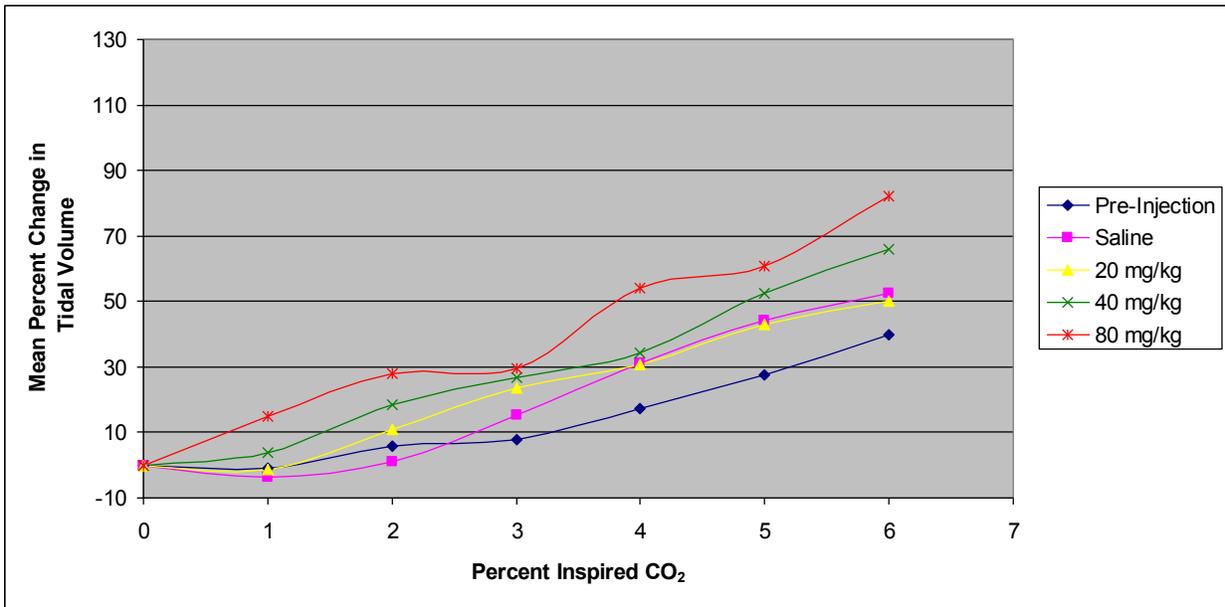


Fig. 9. Mean percent change from the 0% CO₂ measurement in tidal volume of 8 neonatal rats 30 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

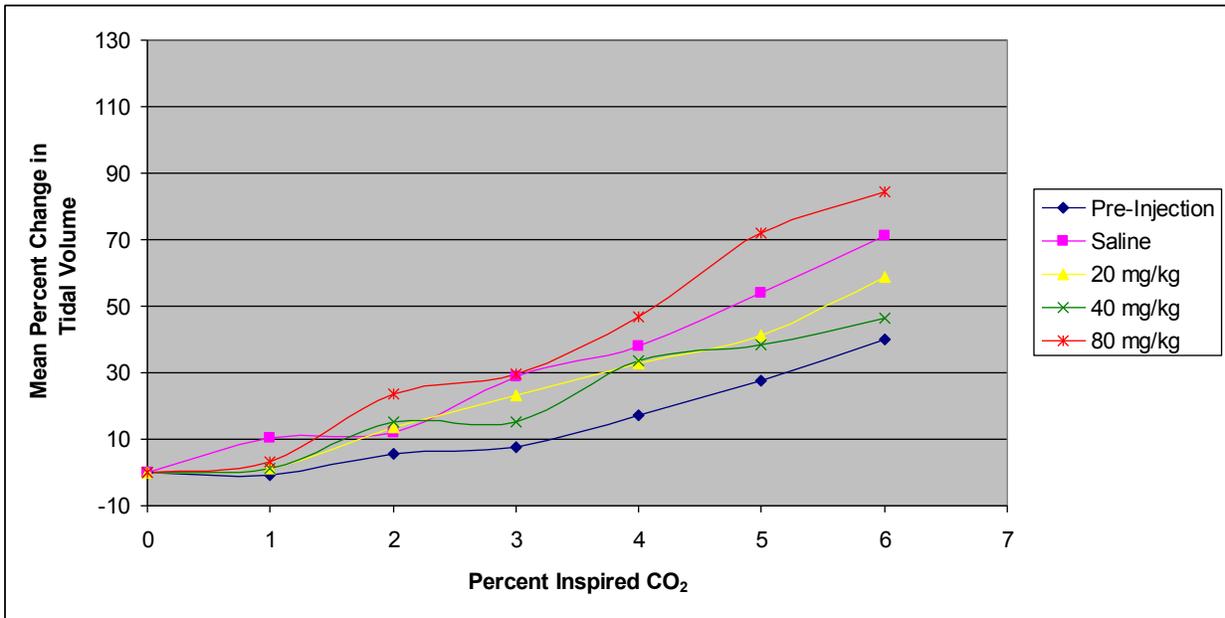


Fig. 10. Mean percent change from the 0% CO₂ measurement in tidal volume of 8 neonatal rats 45 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

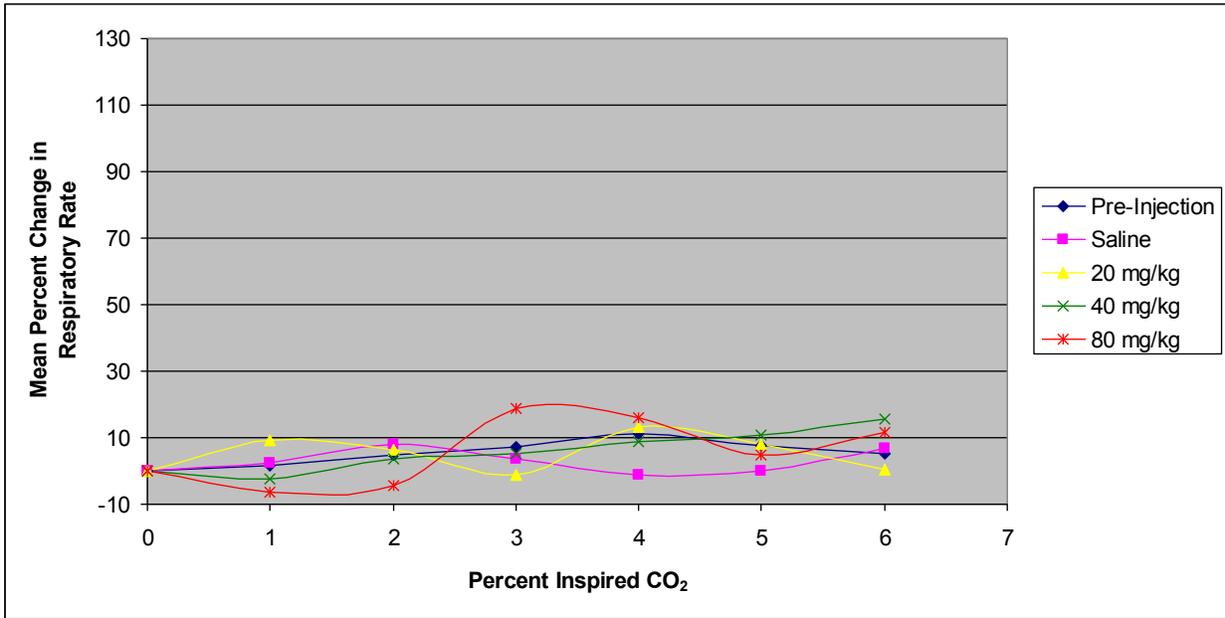


Fig. 11. Mean percent change from the 0% CO₂ measurement in respiratory rate of 8 neonatal rats 15 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

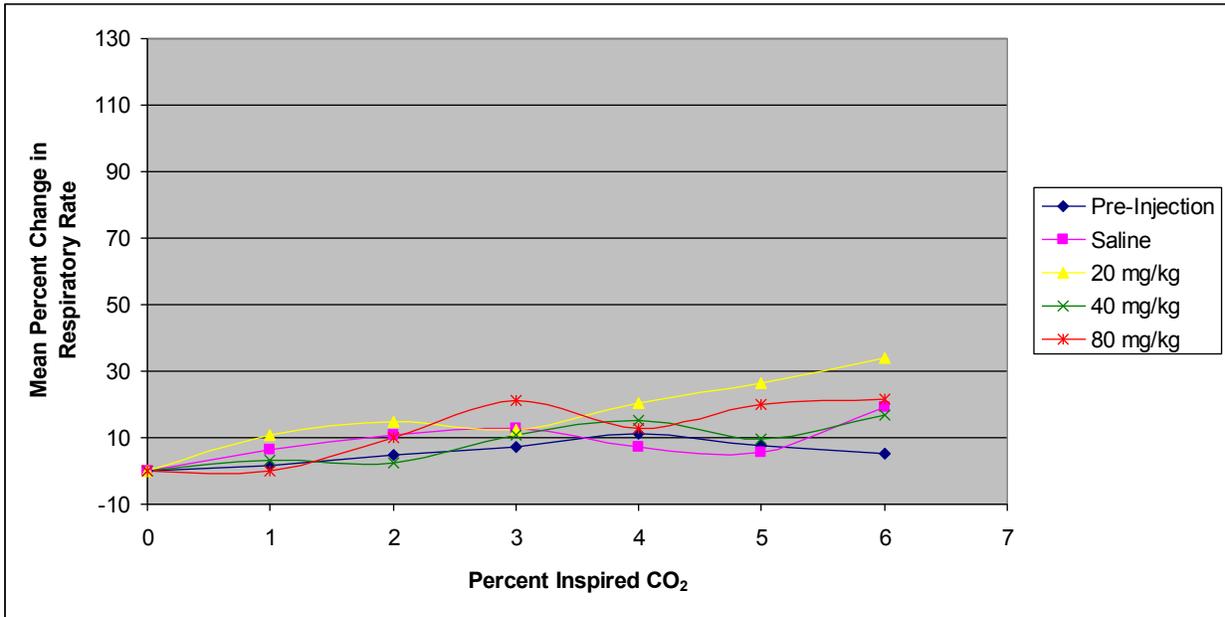


Fig. 12. Mean percent change from the 0% CO₂ measurement in respiratory rate of 8 neonatal rats 30 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

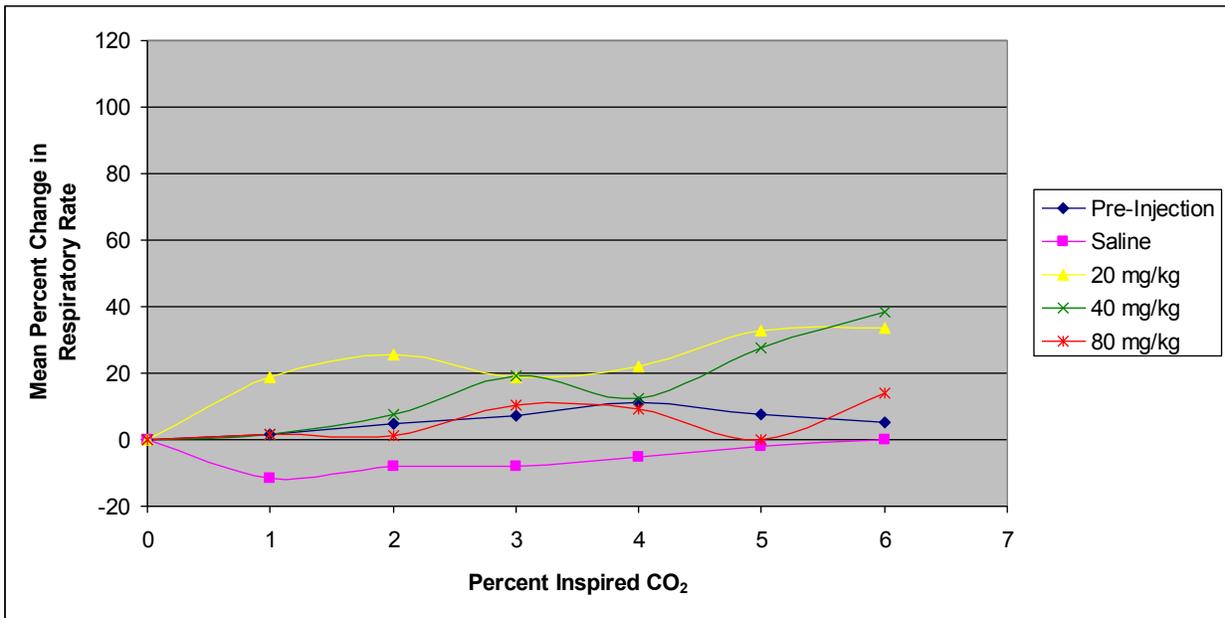


Fig. 13. Mean percent change from the 0% CO₂ measurement in respiratory rate of 8 neonatal rats 45 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

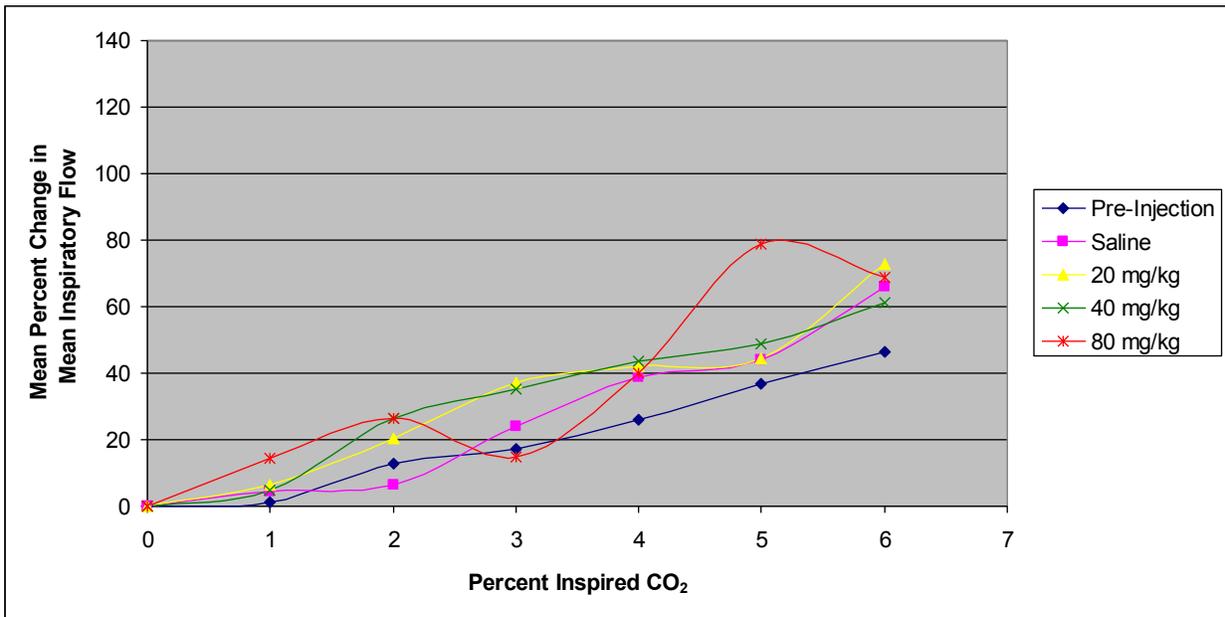


Fig. 14. Mean percent change from the 0% CO₂ measurement in mean inspiratory flow of 8 neonatal rats 15 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

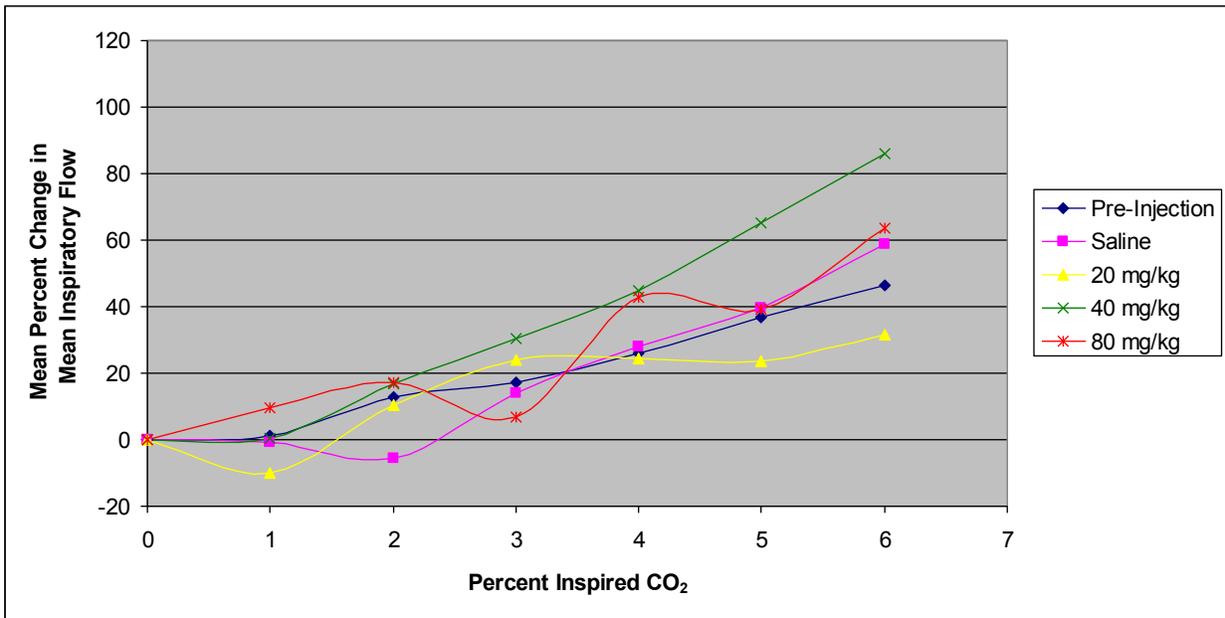


Fig. 15. Mean percent change from the 0% CO₂ measurement in mean inspiratory flow of 8 neonatal rats 30 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

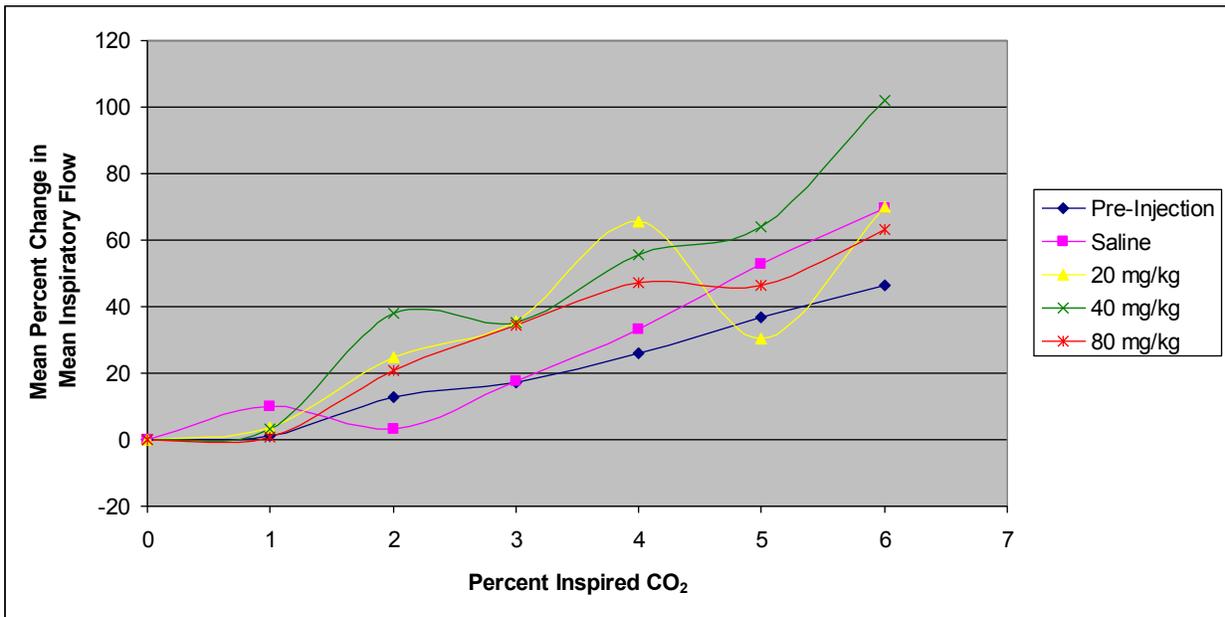


Fig. 16. Mean percent change from the 0% CO₂ measurement in mean inspiratory flow of 8 neonatal rats 45 minutes post-injection of 20 mg/kg, 40 mg/kg, and 80 mg/kg of 1-propylxanthine and saline.

Discussion

The results demonstrate that 1-PX stimulates respiration in neonatal rats and increases the ventilatory response to CO₂. The response was dose-related, with the 80 mg/kg 1-PX dose eliciting the greatest increase in mean percent change in f and V_E . For f , the 20, 40, and 80 mg/kg 1-PX doses were all significantly different from saline. These results exhibit similarities to the respiratory effects produced by 1-methylxanthine (1-MX) (10). Both 1-PX and 1-MX increase f and V_E without increasing V_T . This study provides more supporting evidence that substitution in the 1-position is essential for stimulation of respiration by xanthine analogs. Comparison with 1-MX suggests that the potency as a respiratory stimulant is not affected by the size of the alkyl group on the 1-position. A previous study indicated that 3-propylxanthine (enprofylline) did not stimulate respiration at doses up to 40 mg/kg (9), providing further supporting evidence that the 1-position is essential for stimulation of respiration by xanthine analogs. The increase in mean percent change in V_E produced by 80 mg/kg 1-PX is equivalent to the increase produced by 20 mg/kg theophylline (1,3-dimethylxanthine) (10), results indicating that 1-PX is less potent than theophylline.

Mean percent change in V_E was unusually high at 30 minutes post-injection of the highest dose of 1-PX. Five out of the 8 rats illustrated this jump in V_E (a 4-day-old female, two 4-day-old males, a 6-day-old female, and a 7-day-old female). Also, a 6-day-old male had increased V_E , but not an extreme jump like the other 5 rats. Two samples (one from the 20 mg/kg data and one from the 40 mg/kg data) were thrown out and repeated due to computer problems and excessive rat movement. The effectiveness of 1-PX correlates with the dose and thus supports the hypothesis that 1-PX stimulates respiration in neonatal rats.

The CO₂-response results demonstrate that 1-PX stimulates respiration in neonatal rats under hypercapnic conditions. A flat f response to CO₂ was observed and was unchanged by 1-PX doses. Several previous studies have also observed this blunted f response to CO₂ in the respiration of neonatal rats (11, 12). A similar flat f response to CO₂ has been reported in premature human infants (13), justifying the use of newborn rats as a model for premature infants with breathing problems. The ventilatory response to CO₂ was dose-related, with the 80 mg/kg 1-PX dose eliciting the greatest response in V_E. A similar increase in the V_E response to CO₂ has been observed in preterm infants receiving theophylline (5). The results from the CO₂-response curve also exhibit similarities between 1-PX and theophylline since both drugs increased V_E primarily by increasing V_T (14). While 1-PX does not appear to be superior to theophylline as a respiratory stimulant, the possibility that 1-PX has fewer side effects should be explored.

Works Cited

1. Brouillette, R.T., Weese-Mayer, D.E., Hunt, and Carl E. Breathing control disorders in infants and children. *Hosp. Prac.* 1990; 25(8): 82-103.
2. Martin, R.J. and Abu-Shaweesh, J.M. Control of breathing and neonatal apnea. *Biol. Neonate.* 2005; 87: 288-295.
3. Millar, D. and Schmidt, B. Controversies surrounding xanthine therapy. *Sem. Neonatol.* 2004; 9: 239-244.
4. Barnes, P.J. Drugs for asthma. *Br. J. Pharmacol.* 2006; 147: 297-303.
5. Aranda, J.V., Chemtob, S., Laudignon, N., Sasyniuk, B.I. Pharmacologic effects of theophylline in the newborn. *J. Allergy Clin. Immunol.* 1986; 78(4): 773-780.
6. Rall, T.W. 1990. Drugs used in the treatment of asthma: The methylxanthines, cromolyn sodium, and other agents. Goodman and Gillman. The Pharmacological Basis of Therapeutics (8thed). Pergamon Press, New York. p. 618-630.
7. Herlenius, E., Lagercrantz, H., and Yamamoto, Y. Adenosine modulates inspiratory neurons and the respiratory pattern in the brainstem of neonatal rats. *Pediatr. Res.* 1997; 42(1): 46-53.
8. Persson, C.G.A. Xanthines for asthma - present status. *Trends Pharmacol. Sci.* 1982; 312-313.
9. McGilliard, K.L., Reynolds, S.M., and Gatto, C. Effects of xanthine analogs on respiratory control in newborn rats. *Modulations of Respiratory Pattern: Peripheral and Central Mechanisms*, 1990; p. 79.
10. Gatto, C. Effects of Methylxanthines on Newborn Rat Respiration. Thesis. Eastern Illinois University, 1989.

11. Martino, E.R. and McGilliard, K.L. Age related effects of aminophylline on the respiratory response to CO₂ in newborn rats. Abstracts, Board of Governors Universities Student Research Conference, 1993; p. 22.
12. Saeki, Y. and McGilliard, K.L. Effect of caffeine on the ventilatory response to CO₂ in newborn rats. Abstracts, 13th Annual Student Research Conference, 2002; p. 39.
13. Rigatto, H. Brady, J.P., and Verduzco, R.T. Chemoreceptor reflexes in preterm infants: II. The effect of gestational and postnatal age on the ventilatory response to inhaled carbon dioxide. *Pediatr.* 1975; 55: 614-620.
14. Davi, M.J., Sankaran, K., Simons, K.J., Simons, F.E.R., Seshia, M.M., Rigatto, H. Physiological changes induced by theophylline in the treatment of apnea in preterm infants. *J. Pediatr.* 1978; 92(1): 91-95.