

TITLE: PREVENTIVE EFFECTS OF PHENOXYBENZAMINE ON N₂O-INDUCED REPRODUCTIVE TOXICITY IN SPRAGUE-DAWLEY RATS

AUTHORS: M. Fujinaga, M.D., J.M. Baden, M.D., A. Suto, M.D., J.K. Myatt, M.D., and R.I. Mazze, M.D.

AFFILIATION: Dept of Anesth, Stanford University, Stanford, CA 94305 and Palo Alto V.A. Medical Center, Palo Alto, CA 94304

The reproductive toxicity of N₂O in rats is prevented by the co-administration of either halothane or isoflurane, whereas, treatment with folic acid, which should reverse the effects of N₂O on DNA production, does not prevent toxicity.^{1,2} These results cast doubt on the commonly held theory that inactivation of methionine synthase is the sole cause of N₂O-induced reproductive toxicity, and suggest the need for other hypotheses. One such possibility is that the adverse reproductive effects of N₂O are secondary to decreased uterine blood flow. To test this hypothesis, we studied the effects of phenoxybenzamine (PX), an alpha-1 adrenergic antagonist, on N₂O-induced reproductive toxicity using an in vivo rat model.³ (PX prevents the teratogenic effects of acetazolamide while normalizing uterine blood flow.⁴)

On day 8 of gestation (plug day = day 0), 130 timed-pregnant rats were injected s.c. with either 0.5 ml of either 0.9% saline (control and N₂O alone groups) or PX (0.5, 5, or 50 ug/kg) in 0.9% saline, the latter the maximum tolerated PX dose. They were then exposed to either air (control) or 60% N₂O

for 24 hours (all other groups). On day 20, cesarean sections were performed, resorptions counted, live fetuses removed, fixed and subsequently examined for either visceral or skeletal abnormalities. Mean values/litter were calculated and statistical comparisons were made by ANOVA; arcsin transformation was performed for nonparametric data, i.e., incidences.

Compared with control, treatment with N₂O alone resulted in increased incidences of resorptions, and visceral and skeletal abnormalities. The two highest PX doses partially reduced the incidence of resorptions but none of the PX doses prevented teratogenicity. These results suggest that N₂O-induced reproductive toxicity may only be partially related to decreased uterine blood flow.

This study was supported by Veterans Administration and March of Dimes BDF grant.

References

1. Anesthesiology 67:960-964, 1987.
2. Teratology 38:121-127, 1988.
3. Nature 214:146-148, 1967.
4. Teratology 34:195-200, 1986.

	Cont	N ₂ O	N ₂ O + PX (ug/kg)		
			0.5	5	50
No. of litters	30	25	25	25	25
No. of fetuses	337	150	159	199	179
Resorption (%)	5	48*	42*	25**	29**
Visceral abnorm. (%)	6	49*	42*	38*	35*
Skeletal abnorm. (%)	38	90*	77*	83*	79*

* p < 0.05 vs. Cont, # p < 0.05 vs. N₂O

A921

TITLE: DISTRIBUTION OF SELF-ADMINISTERED MORPHINE AND MEPERIDINE INTO HUMAN BREAST MILK: ACUTE NEONATAL NEUROBEHAVIORAL EFFECTS

AUTHORS: B. Wittels, M.D., Ph.D., D.T. Scott, M.D. and R.S. Sinatra, M.D., Ph.D.

AFFILIATION: Depts. of Anesth. and Peds., Yale University, New Haven, CT 06510

Patient-controlled analgesia (PCA) with opioids has been successfully employed by parturients after cesarean delivery, however no study to date has evaluated opioid secretion into breast milk or its effect on nursing neonates in this setting. Opioid analgesia requirements, distribution into breast milk, and influence on neonatal neurobehavior were evaluated in 10 nursing parturient-neonate pairs, after elective cesarean delivery.

Following approval by the H.I.C., written informed consent was obtained from 10 parturients, opting to breast-feed, and undergoing elective cesarean delivery with epidural anesthesia using lidocaine 2% with epinephrine 1:200,000. After umbilical cord clamping, 5 patients received first a loading dose of meperidine (1mg/kg IV), then PCA with meperidine (12.5mg q 6 min.), and finally meperidine pills as needed. Five patients received morphine in a similar manner (0.1mg/kg IV loading dose, then PCA 1.0-1.5mg q 6 min.). Visual analog scales (VAS) for analgesia and satisfaction were administered at 24 and 48 hrs postpartum (PP); side effects were documented and treated, when necessary.

Breast milk specimens were obtained at intervals of 12, 24, 36, 48, 72 and 96 hrs PP and analyzed for meperidine and normeperidine (mass spectrometry) or for morphine and morphine-3-glucuronide (RIA). Neonatal outcome was assessed on the third day of life with Brazelton's Neonatal Behavioral Assessment Scale (NBAS), as administered by a blinded pediatric psychologist certified in its use.

Treatment groups showed no differences in neonatal Apgar scores or VAS pain or satisfaction scores at 24 and 48 hrs PP. The complication rate was also not significantly different between groups (P=.524). Analysis of breast milk specimens showed persistently elevated normeperidine concentrations (mean=310ng/ml at 96 hrs PP), compared to morphine (mean=14ng/ml at 96 hrs PP). A priori, the "alertness" and 3 "human orientation" outcomes of the NBAS were chosen for analysis as best measures of opioid-induced effects. On all four outcomes, neonates in the morphine group scored significantly higher (P<.05) than neonates in the meperidine group. No child in the latter group was arousable to a fully alert state during the exam.

Thus, post-cesarean PCA with morphine provides equivalent maternal analgesia and satisfaction at 24 and 48 hrs PP as PCA with meperidine, with significantly less neurobehavioral depression among breast-fed neonates on their third day of life. Relatively high concentrations of normeperidine persist in breast milk through 96 hrs PP and are thought to contribute to decreased neonatal alertness and orientation, although further studies are needed to assess the chronicity and severity of these effects.