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Effect of Tolazoline on Persistent Hypoxemia in Severe Hyaline Membrane Disease

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Ten critically-ill preterm infants with severe hyaline membrane disease received tolazoline because of persistent hypoxemia refractory to the administration of 100% oxygen and mechanical ventilation. Seven infants (70%) responded immediately with an increase in $PaO_2 \geqslant 20$ mmHg in the umbilical arterial gas within 60 minutes after bolus infusion (1 to 2 mg/kg) of tolazoline. Twenty-four hours later after the tolazoline infusion, the FiO_2 had been decreased from 1.0 to a mean of 0.82±0.16, and the MAP from 16.5±1.8 to 15.6±4.5cm H_2O. Four of 7 infants (57%) who had an immediate response survived, whereas none survived out of 3 infants who failed to respond initially. Three infants experienced relatively severe complications possibly related to tolazoline. There appears to be a place for the use of tolazoline in a severely hypoxemic infant with hyaline membrane disease who is being ventilated, and in whom arterial oxygenation cannot be improved by a further increase in the inspired oxygen concentration or by an alteration of ventilator settings.

Key Words: Tolazoline, hyaline membrane disease, persistent hypoxemia

Persistent pulmonary hypertension of the newborn (PPHN) is not a distinct disease, but rather an example of the fetal circulation that has not made an adequate transition to a normal neonatal circulation. The entire clinical picture of PPHN-high pulmonary artery pressure, low pulmonary blood flow, and massive right-to-left shunting at the foramen ovale and ductus arteriosus levels, causing profound hypoxemia minimally responsive to supplemental oxygen–is a reflection of the persistently high pulmonary vascular resistance that ensues when the transitional circulation does not proceed normally.

PPHN accompanies various cardiopulmonary disorders, including asphyxia, meconium aspiration, sepsis, hyaline membrane disease, and congenital diaphragmatic hernia, or occurs as an indiopathic disorder ("persistent fetal circulation") (Brown and Pickering 1974; Chu *et al.* 1965; Fox *et al.* 1977; Gersony *et al.* 1969; Goetzman *et al.* 1976; Riemenschneider *et al.* 1976; McIntosh and Walters 1979). The morbidity and mortality of PPHN remains high, despite aggressive therapeutic interventions, including hyperventilation, inotropic support of the systemic circulation, and pharmacologic manipulation of the pulmonary vascular bed (Drummond *et al.* 1981; Peckham and Fox 1978).

Attempts to find a vasodilator which selectively and consistently lowers pulmonary vascular resistance without causing systemic hypotension or other side effects have been unsuccessful. Despite its complex pharmacology, and although its current use is largely based on case reports or uncontrolled clinical studies, tolazoline has evolved as the primary vasoactive drug in the treatment of PPHN (Gersony *et al.* 1969; Goetzman *et al.* 1976; Drummond *et al.* 1981; Cotton 1965; Korones and Fabien 1975; Stevens *et al.* 1980; Stevenson *et al.* 1979).

This study was undertaken to evaluate the effect of tolazoline in 10 preterm infants with persistent hypoxemia due to severe hyaline membrane disease (HMD), where other appropriate forms of intensive care therapy had failed.

MATERIALS AND METHODS

Between February 1987 and June 1988, 10 critically

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ill preterm infants, who were diagnosed as having severe HMD in the neonatal intensive care unit (NICU), were selected to receive tolazoline because of refractoriness to mechanical ventilation. This was usually indicated by a failure to consistently maintain PaO_2>50 mmHg at an FiO_2 of 1.0 and various manipulations of ventilator settings intended to raise the PaO_2 (Blake *et al.* 1973; Herman and Reynolds 1973).

The clinical details of the infants are shown in Table 1. The mean birth weight and gestational age were 1,460±260 gm and 30.6±3.0 weeks, respectively. Attempts to rule out alterations in cardiac, metabolic, and blood volume status, or in blood viscosity, as causes of hypoxemia, preceded tolazoline therapy. All infants had umbilical artery catheters sited in the middle thoracic aorta, and had frequent blood gas analyses performed using the Blood Gas Analyzer (AVL 995). The arterial samples were obtained from either the arterial catheters or peripheral arteries.

The infants were all ventilated via an oroendotracheal tube with a constant flow, pressure-controlled ventilator (Sechrist IV-1001). The mean peak inspiratory pressure (PIP) was 32.5±2.9cm H_2O and the mean respiratory frequency was 39.5±3.6/min, before the tolazoline infusion. Ventilator settings were recorded before and after each dose of tolazoline, and blood gas analyses were performed before and after each dose of tolazoline. The mean airway pressure (MAP) was calculated for each of the ventilator settings, using the formula [(PIP–PEEP)*Fq*Ti/60+PEEP] (PEEP; positive end expiratory pressure, Fq; ventilatory frequency, Ti; inspiratory time). MAP has been shown to correlate well with alveolar arterial oxygen difference at slow respiratory rates (Herman and Reynolds 1973). It therefore was used to measure changes in ventilation which might have contributed to changes in PaO_2. Changes in pH, $PaCO_2$ and base excess were also noted.

Tolazoline hydrochloride (Imidalin®) was administered according to protocols as follows: (1) a loading dose of 1-2 mg/kg was infused over a 10 minute period, through a peripheral vein draining into the superior vena cava (scalp or upper extremities), (2) blood pressure (BP), pulse rate and arterial blood gases were monitored pre- and postloading of tolazoline, and (3) thereafter, bolus infusions of the same dose were repeatedly administered if more than 1 hour had elapsed from the previous tolazoline infusion. The infusion was continued for a mean of 12 hours (range 3 to 26 hours) if no effect had been achieved, or until clinical improvement permitted the FiO_2 to be decreased to 0.7. An immediate positive response to tolazoline was defined as a rise in PaO_2 of 20 mmHg or more within 60 minutes of the initial dose. Further evidence of a sustained effect was obtained by analysis of the FiO_2 and MAP required to maintain the PaO_2>50 mmHg until 24 hours after initiating therapy.

Data were computed into means and standard deviations. The Wilcoxon signed rank test was used for the significance testing of differences between pre-tolazoline values and post-tolazoline values. The differences were considered significant if $p<0.05$.

RESULTS

The immediate response to the tolazoline infusion in 10 HMD infants with persistent hypoxemia is shown in Table 2. One hour after the tolazoline infusion, there was a significant increase in the PaO_2 values. But no significant changes in the mean $PaCO_2$ and pH values were seen after the tolazoline infusion.

Seven infants responded to tolazoline with a rise in PaO_2 of 20 mmHg or more within 60 minutes. The PaO_2 values in 3 infants who failed to respond initially rose after 3 hours of bolus infusion of tolazoline (Fig. 1). Four of 7 infants who had an immediate response to tolazoline survived (57%), whereas none of 3 infants who failed to respond initially survived (Table 1). But, as a whole, only 4 of 10 infants survived. The leading causes of death in the 6 expired cases

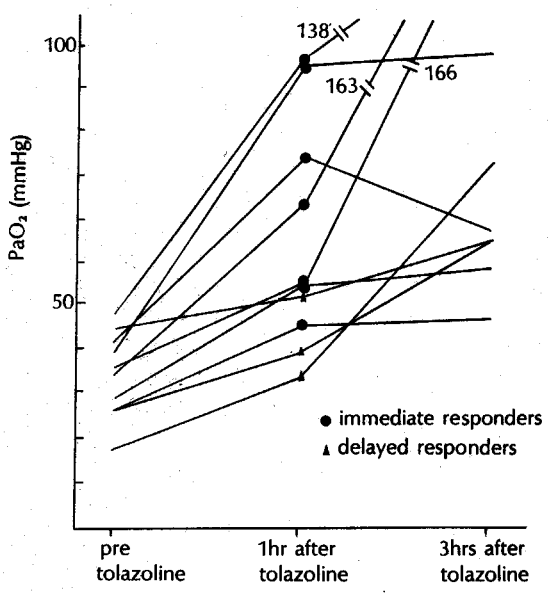

Fig. 1. Immediate PaO_2 response to tolazoline in 10 infants with hyaline membrane disease.

Table 1. Clinical characteristics in 10 infants with hyaline membrane disease (HMD)

Case	B.W.* (gm)	G.A.** (weeks)	Sex	Delivery type	Tolazoline start age (hr)	Outcome	Immediate response
1	1,490	31	F	C/S#	53	survived	yes
2	1,600	34	M	V/D##	11	survived	yes
3	1,610	30	M	V/D	6.4	survived	yes
4	1,600	34	F	C/S	40	survived	yes
5	1,600	32	F	V/D	9	expired	yes
6	1,600	32	F	V/D	26	expired	yes
7	1,700	30	M	V/D	3	expired	no
8	1,210	28	F	C/S	31	expired	no
9	1,350	28	M	V/D	5	expired	no
10	850	26	M	V/D	3.4	expired	yes

* Birth weight, ** Gestational age, # Cesarean section, ## Vaginal delivery

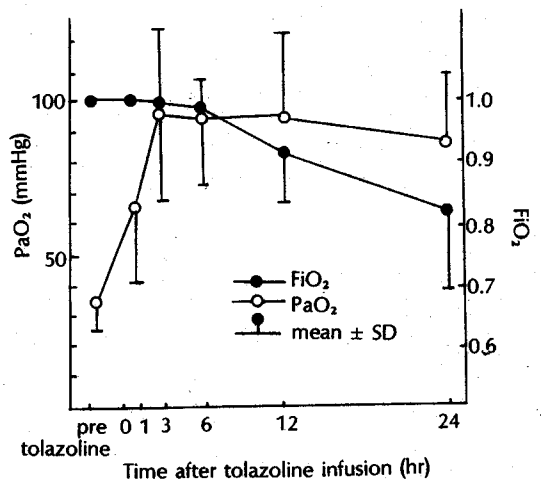

Fig. 2. *Changes in PaO_2 and FiO_2 values during the first 24 hours of the tolazoline infusion period in 10 infnats with hyaline membrane disease.*

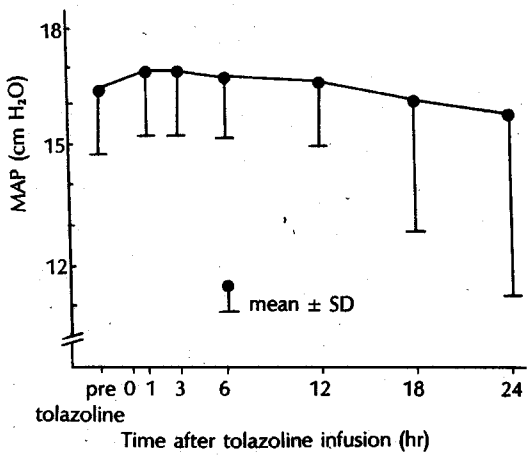

Fig. 3. *Changes in mean airway pressure (MAP) during the first 24 hours of the tolazoline infusion period in 10 infants with hyaline membrane disease.*

were: intraventricular hemorrhage, severe perinatal asphyxia, pneumothorax, sepsis, and pulmonary hemorrhage, with the exception of HMD itself.

Twenty-four hours later, the FiO_2 had been decreased to a mean of 0.82±0.16 (Fig. 2) and the MAP to 15.6cm±4.5cm H_2O (Fig. 3). But these values were not statistically significant compared to the values before the tolazoline infusion.

Complications possibly related to the tolazoline administration were noted in 6 infants. Three of these infants had more than one complication. Six infants showed the typical splotchy, histamine-like flush during the tolazoline infusion. Isolated hypotension oc-

Table 2. Immediate response to tolazoline infusion in 10 infants with HMD

	Before tolazoline infusion (mean ± SD)	1 hour after tolazoline infusion (mean ± SD)
PaO_2 (mmHg)	34.1± 9.4	65.5±26.2*
$PaCO_2$ (mmHg)	53.1±16.1	47.0±12.1
pH	7.2± 0.1	7.2± 0.1

* $p<0.05$ compared with values before tolazoline infusion

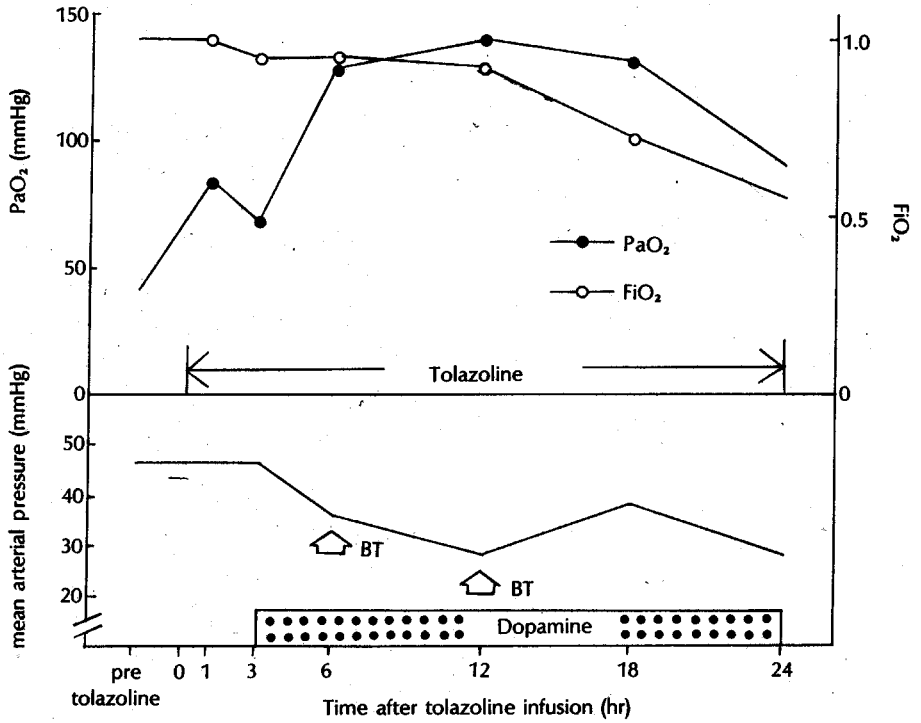

Fig. 4. Effect of tolazoline on PaO_2, FiO_2 and mean arterial blood pressure in a patient. When hypotension was noted, dopamine infusion and whole blood transfusion (BT) were taken.

Table 3. Deleterious effects associated with tolazoline infusion in 10 infants with HMD

	No. of infants (%)
Erythema	6 (60)
Hypotension	2 (20)
Thrombocytopenia	2 (20)
Pulmonary hemorrhage	1 (10)
Gastrointestinal tract bleeding	1 (10)
Abdominal distension	1 (10)

curred in 2 infants, which was defined as less than 30 mmHg in mean arterials BP at any time during the administration of tolazoline, excluding a terminal event. This hypotensive reaction was corrected by volume expanders and dopamine administration (Fig. 4). Thrombocytopenia (platelet count<100,000/cubic mm after a normal pre-tolazoline platelet count) was noted in 2 infants. One infant had abdominal distension and blood in his stool in the presence of normal coagulation studies. One infant died of pulmonary hemorrhage, and it is possible that the drug contributed to the patient's death (Table 3).

We found no distinguishing features in the maternal history, labor, delivery records, Apgar scores or diagnostic distribution that might differentiate tolazoline responders from nonresponders. Statistical comparison of arterial blood gases and ventilatory data prior to tolazoline therapy did not reveal any significant differences between responders and nonresponders.

DISCUSSION

Traditionally, tolazoline has been classified as an alpha-adrenergic antagonist (Ahlquist *et al.* 1947). Studies of tolazoline have ascribed many pharmacologic properties to tolazoline, some of them contradictory, including alpha-adrenergic agonist (Sanders *et al.* 1975) and antagonist (Brodie *et al.* 1952); cholinergic agonist and antagonist (Ward 1984); histaminergic agonist (Yellin *et al.* 1975) and direct vasodilator (Nickerson 1949). Such diverse properties may result from the 2-benzyl-2-imidazoline structure of tolazoline, which resembles several compounds

with diverse activities. It is not surprising, therefore, that tolazoline can interact both negatively and positively with multiple receptors.

After the description of PPHN by Gersony *et al.* (1969), many reports described the use of tolazoline infusions in neonates with severe hypoxemia from various causes (Gersony *et al.* 1969; Goetzman *et al.* 1976; Stevens *et al.* 1980; Stevenson *et al.* 1979). Most authors judged improvement in pulmonary perfusion indirectly, by increases in aortic PaO_2, as in this study. In three series, 60 to 69% of infants had an increase in PaO_2 of 15-24 mmHg. Patients with idiopathic PPHN had a higher rate of improvement (80 to 89%). Despite the initial improvement in PaO_2 following a tolazoline infusion, the overall survival ranged only from 44 to 57%. These results are comparable to the 70% incidence of initial relief of hypoxemia following tolazoline and the 40% survival rate in our study, and therefore suggest that there is poor correlation between initial positive response of tolazoline administration and ultimate survival. One recent study also showed that there were no clinical variables that consistently predicted a successful or an unsuccessful response of PaO_2 to tolazoline before tolazoline administration, and a positive response to tolazoline had no predicted value for an ultimate outcome (Meadow *et al.* 1986). "Tachyphylaxis" to tolazoline, described as the failure to sustain improvement in oxygenation and other paramters following an initial positive response to therapy, is a common clinical problem. The clinical significance of this problem may be related to the poor correlation between the initial response to tolazoline, and the subsequent outcomes reported in many studies. One recent study suggests that refractoriness to the drug is a calcium-dependent process which may be partially mediated by an alpha-adrenergic mechanism (Abman *et al.* 1986).

In one study in which pulmonary artery pressure (PAP) was actually monitored, tolazoline did not selectively lower the PAP, although it lowered the PAP below the systemic artery pressure (SAP) when infused with dopamine. These vascular changes were similar to the changes obtained with hyperventilation; the combined effects of pulmonary vasodilatation by hyperventilation and by tolazoline-dopamine appeared to be additive (Drummond *et al.* 1981). To evaluate the cardiovascular effects of tolazoline, some investigators have studied it in hypoxic newborn animals. Goetzman and Milstein (1979) demonstrated its vasodilating properties in newborn lambs with hypoxic pulmonary vasoconstriction. Lock *et al.* (1979) demonstrated that tolazoline directly dilates pulmonary vasculature constricted by hypoxia, but that some of the response was indirect, secondary to an improved cardiac output and related changes, such as recruitment or improved mixed venous PO_2. This vasodilatation was not selective for the pulmonary vasculature, since the SVR decreased to a similar degree. Both studies administered tolazoline as a bolus infusion, and found a short duration of action. In the only reported study of prolonged infusion in the hypoxic newborn lamb, tolazoline's vasodilating effect was sustained throughout a 2 hour infusion period (Bressack and Bland 1981). In another study, the decrease in PVR with tolazoline was significantly greater than the decrease in PVR in controls, and greater than the rate of decrease in SVR with tolazoline (Ward 1984).

Histamine is likely involved in hypoxic pulmonary vasoconstriction in many species, either directly or by modulating the effects of other mediators (Ward 1984). Studies on the circulatory effects of histamine and H1 and H2 receptor blockade have produced conflicting results, suggesting that there may be age and species related differences in effects (Bush *et al.* 1987). The nature of tolazoline's interaction with histamine and pulmonary vessels is unclear. An analysis of the role of H1 and H2 receptors in the pulmonary vasodilating action of tolazoline suggested that both receptors were involved (Goetzman and Milstein 1979). One recent study also showed that tolazoline was a pulmonary vasodilator in nomrally oxygenated sheep and this vasodilation was mediated by histamine receptors (Abman *et al.* 1986). Other workers have suggested that tolazoline may mediate some of its effects through H2 receptors, rather than by an alpha adrenergic receptor blockade (Bush *et al.* 1987). Tolazoline may also act by liberating histamine from tissues (Light and Hughes 1979), and thus produce further indirect stimulation of histamine receptors. Intraspecies differences in cardiac responsiveness to tolazoline seem to reflect differences in endogenous concentrations of mast cells, the primary storage form of histamine in mammals (Hughes and O'Brien 1977). But there presently is no information on histamine release following tolazoline administration in neonates. So, a more thorough study of the role of histamine receptors in the cardiovascular effects of tolazoline is needed.

Since the introduction of tolazoline treatment in neonates, dosages have increased from pulse doses of 1 to 2 mg/kg to continuous infusions of 10 mg/kg/hr without pharmacokinetic studies (Ward *et al.* 1986). Recently, after the microassay for tolazoline was developed, one study suggested that a decrease in urine output to <0.9 ml kg/hr slowed tolazoline's

clearance, indicating that tolazoline is not significantly metabolized, and that neonatal clearance requires urine production (Ward *et al.* 1982). Plasma tolazoline concentrations in this study have approached the concentrations that produce lethal cardiotoxicity in lambs. This implies that the current tolazoline infusion doses exceed the neonatal tolazoline clearance. They also calculated an infusion dose of 0.28 mg/kg/hr for every 1.0 mg/kg loading dose of tolazoline as specific recommendations, but these should serve as general guidelines (Ward *et al.* 1986). When urine flow is decreased or when renal tubular function is impaired, neonatal tolazoline elimination decreases, and the dose should be reduced further.

Adverse reactions while receiving tolazoline have been reported in 3 retrospective studies (Goetzman *et al.* 1976; Stevens *et al.* 1980; Stevenson *et al.* 1979). The earliest study reported the lowest overall incidence of adverse reaction at 30 percent (Goetzman *et al.* 1976), which may reflect increasing awareness by later inventigators, as well as increasing doses of tolazoline. In our study, only a 30% incidence of adverse reaction was observed, except erythema because of the lowered awareness. Consistent with tolazoline's histamine-like effects on gastrointestinal secretions and motility, some reports described problems ranging from abdominal distension, to mild gastric hemorrhage, to severe gastrointestinal hemorrhage, and to even perforating gastric ulceration (Stevens *et al.* 1980; Muhlendahl 1988). Hyponatremia was observed, possibly related to oliguria or increased gastrointestinal loss. The hypotension during a tolazoline infusion had ranged from 2 to 67%, possibly reflecting higher doses (up to 10 mg/kg/hr) in the latter series (Stevenson *et al.* 1979). Renal abnormalities of oliguria and hematuria occurred in 11 to 23%. Pulmonary hemorrhage, thrombocytopenia and seizures were also observed. Negative inotropic effects have been observed in animals perfused with high concentrations of tolazoline (Ahlquist *et al.* 1947; Yellin *et al.* 1975). In view of the limited capacity of the neonate to excrete tolazoline, prolonged infusions, especially in the presence of oliguria, may produce plasma concentrations that are cardiotoxic and may explain the hypotensive reactions (Ward 1984).

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