Pulmonary Vasodilator Action of Tolazoline

BOYD W. GOETZMAN AND JAY M. MILSTEIN

Department of Pediatrics, University of California, Davis, School of Medicine, Davis, California, USA

Summary

The pulmonary vasodilator action of tolazoline in newborn lambs was shown to be mediated via histamine receptors. Maximal changes in pulmonary vascular resistance, Δ PVR, were calculated as percents of the base line value, % Δ PVR. The mean % Δ PVR after tolazoline, 1 mg/kg, was $-25 \pm 4\%$ for eight lambs. Four lambs then received the histamine H_1 receptor antagonist, diphenhydramine, and the mean % Δ PVR due to tolazoline was $-12 \pm 4\%$. Four lambs received the H_2 receptor antagonist, metiamide, and the mean % Δ PVR due to tolazoline was $-18 \pm 5\%$. After both H_1 and H_2 antagonists, the mean % Δ PVR due to tolazoline was $+6 \pm 8\%$. Therefore, both histamine H_1 and H_2 receptors were involved in the vasodilator response to tolazoline.

Speculation

If the pulmonary vasodilator action of tolazoline is mediated by histamine receptors in human infants, as it is in newborn lambs, it may be possible to select a more specific therapeutic agent for infants with pulmonary vasospasm. Histamine, 2-methylhistamine, a specific H_1 agonist, or 4-methylhistamine, a specific H_2 agonist, may be such agents in certain situations.

Tolazoline hydrochloride has been reported to reduce the elevated pulmonary vascular resistance seen in primary pulmonary hypertension (7, 8), mitral stenosis (5), congenital heart disease (4, 11), cystic fibrosis (12), respiratory distress syndrome of the newborn (6), and "persistence of the fetal circulation" (10, 13).

Tolazoline is classified pharmacologically as an α -adrenergic blocking agent. In addition, it has direct actions on cardiac and smooth muscle which are described as sympathomimetic, parasympathomimetic, and "histamine-like" (15). Dual histamine receptors, called H_1 and H_2 receptors, have recently been described (3). Tolazoline has been shown to interact with histamine H_2 receptors in gastric mucosa and cardiac atria to produce its histamine-like effect (16, 19), however, the blood vessels of the lung have not been studied in this regard. In the pulmonary circulation of adult animals, histamine H_1 receptors mediate vasoconstriction and H_2 receptors mediate vasodilatation (18), whereas in the fetus both receptors may mediate pulmonary vasodilatation (18).

The purpose of the present study was to demonstrate that the pulmonary vasodilator action of tolazoline is mediated *via* histamine receptors.

EXPERIMENTAL METHOD

Newborn lambs, 0- to 3-days-old, weighing 3.1-5.4 kg, were anesthetized with a α -chloralose, tracheotomized, and ventilated with a Harvard small animal ventilator. Cannulae were placed in the aorta and inferior vena cava from a femoral approach. The heart and great vessels were exposed through a left lateral thoracotomy and the ductus arteriosus was ligated. Cannulae were inserted into the left atrium and pulmonary artery. All cannulae were connected to pressure transducers and appropriate electronic amplifiers. The following were recorded on a strip chart recorder: Mean pulmonary blood flow, $\bar{Q}_p$; mean pulmonary artery pressure,

$\bar{P}_{PA}$; mean left atrial pressure, $\bar{P}_{LA}$; and mean aortic pressure, $\bar{P}_{AO}$, and airway pressure was monitored and end expiratory pressure was maintained below $\bar{P}_{LA}$. PVR was calculated as $(\bar{P}_{PA} - \bar{P}_{LA})/\bar{Q}_p$. The units of pressure measurement were mm Hg and the flow measurements were measured as ml/min and then standardized per kg of body, ml/min/kg, for the resistance calculations.

Intermittent arterial blood gas analysis was performed to assess acid-base and oxygenation status. Rectal temperature was maintained at 38.5-40°C.

Pharmacologic agents were administered in boluses *via* the inferior vena cava cannula in the following doses: tolazoline (Priscoline, CIBA Pharmaceuticals, Summit, NJ), 1 mg/kg; diphenhydramine (H_1 receptor antagonist) 5 mg/kg; and metiamide (kindly supplied by John G. Paul of Smith, Kline, and French Laboratories, Philadelphia, PA) (H_2 receptor antagonist), 5 mg/kg. Initially, the effect of tolazoline, 1 mg/kg, on PVR was determined before the administration of antagonists in all eight lambs. In lambs 1-4, the effect of tolazoline on PVR was then evaluated after H_1 receptor blockade with diphenhydramine and in lambs 5-8 the effect of tolazoline was evaluated after H_2 receptor blockade with metiamide. Finally, the effect of tolazoline on PVR was evaluated in all eight lambs after both H_1 and H_2 receptor blockade.

In lambs 3-7, before administration of any histamine antagonists, the PVR was elevated by ventilating the lambs with an 8-10% oxygen mixture balanced with nitrogen. The effect of tolazoline on the increased PVR due to alveolar hypoxia was then evaluated.

In four additional lambs, tachyphylaxis to tolazoline was evaluated by the administration of four consecutive 1 mg/kg doses of tolazoline at 10-min intervals with the determination of fall in PVR after each dose. No histamine antagonists were used in these animals.

For purposes of analysis, maximal changes in PVR after tolazoline administration, Δ PVR, were calculated as percents of the base line value, % Δ PVR. Means of % Δ PVR, before and after histamine receptor antagonists, were then compared using the Student's *t* test.

RESULTS

The mean $\pm$ SD base line values for the eight lambs studied were $\bar{P}_{PA} = 37.9 \pm 8.6$ mm Hg, $\bar{P}_{LA} = 4.5 \pm 2.5$ mm Hg, $\bar{Q}_p = 287 \pm 60$ ml/kg/min, and $PVR = 0.11 \pm 0.4$ mm Hg/ml/kg/min (Table 1).

After the administration of tolazoline, 1 mg/kg, the mean % Δ PVR $\pm$ SD for all eight lambs was $-25 \pm 4\%$. In lambs 1-4, in the presence of the H_1 receptor antagonist, diphenhydramine, the mean % Δ PVR $\pm$ SD produced by tolazoline was $-12 \pm 4\%$. In lambs 5-8, in the presence of the H_2 receptor antagonist, metiamide, the mean % Δ PVR $\pm$ SD produced by tolazoline was $-18 \pm 6\%$. The mean % Δ PVR $\pm$ SD produced by tolazoline after administration of both H_1 and H_2 antagonists to all eight lambs was $+6 \pm 8\%$ (Table 2). The mean % Δ PVR's due to tolazoline after the administration of each single histamine antagonist as well as the combined H_1 and H_2 antagonists were significantly different from the mean % Δ PVR produced by tolazoline alone ($P < 0.01$). Lambs

1 and 5 appeared to have considerably less H₂ receptor activity than H₁ receptor activity (Table 2).

The duration of action of tolazoline on the pulmonary circulation varied from 40–210 sec with a mean of 122 sec.

Lambs 3–7 were ventilated with 8–10% O₂ (resultant arterial PaO₂ (17–29 torr) and the PVR rose from a mean of 0.133 ± 0.044 to 0.186 ± 0.052 mm Hg/ml/kg/min (Table 3). The administration of tolazoline, 1 mg/kg, lowered the mean PVR to 0.139 ± 0.049 mm Hg/ml/kg/min, not statistically different from the base line mean PVR before alveolar hypoxia. The duration of action of tolazoline during alveolar hypoxia was similar to that for the nonhypoxic state.

Table 1. Base line hemodynamic measurements for 0- to 3-day-old lambs

Lamb	$\bar{P}_{PA}$ (mm Hg)	$\bar{P}_{LA}$ (mm Hg)	$\dot{Q}_P$ (ml/kg/min)	PVR (mm Hg/ml/ kg/min)
1	37.5	9.0	325	0.088
2	25.5	7.0	275	0.067
3	50.0	5.0	231	0.214
4	44.0	2.5	285	0.145
5	34.0	5.0	255	0.114
6	27.5	2.0	234	0.096
7	40.0	2.0	415	0.091
8	45.0	3.5	278	0.149
Mean	37.9 ± 8.6	4.5 ± 2.5	287 ± 60	0.110 ± 0.064

Table 2. Effect of tolazoline on PVR before and after histamine antagonists

Lamb	% Change in PVR after tolazoline, 1 mg/kg			
	No antagonist	H ₁ antagonist	H ₂ antagonist	H ₁ + H ₂ antagonist
1	-26	-8		+24
2	-17	-11		+2
3	-28	-16		+7
4	-21	-12		0
5	-25		-22	+2
6	-36		-23	0
7	-33		-16	+3
8	-19		-10	+11
Mean	-26 ± 8	-12 ± 4^1	-18 ± 6^1	$+6 \pm 8^2$

¹ Statistically different from means in columns 1 and 4 at $P < 0.01$.

² Statistically different from mean in column 1 at $P < 0.005$.

Table 3. Tolazoline reversal of pulmonary vasoconstriction secondary to alveolar hypoxia

Lamb	PVR (mm Hg/ml/kg/min)		
	Alveolar hypoxia		
	Base line 21%O ₂	Before tolazoline	After tolazoline
3	0.177	0.226	0.180
4	0.183	0.220	0.190
5	0.114	0.130	0.087
6	0.096	0.225	0.142
7	0.095	0.129	0.096
Mean	0.133 ± 0.044	0.186 ± 0.052^1	0.139 ± 0.049

¹ Significantly different from means in first and third columns at $P < 0.05$.

In the four additional lambs receiving four consecutive doses of tolazoline, 1 mg/kg, at 10-min intervals, no tachyphylaxis in the PVR response to tolazoline was observed. The fall in PVR consistently slightly increased with consecutive doses of tolazoline, with the means of % Δ PVR of -21% on the fourth dose being similar to the initial % Δ PVR of -26% for lambs 1–8.

DISCUSSION

These results demonstrate that the pulmonary vasodilator effect of tolazoline in the newborn lamb is mediated by both histamine H₁ and H₂ receptors. Work in our laboratory (unpublished) with histamine and specific H₁ and H₂ receptor antagonists has demonstrated that both H₁ and H₂ receptors mediate pulmonary vasodilatation in newborn lambs, 0- to 3-days-old. This finding is compatible with those of Woods *et al.* (18) that both H₁ and H₂ receptors mediate pulmonary vasodilatation in the sheep fetus. However, H₁ receptors appear to mediate pulmonary vasoconstriction and H₂ receptors to mediate pulmonary vasodilatation in adult dogs (17). Thus, tolazoline may not be an effective pulmonary vasodilator in the older animals.

The increase in PVR produced by tolazoline after histamine H₁ and H₂ receptor blockade in this study may be due to the unmasking of an adrenergic vasoconstrictor action. Benfey and Varma (2) have previously demonstrated such an adrenergic vasoconstrictor action of tolazoline in the peripheral circulation of cats treated with reserpine. It should be noted that, unlike tolazoline, histamine, 0.5–1.0 μ g/kg, continues to have a pulmonary vasodilator effect after administration of both H₁ and H₂ blocking agents. A non-H₁-H₂ receptor effect has been postulated at these large histamine doses (9).

Our findings, that the pulmonary vasodilator action of tolazoline is due to its histamine-like effect and not its α -adrenergic blocking effect are in agreement with the findings of MacKinnon *et al.* (14) that another adrenergic blocking agent, hydergine, when injected directly into the pulmonary artery had no significant effect on pulmonary hemodynamics regardless of the initial level of total PVR.

The duration of the vasodilator action of tolazoline after administration as a bolus dose was short, mean 122 sec, and similar to the duration of action of histamine, 0.05 μ g/kg, administered to newborn lambs in our laboratory. In preliminary studies in our laboratory (unpublished), continuous infusion of tolazoline at rates of 6–10 mg/kg/hr has been required before obtaining any effect on pulmonary vascular resistance. This raises a question about the use of continuous infusions of tolazoline in human infants with pulmonary vasospasm (10). Further study is necessary to demonstrate whether continuous infusion or bolus administration is more effective in humans.

The effectiveness of the bolus administration of tolazoline, with its short duration of action in reversing pulmonary vasospasm in human infants (10, 13) suggests that a reflex mechanism for maintaining high PVR once it is established may be present in the newborn and probably in the fetus. We have observed one lamb (#5) that maintained a high PVR after the change of ventilatory gas from 8% O₂ to room air. The PaO₂ was 26 torr while receiving 8% O₂ and rose only to 29 torr after 5–8 min of ventilation with room air. Because the ductus arteriosus had been ligated, it was presumed that a large atrial right-to-left shunt was responsible for the continued hypoxemia. After the administration of tolazoline (1 mg/kg), the PVR fell to the base line level (Table 3) and the PaO₂ immediately rose to 69 torr. We were able to reproduce this set of circumstances in this lamb, but not in its twin.

Because tolazoline has so many different pharmacologic actions, it must be used with care therapeutically. If the pulmonary vasodilator action of tolazoline in humans is due solely to its histamine-like activity, as in the lamb, then it may be reasonable to select a histamine or histamine derivative for use as a pulmonary vasodilator agent in newborn infants with pulmonary vasospasm. The pure H₁ receptor agonist, 2-methylhistamine, might be a good choice because it would minimize the gastric and cardiac effects

of histamine mediated by histamine H_2 receptors (1). However, in older infants, the H_1 receptor may mediate pulmonary vasoconstriction and an H_2 receptor agonist may be more appropriate. Another advantage of histamine is its rapid destruction by histaminases present in the blood. Little emphasis should be necessary that these hypotheses require rigorous testing.

CONCLUSION

Tolazoline was found to produce pulmonary vasodilatation in newborn lambs with normal PVR as well as when PVR was elevated by alveolar hypoxia. This vasodilator action of tolazoline was shown to be mediated *via* histamine receptors. Both histamine H_1 and H_2 receptors were involved in the vasodilator response.

REFERENCES AND NOTES

1. Beaven, M. A.: Histamine. *N. Engl. J. Med.*, 294: 30 (1976).
2. Benfey, B. G., and Varma, D. R.: Vasoconstrictor action of tolazoline. *Br. J. Pharmacol.*, 22: 66 (1964).
3. Blac, J. W., Duncan, W. A. M., Durant, C. J., Gannellin, C. R., and Parsons, E. M.: Definition and antagonism of histamine H_2 receptors. *Nature*, 236: 285 (1972).
4. Blount, S. G., and Woodwork, G. M.: Consideration involved in the selection for surgery of patients with ventricular septal defects. *Am. J. Cardiol.*, 5: 223 (1960).
5. Braun, K., Izak, G., and Rosenberg, S. Z.: Pulmonary arterial pressure after Priscoline in mitral stenosis. *Br. Heart J.*, 19: 217 (1957).
6. Cotton, E. K.: The use of Priscoline in the hypoperfusion syndrome. *Pediatrics*, 36: 149 (1965).
7. Dresdale, D. T., Schultz, M., and Michtom, R. J.: Primary pulmonary hypertension; a clinical and hemodynamic study. *Am. J. Med.*, 11: 680 (1951).
8. Gardiner, J. M.: The effect of "Priscol" in pulmonary hypertension. *Austr. Ann. Med.*, 3: 59 (1954).
9. Goetzman, B., and Milstein, J.: Histamine receptors in the newborn lamb's pulmonary circulation. *Pediatr. Res.*, 11: 571 (1977).
10. Goetzman, B. W., Sunshine, P., Johnson, J. D., Wennberg, R. P., Hackel, A., Merten, D. F., Bartoletti, A. L., and Silverman, N. H.: Neonatal hypoxia and pulmonary vasospasm: response to tolazoline. *J. Pediatr.*, 89: 617 (1976).
11. Grover, R. F., Reeves, J. T., and Blount, S. G.: Tolazoline hydrochloride (Priscoline)—an effective pulmonary vasodilator. *Am. Heart J.*, 61: 5 (1961).
12. Kelminson, L. L., Cotton, E. K., Vogel, J. H. K.: The reversibility of pulmonary hypertension in patients with cystic fibrosis. Observations on the effects of tolazoline hydrochloride. *Pediatrics*, 39: 24 (1967).
13. Korones, S. B., and Eyal, F. B.: Successful treatment of "persistent fetal circulation" with tolazoline. *Pediatr. Res.*, 9: 367 (1975).
14. Mackinnon, J., Vickers, C. F. H., and Wade, E. G.: The effects of adrenergic blocking agents on the pulmonary circulation in man. *Br. Heart J.*, 18: 442 (1956).
15. Nickerson, M.: The pharmacology of adrenergic blockade. *Pharmacol. Rev.*, 1: 27 (1949).
16. Sanders, J., Miller, D. D., and Patil, P. N.: Alpha adrenergic and histaminergic effects of tolazoline-like imidazoles. *J. Pharmacol. Exp. Ther.*, 195: 362 (1975).
17. Tucker, A., Weir, E. K., Reeves, J. T., and Grover, R. F.: Histamine H_1 - and H_2 -receptors in pulmonary and systemic vasculature of the dog. *Am. J. Physiol.*, 229: 1008 (1975).
18. Woods, J. R., Brinkman, C. R., III, and Assali, N. S.: Fetal and neonatal cardiopulmonary response to histamine. *Obstet. Gynecol.*, 48: 195 (1976).
19. Yellin, T. O., Speron, J. W., Burk, S. H.: Antagonism of tolazoline by histamine H_2 -receptor blockers. *Nature*, 253: 561 (1975).
20. The authors acknowledge the technical assistance of Stephen Bennet and David Whittlesey.
21. This research was supported by a grant from the California Research and Medical Education Fund of the California Lung Association.
22. Requests for reprints should be addressed to: Boyd W. Goetzman, M. D., Ph. D., Department of Pediatrics, 4301 X Street, Sacramento, CA 95817, USA.
23. Received for publication May 15, 1978.
24. Accepted for publication August 15, 1978.