Effect of tolazoline in severe hyaline membrane disease

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SUMMARY Tolazoline hydrochloride was given as a pulmonary vasodilator to 20 preterm infants with severe hyaline membrane disease requiring mechanical ventilation who developed persistent severe hypoxaemia. The drug was only given when deterioration persisted despite changes in ventilation techniques and thus there were no control infants. A significant improvement in arterial oxygenation was observed, particularly in those infants without intracranial haemorrhage or pneumothorax. Nine of 10 infants who had an obvious clinical response to tolazoline survived, whereas only 2 survived out of 10 who failed to respond, both being subsequently shown to have pneumothoraces. There appears to be a place for the use of tolazoline in a severely hypoxaemic infant with hyaline membrane disease who is being ventilated and in whom arterial oxygenation cannot be improved by further increase in the inspired oxygen concentration or by alteration of ventilator settings, provided pneumothorax has been excluded.

The normal increase in pulmonary vascular resistance in response to hypoxaemia occurs in an exaggerated form in the newborn infant. Pulmonary artery pressure rises to systemic levels with the reappearance of a transitional pattern of circulation (James and Rowe, 1957; Rudolph and Yuan, 1966). In infants with severe hyaline membrane disease, this response increases the right-to-left shunting of blood leading to increasing hypoxaemia, which is unresponsive to either increases in the fractional inspired oxygen concentration ($F_{I}O_2$) or to alterations in mechanical ventilator settings (Chu *et al.*, 1967; Stahlman *et al.*, 1972; Gersony *et al.*, 1976). Tolazoline hydrochloride has been suggested as a therapeutic agent for dilating the pulmonary arteries which might be used to improve arterial oxygenation (Cotton, 1965; Korones and Eyal, 1975; Goetzman *et al.*, 1976). This report describes our experience with the use of tolazoline in 20 consecutively admitted infants with severe hypoxaemia due to hyaline membrane disease.

Patients and methods

Twenty critically ill preterm newborn infants with severe hyaline membrane disease born between October 1976 and July 1977, developed persistent severe hypoxaemia while being mechanically ventilated, and were given 48 doses of tolazoline. The clinical details of the infants are shown in Table 1.

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None of the infants had polycythaemia or hypoglycaemia, and all were managed by methods previously described (Blake *et al.*, 1973). Six babies had coagulation abnormalities, 4 disseminated intravascular coagulation, and 2 had less specific abnormalities. Two infants had severe rhesus isoimmunisation requiring exchange transfusions.

The infants were all ventilated via an oroendotracheal tube with a constant flow pressure-controlled ventilator (Bourns BP 200). Mean peak airway pressure (PAP) was 29 cm (range 20-40) H_2O ; mean end expiratory pressure (EEP) was 3.5 cm (range 0-5) H_2O ; median inspiration/expiratory ratio (I/E ratio) 1:1 (range 1:2-3:1); mean respiratory frequency (f) 30/min (range 25-40/min).

Seventeen infants had umbilical artery catheters sited in the lower abdominal aorta. Fifteen of the catheters had oxygen electrodes at their tips (Searle), allowing the continuous monitoring of arterial oxygen tension ($P_{a}O_2$) (Conway *et al.*, 1976). In all infants, frequent blood-gas analyses were performed* on arterial samples obtained from either the arterial catheters or peripheral arteries.

The indication for giving the first dose of tolazoline was deteriorating hypoxaemia in the presence of an inspired oxygen concentration of 100% ($F_{I}O_2 = 1.0$) and the failure to respond to various manipulations of ventilator settings intended to raise $P_{a}O_2$ (Blake *et al.*, 1973; Herman and Reynolds, 1973). In 10 infants the $P_{a}O_2$ was less than 20 mmHg, in 6 it was between 20 and 30 mmHg, in 3 between 30 and 40

*IL 413 Blood-gas analyser calibrated with known gases.

Table 1 Clinical details of 20 infants given tolazoline

Group	Case	Sex	Birthweight (g)	Gestation (weeks)	Diagnosis*	Outcome
B	1	M	1360	31	HMD, PIE, PT, S	Survived
A	2	M	2013	33	HMD, PT, C	Survived
B	3	M	1333	28	HMD, PT, IVH	Died
A	4	M	1825	31	HMD, C, RF, PH	Died
A	5	F	1080	27	HMD	Survived
B	6	F	1930	37	Rh, HMD, SAH	Died
B	7	M	1798	33	HMD, S, C, IVH	Died
B	8	M	2430	33	HMD, IVH, SAH	Died
A	9	F	930	26	HMD, PT	Survived
A	10	M	2000	33	HMD	Survived
A	11	M	1750	32	HMD	Survived
B	12	F	700	26	HMD, PT, C, SAH, IVH	Died
A	13	F	890	30	HMD	Survived
A	14	M	2020	35	HMD	Survived
B	15	F	2100	31	HMD, Rh, PT	Survived
A	16	M	1158	32	HMD	Survived
B	17	F	1000	28	HMD, PIE, C, PH, SAH	Died
A	18	M	750	31	HMD, S	Died
A	19	F	1300	30	HMD	Survived
B	20	M	1045	30	HMD, PT, C, SAH, IVH	Died
Mean			1486	30.8		

*HMD = hyaline membrane disease, IVH = intraventricular haemorrhage, PIE = pulmonary interstitial emphysema, RF = renal failure, PT = pneumothorax, Rh = severe rhesus isoimmunisation (see text), S = septicaemia, C = coagulopathy (see text), PH = pulmonary haemorrhage, SAH = subarachnoid haemorrhage.

mmHg, and in the remaining infant the P_{aO_2} was 66 mmHg. Subsequent doses of tolazoline were given in 11 infants, who responded to the first dose, and in whom hypoxaemia recurred. Chest x-rays were taken before the use of tolazoline if time allowed, so as to exclude pneumothorax as a cause for the infant's deterioration. In 7 infants, pancuronium bromide in a dose sufficient to paralyse spontaneous respiration (0.03–0.05 mg/kg repeated as necessary) was given without improvement before the administration of tolazoline.

The dose of tolazoline hydrochloride was 1–2 mg/kg body weight given over 30 seconds, into a scalp vein (10 infants), into another vein (2 infants), or into the umbilical artery (8 infants).

Ventilator settings were recorded before and after each dose of tolazoline. In the 15 infants in whom the abdominal aortic P_{aO_2} was recorded continuously, the records were analysed to determine the P_{aO_2} one min before and the peak P_{aO_2} within 10 min after the administration of tolazoline. In addition blood–gas analysis was performed before and after each dose of tolazoline.

Mean airway pressure (MAP) was calculated for each of the ventilator settings, using the formula

$$\frac{(PAP \times \text{inspired ratio}) + (EEP \times \text{expired ratio})}{\text{inspired} + \text{expired ratio}}$$

and changes in P_{aO_2} were determined from the blood–gas and abdominal aortic oxygen electrode data. MAP has been shown to correlate well with alveolar arterial oxygen difference at slow respiratory rates (Herman and Reynolds, 1973), and so was used to

measure changes in ventilation which might have contributed to changes in P_{aO_2} . Changes in pH, P_{aCO_2} , and base excess (BE) were also noted.

Blood pressure was measured by ultrasound using a Doppler (1 infant) or by a transducer (Hewlett Packard) attached to the umbilical arterial catheter (12 infants).

Tolazoline administration is followed by peripheral vasodilatation (Grover *et al.*, 1961), and this was apparent in our infants. In 13 of them infusion of either whole blood, normal saline, or 5% sodium bicarbonate was needed after the administration of tolazoline to maintain an adequate circulating blood volume and a normal blood pressure.

The data obtained relating to each dose of tolazoline were analysed, using Student's paired or unpaired *t* test, as appropriate.

Results

Data obtained from continuously recorded abdominal aortic P_{aO_2} are summarised in Table 2. An example of such a record showing the response to tolazoline from which these data were obtained is shown in the Figure. Data obtained from analysis of samples of arterial blood are summarised in Table 3.*

The 15 infants in which abdominal aortic P_{aO_2} was continuously recorded received 41 doses of tolazoline (Table 2). There was a highly significant rise of 26 mmHg in the abdominal aortic P_{aO_2} after tolazoline injection ($P < 0.001$), while F_{IO_2} and MAP did not change significantly.

*Complete data may be obtained from the authors on request.

Table 2 Summary of data obtained from abdominal aortic oxygen electrode

Group	Doses	Before tolazoline			After tolazoline		
		Mean MAP (cm H ₂ O)	Mean F _I O ₂	Mean PaO ₂ (mmHg)	Mean Δ MAP (cm H ₂ O)	Mean Δ F _I O ₂	Mean Δ PaO ₂ (mmHg)
Response to all doses of tolazoline							
All patients (n = 15)	41	17.0	1.0	28	-0.02 (NS)	0	+26 (P<0.001)
Group A (n = 9)	24	16.2	1.0	34	0	0	+38 (P<0.001)
Group B (n = 6)	17	18.2	1.0	21	-0.05 (NS)	0	+8 (P<0.05)
Response to 1st dose tolazoline only							
All patients (n =15)	15	18.6	1.0	22	+0.2 (NS)	0	+39 (P<0.005)
Group A (n = 9)	9	17.4	1.0	27	0	0	+56 (P<0.005)
Group B (n = 6)	6	20.3	1.0	14	+0.4 (NS)	0	+14 (P<0.01)

Group A: Infants without intracranial haemorrhage or pneumothorax; Group B: infants with either intracranial haemorrhage (4) or pneumothorax (2).

In the 9 infants who were not shown subsequently to have intracranial haemorrhage or pneumothorax (group A), the mean rise of 39 mmHg in abdominal aortic PaO₂ was significantly greater than in the 6 infants with either intracranial haemorrhage or pneumothorax (group B) in whom the mean rise in abdominal aortic PaO₂ was 8 mmHg (P<0.01). The response to tolazoline was more marked after the first dose, the mean rise in abdominal aortic PaO₂ in all patients being 39 mmHg. In group A the mean rise of 56 mmHg was significantly greater than in group B, in which the mean rise was 14 mmHg (P<0.01).

Blood-gas data were obtained before and after 33 doses of tolazoline in 20 infants (Table 3). There was a significant rise of 21 mmHg in PaO₂ after tolazoline injection (P<0.01) which occurred despite a fall in F_IO₂, while MAP did not change significantly. No significant change in pH, PaCO₂, or base excess occurred. In the 11 infants who were not shown subsequently to have intracranial haemorrhage or pneumothorax (group A), the mean rise in PaO₂ was 26 mmHg compared with the mean rise in PaO₂ of 10 mmHg in the 9 infants with intracranial haemorrhage or pneumothorax (group B). This difference is not statistically significant. If the 2 patients with pneumothorax are excluded from group B, the mean rise in PaO₂ for the group is 4 mmHg which is significantly different from the rise in group A (P<0.05). When only the response to the first dose of tolazoline is considered, the mean rise in PaO₂ after tolazoline was 33 mmHg (P<0.01) which occurred despite of a fall in F_IO₂, while MAP did not change significantly. In group A the mean rise in PaO₂ of 49 mmHg was significantly greater than in group B in which the mean rise was 14 mmHg (P<0.05).

Discussion

Tolazoline hydrochloride is chemically related to the sympathomimetic amines and histamine. It is a short-acting alpha adrenergic blocking agent, but in the doses used in the clinical situation this effect is negligible. It is also a histaminic agent and has a direct nonadrenergic relaxant action upon vascular smooth muscle, the vasodilator effect being greatest in regions where vasoconstriction is most pronounced (Grover *et al.*, 1961). Tolazoline has been shown to relieve pulmonary vasoconstriction and in this respect it is believed to be most effective in those cases where pulmonary vascular resistance is increased due to a generalised constriction of hypertrophied small muscular arteries (Grover *et al.*, 1961). This situation is similar to that seen in severe hyaline membrane disease with hypoxaemia, and pulmonary vasospasm has been demonstrated in such infants by Chu *et al.* (1967). The possible value of tolazoline in the management of severe hypoxaemia in infants with hyaline membrane disease has been suggested (Goetzman *et al.*, 1976).

In our 20 deteriorating infants we demonstrated a significant rise in arterial PaO₂ in response to tolazoline. The babies acted as their own controls as the drug was given only as a last resort when all other treatments had failed and it was felt that death was imminent. In infants who did not have intracranial haemorrhage or pneumothorax as a cause for their severe refractory hypoxaemia the improvement was more pronounced. The difference in response to tolazoline between the two groups was more marked with the first dose than with subsequent ones.

Of the 10 infants who had an obvious clinical

Figure Continuous Pao_2 trace from baby in group A given intravenous tolazoline. Read trace from below up. Abbreviations as in text.

response to tolazoline, 9 survived, whereas only 2 out of 10 who failed to respond survived; both of these infants were subsequently shown to have pneumothoraces which were satisfactorily drained. These results suggest that the improvement in oxygenation resulting from the administration of tolazoline may lead to better survival in a group of infants who would otherwise have a high mortality. It is suggested that the mechanism for improvement is the breaking of the progressive vicious circle of increasing hypoxaemia, acidosis, and pulmonary vasoconstriction.

The known potential side effects of tolazoline are

related to systemic hypotension and histaminic effects on the gastrointestinal tract. In our series systemic hypotension was not a significant problem because care was taken to maintain the circulating blood pressure. However, we consider that monitoring blood pressure is essential if this drug is used. Renal failure was observed in one patient, who died. This could be attributed in part to tolazoline, but the failure may have been due to hypoxic damage caused before the use of tolazoline. Extreme irritability accompanied by bloodstained cerebrospinal fluid observed in 2 patients, both of whom survived, might have resulted from leakage of red

Table 3 Summary of data obtained from blood-gas analysis

	Doses				After tolazoline													
	Before tolazoline				Mean MAP (cmH ₂ O)	Mean f	Mean F _{IO₂}	Mean PaO ₂ (mmHg)	Mean pH	Mean PaCO ₂ (mmHg)	Mean BE	Mean ΔMAP (cmH ₂ O)	Mean Δf	Mean ΔF _{IO₂}	Mean ΔPaO ₂ (mmHg)	Mean ΔpH	Mean ΔPaCO ₂ (mmHg)	Mean ΔBE
Response to all doses of tolazoline																		
All patients (n = 20)	33	16.5	32	1.0	33	7.02	69	-11	-1.0 (NS)	+3.0 (P<0.05)	-0.06 (P<0.05)	+21 (P<0.01)	0.01 (NS)	-3.3 (NS)	-3.7 (NS)	-1.2 (NS)	-1.0 (NS)	
Group A (n = 11)	19	15.8	30	1.0	38	7.13	55	-9	0.4 (NS)	+2.4 (P<0.05)	-0.09 (P<0.05)	+29 (P<0.01)	0.01 (NS)	-3.7 (NS)	-2.9 (NS)	-0.8 (NS)	-1.2 (NS)	
Group B (n = 9)	14	17.6	33	0.98	26	6.95	89	-12	-1.7 (NS)	+3.9 (NS)	-0.02 (NS)	+9 (NS)	0.01 (NS)	-2.9 (NS)	-0.01 (NS)	-0.8 (NS)	-0.8 (NS)	
Response to 1st dose of tolazoline only																		
All patients (n = 20)	20	17.6	30	1.0	27	7.03	75	-10	-2.0 (NS)	+4.0 (P<0.01)	-0.09 (P<0.05)	+33 (P<0.01)	0.01 (NS)	-7.2 (NS)	-8.4 (NS)	-2.5 (NS)	-2.2 (NS)	
Group A (n = 11)	11	16.4	29	1.0	29	7.11	61	-9	-1.3 (NS)	+3.6 (P<0.05)	-0.14 (P<0.05)	+45 (P<0.01)	0.01 (NS)	-8.4 (NS)	-5.8 (NS)	-1.1 (NS)	-1.8 (NS)	
Group B (n = 9)	9	19.0	32	1.0	23	6.94	92	-13	-2.9 (NS)	+4.4 (NS)	-0.03 (NS)	+19 (NS)	0.02 (NS)	-5.8 (NS)	-0.02 (NS)	-1.1 (NS)	-1.8 (NS)	

Group A: infants without intracranial haemorrhage or pneumothorax; Group B: infants with either intracranial haemorrhage (4) or pneumothorax (6).

cells through a distended cerebral capillary bed to the cerebrospinal fluid. In neither case presenting in this manner was there apparent abnormality in the coagulation status which has been associated with subarachnoid haemorrhage (Chessells and Wigglesworth, 1971). Gastrointestinal problems were not encountered, although a potential hazard from reduced splanchnic flow might be necrotising enterocolitis; abdominal distension and haemorrhage have been well described by Goetzman *et al.* (1976).

We agree with Levin *et al.* (1976) that one definite indication for tolazoline is hypoxaemia with demonstrable difference between upper and lower body Pao_2 , implying persistence of transitional right-to-left circulation through the ductus arteriosus. This, in fact, occurred in only one baby in our series.

We conclude that there is a place for the use of tolazoline in a severely hypoxaemic infant with hyaline membrane disease who is being ventilated with an inspired oxygen concentration of 100% and in whom the Pao_2 is unresponsive to alteration of ventilator settings. In these cases where chest movement is clinically normal and where pneumothorax has been radiologically excluded, tolazoline may have a dramatic effect.

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