Cardiovascular effects of tolazoline and ranitidine

A BUSH, C M BUSST, W B KNIGHT, AND E A SHINEBOURNE

Departments of Respiratory Physiology and Paediatric Cardiology, Brompton Hospital, London

SUMMARY   The cardiovascular effects of ranitidine were studied in 12 children with congenital heart disease who had been given tolazoline as a pulmonary vasodilator. Ranitidine was given as prophylaxis against gastrointestinal haemorrhage induced by tolazoline. Tolazoline 1–2 mg/kg caused significant falls in pulmonary and systemic vascular resistances and a rise in heart rate. After intravenous administration of ranitidine 3 mg/kg both resistances rose again and neither resistance then differed significantly from baseline levels. Heart rate also fell and the final heart rate was significantly below baseline levels. We conclude that there may be H_2 receptors within the pulmonary and systemic circulations and that tolazoline may mediate some of its effects through these H_2 receptors rather than by alpha adrenergic receptor blockade. The safety of H_2 blockade in children, particularly those with pulmonary hypertension, needs further investigation.

Tolazoline is an alpha adrenergic blocking agent that has been widely used as a pulmonary vasodilator, particularly in babies and small children.[1–3] Indications for its use include preoperative assessment of pulmonary vascular damage in children with congenital heart disease,[1] management of postoperative pulmonary hypertensive crisis,[2] and pulmonary hypertension secondary to pulmonary parenchymal disorders.[3] Although effective, tolazoline is associated with a high incidence of complications, including systemic hypotension, renal failure, and acute upper gastrointestinal haemorrhage, this last effect being presumably related to its H_2 agonist properties.[3] It would be logical to try to prevent this potentially life threatening side effect by the prophylactic administration of an H_2 blocker, such as ranitidine or cimetidine.

The specific H_2 antagonist ranitidine has been used to treat many children with peptic ulcer, short bowel syndrome, and other gastrointestinal conditions.[4] It has also been administered to more than 2400 women in labour as prophylaxis against gastric aspiration.[5] There were no ill effects on the babies, despite equal ranitidine concentrations in umbilical cord and maternal blood when it was given intravenously.[5] On this basis, ranitidine seems to be a safe prophylaxis against upper gastrointestinal bleeding induced by tolazoline. It has been suggested, however, that tolazoline may affect the pulmonary circulation through histamine receptors.[6] The less selective H_2 blocker cimetidine may antagonise the pulmonary vasodilator effect of tolazoline.[2]

The aim of this study was to assess the effects of tolazoline and ranitidine on the pulmonary and systemic circulation in children with pulmonary vascular disease secondary to congenital heart disease who required diagnostic or therapeutic administration of pulmonary vasodilators.

Patients and methods

Patients. Details of the 12 children studied are given in the Table. Case 1 was studied in the intensive care unit to optimise pulmonary vasodilator treatment, and the other children were studied in the cardiac catheterisation laboratory as part of the assessment of pulmonary vascular disease. In no child was the arterial duct patent at the time of study. Cases 2, 4, and 10 had undergone palliative mustard operations before the study. Informed consent was obtained from the parents in all cases before the procedure, and the protocol had been approved by the ethics committee of our hospital.

Methods. Full details of the measurement techniques have been published elsewhere.[7][8] In summary, the children were anaesthetised for the duration of the study using intravenous etomidate. They were paralysed and ventilated through a close fitting endotracheal tube. Stability and adequacy of ventilation throughout the study were checked by

Table *Details of patients studied, in descending order of baseline pulmonary vascular resistance*

Case No	Age (yrs)	Diagnosis	Pulmonary vascular resistance (mm Hg/l/min/m²)		Pulmonary blood flow (l/min/m²)		Pulmonary artery pressure (mm Hg)	
			Baseline	*Best*	*Baseline*	*Best*	*Baseline*	*Best*
1	1	Endomyocardial fibroelastosis	25·00	14·10	2·95	3·55	88	59
2	7	Transposition of the great arteries, ventricular septal defect,	16·79	16·39	3·46	3·91	63	63
3	5	Down's syndrome, venticular septal defect, patent foramen ovale	9·57	8·74	5·23	6·29	56	53
4	4	Transposition of the great arteries	11·80	8·50	2·60	4·40	38	38
5	4	Atrioventricular septal defect, Down's syndrome	9·37	8·36	5·79	6·84	62	62
6	0·8	Patent arterial duct, broncho-pulmonary dysplasia	8·30	7·35	2·95	3·60	30	30
7	2	Atrioventricular septal defect, pulmonary artery banded	7·90	6·70	2·80	2·80	25	18
8	4	Aortopulmonary window	6·63	4·68	9·50	11·54	68	59
9	4	Patent arterial duct, ventricular septal defect, parachute mitral valve	6·08	4·46	4·85	5·00	55	44
10	3	Transposition of the great arteries, pulmonary artery banded	5·30	5·10	2·90	3·60	24	24
11	4	Double outlet right ventricle, patent arterial duct	3·87	3·54	9·68	9·68	40	31
12	6	Ventricular septal defect, patent arterial duct, coarctation	3·80	3·40	4·40	4·40	27	23

monitoring end tidal gases using remote respiratory mass spectrometry. The children were initially ventilated with air. Catheters filled with fluid were introduced percutaneously into the femoral artery and vein and positioned in the aorta and pulmonary artery, respectively. Any necessary diagnostic procedures, including measurement of left and right atrial pressures but excluding angiography, were performed before the measurements were made.

When a steady respiratory state had been attained, as defined by an end tidal carbon dioxide tension stable to within 0·25 kPa over several minutes,[8] measurements of aortic and pulmonary artery pressure and pulmonary and (where possible) systemic blood flow were made. Flow was measured by the direct Fick principle, oxygen consumption being measured by remote respiratory mass spectrometry[7 8] and blood oxygen contents calculated using the subroutine of Kelman.[9] The respiratory exchange ratio was measured on air and used in the equations to calculate oxygen consumption on 100% oxygen, as described elsewhere.[10]

After the measurements on air the children were ventilated with 100% oxygen. Comparability of ventilation and adequacy of nitrogen washout were checked by monitoring the expired gases. After 10 minutes on 100% oxygen, by which time nitrogen washout was always complete, all measurements were repeated. The patients breathed 100% oxygen for the rest of the study. Tolazoline 1 mg/kg was then given through the pulmonary artery catheter by bolus injection and all measurements were repeated

five and 10 minutes after the drug had been given. Provided that mean aortic pressure had not fallen by more than 20 mm Hg, a further 1 mg/kg of tolazoline was then given and the measurements repeated. Finally, ranitidine 3 mg/kg was administered 10 minutes after the final dose of tolazoline by slow injection over five minutes through a peripheral venous cannula. The final measurements were made five and 10 minutes after the end of the injection of ranitidine.

Results

Measurements were made five and 10 minutes after each dose of each drug. There was no significant difference for any variable between the five and 10 minute measurements after any dose of either drug (Student's paired t test). Analysis of the drug effects was therefore performed on the mean of the two measurements for each drug. The effects of tolazoline and ranitidine on the pulmonary and systemic circulations and heart rate are summarised in the Table and the Figure. For statistical analysis the results have been expressed as percentages of the values on 100% oxygen before administration of the drugs because of the wide variation in baseline measurements between individuals. Paired t tests have been used throughout.

The first dose of tolazoline 1 mg/kg resulted in a fall in pulmonary vascular resistance (PVR) (mean (SEM) fall 10·0 (3·6)%, $p<0·05$). A second bolus of tolazoline 1 mg/kg was given to 10 children, but
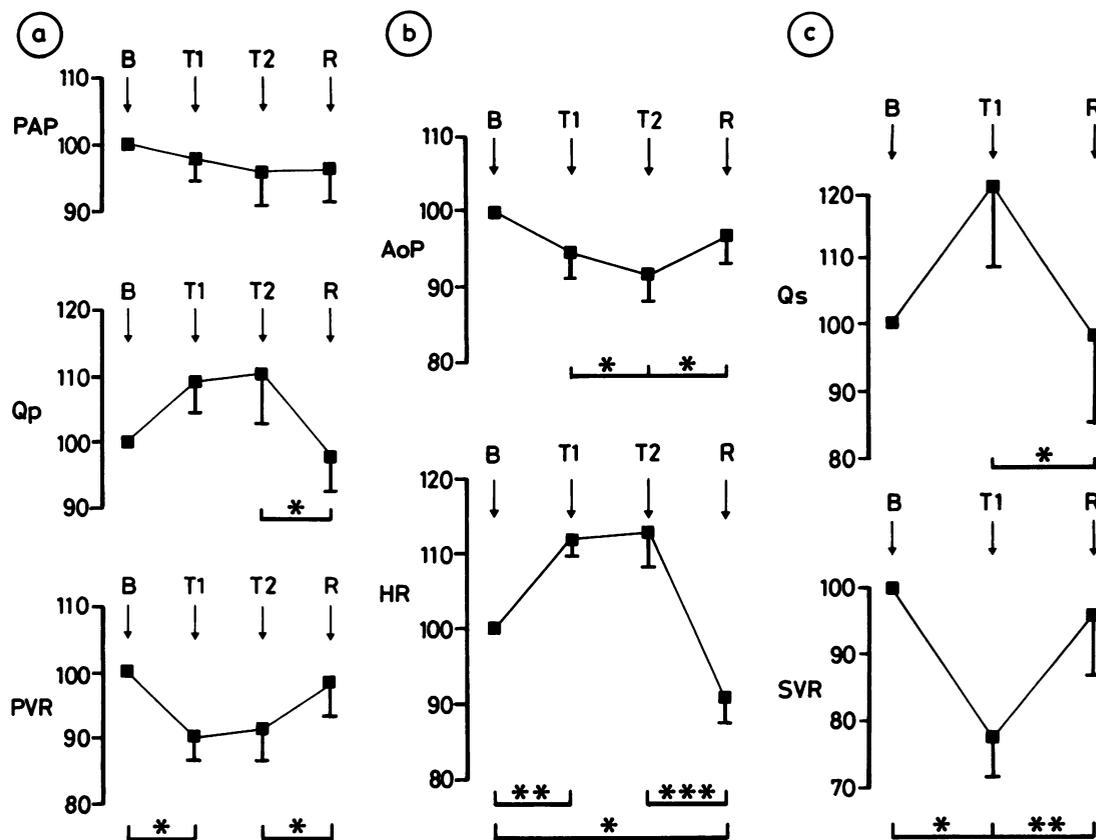
Figure *Effects of tolazoline and ranitidine on the pulmonary and systemic circulations and heart rates. B=baseline; T1=first dose of tolazoline; T2=second dose of tolazoline; R=after ranitidine. All effects are expressed as per cent change over baseline (100% oxygen).*

  (a) Effects on pulmonary artery pressure (PAP), pulmonary blood flow (Qp), and pulmonary vascular resistance (PVR);

  (b) Effects on aortic pressure (AoP) and heart rate (HR);

  (c) Effects on systemic blood flow (Qs) and systemic vascular resistance (SVR). Note only data for the first dose of tolazoline is available, and this figure is based on data for five patients.

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

there was no significant additional fall in PVR for the group as a whole. Two children (cases 7 and 8) showed a further fall in PVR, however, greater than 10%. Infusion of ranitidine reversed the fall in PVR previously produced by the tolazoline injections (mean (SEM) rise 8·7 (3·5)%, $p<0.05$), so that the final PVR, after both tolazoline and ranitidine had been given, did not differ significantly from that on 100% oxygen alone. Changes in PVR were due mainly to changes in pulmonary blood flow; pulmonary artery pressure did not change significantly at any time, in agreement with previous studies.[8 10]

  Similar effects were found on the systemic circulation. The first dose of tolazoline caused a fall in mean aortic pressure (mean (SEM) fall 5·4 (3·1)%, p=NS) and the second dose resulted in more pronounced hypotension (a further fall of 6·3 (2·4)%, $p<0.05$). This effect was also reversed by ranitidine (mean (SEM) rise in aortic pressure 7·4 (2·9)%, $p<0.05$), and the aortic pressure after administration of ranitidine did not differ significantly from that on 100% oxygen (baseline). We were able to measure systemic blood flow and systemic vascular resistance in five children in whom there were no intracardiac shunts at the time of study. There were sufficient data to analyse only the effects of the first dose of tolazoline. Systemic blood flow rose in four of the five children, but the result

was not significant. When ranitidine was given systemic blood flow fell (mean (SEM) fall 21·1 (9·8)%, p<0·01) and returned to baseline rates. Similarly, systemic vascular resistance fell when tolazoline was given (mean (SEM) fall 22·8 (12·9)%, p<0·01) and rose to baseline levels after administration of ranitidine (mean (SEM) rise 21·8 (9·4)%, p<0·01). The ratio of pulmonary to systemic vascular resistance rose significantly after tolazoline (mean (SEM) rise 15·8, (5·3)%, p<0·05) and fell to baseline levels after ranitidine (mean (SEM) fall 18·7 (5·1)%, p<0·05).

The heart rate results were different. The first dose of tolazoline caused tachycardia (mean (SEM) rise in heart rate 12·4 (2·5)%, p<0·001), but there was no significant additional increase in heart rate after the second tolazoline bolus. When ranitidine was given heart rate fell (mean (SEM) fall 19·0 (5·1)%, p<0·01). After the administration of ranitidine heart rate was significantly lower than on 100% oxygen alone (mean (SEM) difference 9·2 (3·1)%, p<0·05), which contrasted with the other haemodynamic measurements.

Discussion

The major finding of this study was that H_2 receptor blockade in children may have important cardiovascular effects. Intravenous ranitidine completely reversed systemic and pulmonary vasodilation induced by tolazoline and, in addition to reversing the tachycardia associated with tolazoline, seemed to have a direct negative chronotropic effect on the heart. The accuracy of the measurements, the assumptions that have had to be made, and the wider importance of these results are discussed below.

Cardiac output was measured by the direct Fick principle. Oxygen consumption was measured by remote respiratory mass spectrometry.[7] [8] This method has been compared with the standard technique using a gas meter and Douglas bag collection and the systematic error found to be equal to or less than 0·6%, with the standard deviation of single estimates plus or minus 3%.[7] Blood gas analysis was performed on an automatic pH and blood gas electrode system (Corning 165). Studies with blood tonometered with physiological concentrations of oxygen and carbon dioxide have shown that this system measures blood gas tensions to an accuracy of 0·27 kPa. The effects of delays up to 20 minutes before analysing the blood samples have been shown to be negligible.[8]

In the presence of intracardiac right to left shunts (seven patients) the use of an aortic rather than a pulmonary vein sample in the Fick equation would result in overestimation of pulmonary blood flow. We therefore used the alveolar air equation to predict the oxygen content of pulmonary end capillary blood, substituting this for pulmonary venous blood in the Fick equation, thus measuring effective pulmonary blood flow. In the presence of parenchymal lung disease this approximation would be inaccurate. None of these seven patients, however, had any clinical or radiological evidence of lung disease. The alternative of repeated manipulations of the right heart catheter from the pulmonary artery into the pulmonary veins through any interatrial communication for each measurement would have prolonged the procedure unacceptably. In three patients we compared predicted pulmonary end capillary blood oxygen content with pulmonary vein blood oxygen content on five occasions. Agreement was good (mean (SE) difference 0·49 (0·17) mg/dl). In three further patients aortic blood saturation was greater than 99% on 100% oxygen, despite angiographic evidence of right to left intracardiac shunting. This suggests that there were no large areas of ventilation to perfusion mismatch in at least six of the children in whom the alveolar air equation was used (cases 3, 5, and 7–11). Further discussion of the use of the alveolar air equation under these circumstances can be found elsewhere.[10]

It is important to keep the duration of general anaesthesia as short as possible and this imposed some constraints on the timing of measurements. The circulatory effects of tolazoline have been reported to reach a plateau within five to 10 minutes of a bolus injection and to remain unchanged for four to six hours.[2] [11] There was no significant difference between the measurements five and 10 minutes after the bolus, and so we assumed that a plateau had been reached, and the mean of the two measurements was used for comparisons. Ideally, we would have checked this assumption by making further measurements before giving ranitidine. There is no information about the speed of onset of any cardiovascular effects of ranitidine in children, and we would have liked to have examined the time course of its effects. Further extending the duration of the catheterisation and the general anaesthetic, however, could not be justified and so we were unable to determine the maximum circulatory response to ranitidine or its duration of action. From our measurements it seemed that the effects may have reached a plateau, but there is no conclusive proof of this.

This study has confirmed that tolazoline is a pulmonary vasodilator that also has pronounced systemic effects, notably tachycardia and hypotension. In the past these effects have generally been attributed to blockade of cardiovascular alpha

adrenergic receptors,[1][3] although there have been suggestions that histamine receptors are important.[6] Systemic hypotension limits the doses of tolazoline that can be given safely. Tolazoline has many other side effects, including gastrointestinal bleeding, presumably related to its H_2 agonist properties.[2] It seemed rational to give an H_2 blocking agent to prevent this potentially life threatening side effect. Ranitidine was chosen because it is reported to have only H_2 antagonist properties, whereas cimetidine also has gonadotrophic and other effects.[12] When ranitidine was infused intravenously, however, the vasodilator effects seen after tolazoline were totally abolished five and 10 minutes after the end of the infusion, suggesting that the cardiovascular effects of tolazoline may be mediated by H_2 receptors. Heart rate after ranitidine was significantly lower than baseline, suggesting that ranitidine has a direct negative chronotropic effect.

Ranitidine acted as a systemic and pulmonary vasoconstrictor. At the time of its administration the children were exposed to two pulmonary vasodilators, 100% oxygen and tolazoline. The effects of ranitidine on the pulmonary circulation could therefore be a result of blockade of either or both vasodilators or by an entirely independent mechanism. We cannot distinguish between these possibilities, but the most probable explanation is that ranitidine blocked the effects of tolazoline on the pulmonary vasculature. Experimental work on animals suggests that histamine is not involved in the modulation of the response of the pulmonary circulation to changes in alveolar oxygen tension.[13] Other workers have suggested that the H_2 agonist effects of tolazoline may be more important than the alpha adrenergic antagonist activity in the pulmonary circulation,[6] and our results support this. A direct effect of ranitidine on pulmonary vascular resistance cannot be excluded as it was not given to patients who had not been pretreated with tolazoline. Ranitidine could also have interacted with receptors other than H_2 receptors, but no such effects have ever been reported.

Studies on the circulatory effects of histamine and H_1 and H_2 receptor blockade have produced conflicting results, suggesting that there may be age and species related differences in effects. When newborn lambs have been made hypoxic to raise the PVR histamine infusions have caused pulmonary vasodilation and, at larger doses, systemic vasodilation.[13] The pulmonary effects were mediated by both H_1 and H_2 receptors. Similar findings have been reported in fetal lambs,[14] calves,[15] and adult cats.[16] In adult animals histamine may constrict or dilate pulmonary arteries.[13–16]

Although histamine causes a fall in pulmonary

and systemic vascular resistances in normal adult humans,[17] it has been shown to cause contraction of isolated strips of human pulmonary artery and vein.[18] There were no changes in pulmonary and systemic haemodynamics in 10 patients with chronic obstructive lung disease and five otherwise normal patients with duodenal ulcers given ranitidine[19] nor in seven adults with portal hypertension given cimetidine.[20] A rise in pulmonary artery pressure was observed in a child given cimetidine for acute gastrointestinal haemorrhage induced by tolazoline, the pressure having previously fallen after tolazoline.[2] No measurements of pulmonary or systemic vascular resistances were made, however, on that child.

We conclude from our data that there may be H_2 receptors within the pulmonary and systemic circulations of children. The most probable explanation of our results is that stimulation of these receptors caused vasodilation and that blockade (at least of the stimulated receptor) caused vasoconstriction in both circulations. In addition, ranitidine seemed to have a direct negative chronotropic effect on the heart. These observations have clinical as well as theoretical importance. Clearly, H_2 receptor antagonists should not be used as treatment or prophylaxis for gastrointestinal haemorrhage induced by tolazoline, confirming previous findings.[2] The possibility of adverse cardiovascular effects in other children receiving oral H_2 blockers, particularly those with pulmonary hypertension, should be borne in mind. The safety of these agents in infants and children requires further investigation.

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Correspondence to Dr E A Shinebourne, Department of Paediatric Cardiology, Brompton Hospital, Fulham Road, London SW3 6HP.