Pronethalol for Cyanotic Attacks

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Various medical measures have been used to terminate the cyanotic spells that occur in severe cases of Fallot's tetralogy. Taussig (1948) reported benefit from oxygen administration and morphine injections, and Wood (1958) recommended cyclopropane anaesthesia. The anoxic attacks have been attributed to sudden, transient, or prolonged spasm of the myocardium of the right ventricular outflow tract (Brock, 1957; Johnson, 1961), and during the attack the systolic murmur diminishes or disappears altogether (Nadas, 1963), because pulmonary blood flow is reduced by increased outflow tract obstruction particularly during late systole. As the patient improves, the outflow tract relaxes and the murmur returns to its original length.

Johnson (1961) suggested that attacks were precipitated by increased norepinephrine production which produces increased muscle tone in the right ventricular outflow tract. Consequently inhibition of sympathetic tone should decrease muscular spasm in the outflow tract, thereby increasing the pulmonary blood flow and aborting the anoxic spell.

Pronethalol (Black and Stephenson, 1962) is a potent beta-receptor adrenergic blocking agent which we have used to treat three prolonged cyanotic spells in two children.

METHODS

The following procedure was carried out. Blood pressure, pulse rate, and phonocardiogram were recorded every five minutes during a control period, during pronethalol administration, and for two hours after the infusion. Microphones were placed in the second left intercostal space and at the apex, and recording was done on an N.E.P. multi-channel recorder with lead II of an electrocardiogram for reference. After a 15-minute control period pronethalol 1-5 mg./kg. body weight diluted in 30 ml. of 5 per cent glucose was infused over a period of 20 minutes. In assessing results the length of the murmur has been expressed as the fraction of mechanical systole, thereby eliminating the effect of changing heart rate.

CASE REPORTS

Case 1. This 2-year-old girl was admitted to the hospital with a history of 8 to 10 anoxic spells every day. The clinical diagnosis of Fallot's tetralogy was confirmed by cardiac catheterization and multiple selective cine-angiography. In view of the repeated and disabling cyanotic spells, an emergency Blalock-Taussig anastomosis was attempted, but failed for technical reasons. Soon after the operation she had repeated prolonged cyanotic attacks and the systolic murmur heard before the operation was almost inaudible. Continuous oxygen administration, phenobarbitone, and parenteral papaveretum had little effect, and about 36 hours after the operation she had a further prolonged anoxic spell during which she lost consciousness. Her pulse was 140 a minute, blood pressure 110/70 mm. Hg, and the systolic murmur had disappeared completely (Fig. 1A).

After pronethalol infusion there was no significant change in the blood pressure, but the pulse rate fell from 140 to 128 a minute, and this effect lasted for about an hour. The cyanosis improved within 15 minutes of starting the infusion and the length of the systolic murmur increased from 0-04 sec. to 0-1 sec. (Fig. 1B). At the end of the procedure she had regained consciousness and looked well (Fig. 1C).

She had a further prolonged attack 24 hours after pronethalol administration with a decrease in the length in the systolic murmur. A second course of treatment produced the same beneficial response.

Case 2. In this 10-month-old, deeply cyanosed and disabled infant, the diagnosis of transposition of the great vessels, ventricular septal defect, and severe infundibular stenosis was confirmed by cardiac catheterization and multiple selective cine-angiography. An early systolic murmur 0-12 sec. in length was present in the second left intercostal space. A Blalock anastomosis failed to improve the subnormal pulmonary blood
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**CASE 1**

(A) Control record before infusion of pronethalol, with the patient unconscious and cyanosed. A short systolic ejection murmur was present. (B) 15 minutes after starting pronethalol infusion, the patient had recovered consciousness and was less cyanosed. The systolic murmur had increased in length and amplitude. (C) After pronethalol infusion, the length of the murmur had increased further.

**CASE 2**

(A) Control record before infusion of pronethalol. The patient had a severe anoxic spell and a short ejection systolic murmur in 2nd left intercostal space. (B) and (C) During and after pronethalol infusion. The patient had improved and the systolic murmur increased in length, relieving cyanosis and lengthening and increasing the amplitude of the systolic murmur (Fig. 2B and 2C). The blood pressure fell slightly, but little change in heart rate occurred.

**DISCUSSION**

Two main factors govern pulmonary blood flow in Fallot's tetralogy: the severity of outflow tract obstruction and the peripheral vascular resistance. The fraction of the right ventricular output passing to the lungs is related directly to systemic peripheral vascular resistance and inversely to right ventricular outflow tract obstruction. An increase of systemic peripheral vascular resistance will reduce the right-to-left shunt and increase the pulmonary blood flow. A reduction of outflow tract obstruction will also increase pulmonary blood flow, and this is the likely cause of improvement in our patients since no significant change in systemic blood pressure was observed.

Vogelpoel and Schrire (1960) have shown that the murmur is relatively loud and long in mild cases of Fallot's tetralogy but short and soft in severe cases, shortening still further and sometimes disappearing...
entirely in profound cyanotic attacks. This suggests that cyanotic attacks are due to spasm of the right ventricular outflow tract.

The changes that occurred in our two patients after pronethalol infusion can be attributed to relief of infundibular obstruction. In both instances, the length of the murmur increased to double its original length within 10 minutes of starting the infusion, and this coincided with the clinical improvement and relief of cyanosis. Pronethalol relieves spasm of the right ventricular infundibulum by blocking the sympathetic beta-receptors which increase cardiac contractility. It is noteworthy that pronethalol prevents the effect of isoproterenol, a sympathomimetic agent which augments the obstruction of hypertrophic subaortic stenosis (Harrison et al., 1964).

CONCLUSION

Pronethalol is a potent agent for relieving anoxic attacks in cyanotic children with pulmonary infundibular stenosis. We have used the drug only for emergency purposes in view of reports of possible carcinogenic effects.

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