Action of a Sympathomimetic Drug and of Theophylline Ethylene Diamine on the Pulmonary Circulation

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The action of two drugs, \( \beta-(2,5\text{-diethoxyphenyl})-\beta\text{-hydroxy-isopropylamine} \) (BW 45/50) and theophylline ethylene diamine, on the pulmonary circulation of dogs and cats was tested. These experiments were made on intact animals, or animals with open chests, or on isolated perfused lungs. BW 45/50 reduced pulmonary arterial pressure in cats and dogs probably because of a fall in cardiac output; pulmonary vascular resistance was usually increased. Theophylline ethylene diamine caused a decrease in pulmonary vascular resistance; its value in pulmonary embolism is suggested.

At the present time there is a widespread search for pulmonary vasodilator drugs. It has been reported by Aviado and Schmidt\(^1\) that a derivative of methoxamine, \( \beta-(2,5\text{-diethoxyphenyl})-\beta\text{-hydroxy-isopropylamine} \) (BW 45/50), synthesized by the Wellcome Research Laboratories, has a selective dilator action on the pulmonary vessels in dogs while causing systemic vasoconstriction. These actions were thought to afford a promising combination for the treatment of burns of the respiratory tract. It was decided to investigate this compound thoroughly in cats and dogs to find out the mechanism by which it leads to a lowering of pulmonary arterial pressure.

In preliminary experiments in cats we found that theophylline ethylene diamine frequently reduced pulmonary arterial pressure while increasing pulmonary blood flow, and there have been several reports of similar effects in man.\(^2\) We therefore undertook to see whether this compound has an action on the pulmonary circulation which might be partly responsible for its therapeutic effect, in addition to its known actions on the heart and bronchial muscle. Quimby, Aviado and Schmidt\(^3\) have recently shown that theophylline ethylene diamine reduces pulmonary vascular resistance in dogs. Our work, completed when their paper was received confirms their results in dogs, and we have also obtained comparable results in cats.

**METHODS**

Both cats and dogs were anesthetised with chloralose (60 mg./Kg.—occasionally slightly more in dogs) or with pentobarbital (a few dogs only). Heparin (Boots Pure Drug Co., 10 mg./Kg.) was used to render the blood incoagulable where necessary. The drugs were tested by the following methods:

**Measurement of Pulmonary Blood Flow and Pulmonary Vascular Resistance with the Chest Open**

The chest was opened in the midsternal line, and a density flowmeter\(^4\) was inserted into the left pulmonary artery. The left pulmonary arterial pressure was measured with a damped mercury manometer, or a bromoform manometer, attached to a side arm of the distal tube of the flowmeter, and the left atrial pressure was read directly or recorded from a water manometer attached to a glass cannula in the left atrial appendage. Pulmonary vascular resistance in P.R.U. was calculated as

\[
\text{mean pulmonary arterial pressure} - \text{mean left atrial pressure, mm. Hg} \\
\text{left pulmonary blood flow, ml/min.}
\]

The details of this method have been published.\(^5\) Artificial respiration was maintained with a Starling Ideal pump, and in many experiments the tidal air was measured by the overflow method.\(^6\) The left pulmonary arterial pressure could be altered by a screw-clip on the flowmeter tubing or by a partial constriction of the right pulmonary artery. In this way pressure-flow curves could be

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constructed without causing any substantial change in left atrial pressure.

**Measurement of Pulmonary Vascular Resistance in Isolated Perfused Lungs**

Isolated lungs of both cats and dogs were perfused by one of two methods: constant flow and constant pressure. The chest was opened in the midsternal line, and respiration was maintained with a Starling Ideal Pump. The left atrium was cannulated with a large glass cannula, and ligatures were placed around the pulmonary artery, the aorta, the superior and inferior venae cavae, and the azygos vein. Blood was then collected rapidly from the animal into a heated reservoir (in cats it was usually necessary to add a little dextran), and a cannula was tied into the main pulmonary artery. Blood flowed into the heated reservoir and respiration was maintained with a Starling Ideal Pump. The left atrial pressure was usually measured with a saline manometer attached to the tubing close to the aortic outflow cannula, or, when the atrium was big enough, to an independent cannula in the left atrial appendage.

**A. Pulsatile Perfusion at Constant Flow.** Blood from the heated reservoir was pumped straight into the main pulmonary artery by means of a Dale-Schuster pump, and pulmonary arterial pressure was measured through a side tube with a damped mercury manometer or a bromoform manometer. Blood flowed out of the left atrium through a Gaddum outflow recorder back to the heated reservoir. The left atrial pressure was usually measured with a saline manometer attached to the tubing close to the atrial outflow cannula, or, when the atrium was big enough, to an independent cannula in the left atrial appendage.

**B. Constant Pressure Perfusion.** Blood flowed from the left atrium into the heated reservoir and was then raised by means of a Dale-Schuster pump to a second heated reservoir maintained at a constant level, whose height could be varied. Thence blood flowed into the pulmonary artery and the rate of flow was measured either on the inflow side with a density flow-meter or on the outflow side with a Gaddum outflow recorder. The pulmonary arterial pressure and left atrial pressure were recorded as in the constant flow method.

**Measurement of Cardiac Output in Intact Dogs**

The cardiac output was measured by the direct Fick principle. A catheter was passed into the right ventricle from the external jugular vein for the collection of mixed venous blood. Right ventricular pressure was recorded by means of a condenser manometer whose output was connected to a Cambridge 3 channel pen recorder. Arterial blood was collected from the femoral artery, and oxygen consumption was continuously recorded by the method of Cross, Dawes, and Mott. Blood gases were analysed by a modification of the Barcroft-Haldane method. Tidal air was measured in a body plethysmograph, as described by Dawes, Mott, and Widdicombe.

The drugs used were BW 45/50 (kindly given by Wellcome Research Laboratories); the following theophylline preparations: Aminophylline (Boots Pure Drug Co.); Cardophyllin (Benger Laboratories); Silbephylline (dihydroxypropyl theophylline, Sitten); ethylene diamine (kindly given by Boots Pure Drug Co.); 5-hydroxytryptamine (May and Baker); and Chlorbismol 10 per cent (bismuth oxychloride suspension, May and Baker). Injections were made intravenously or into the left pulmonary artery (through the tubing connection to the distal end of the flowmeter to the left pulmonary artery).

**RESULTS**

**BW 45/50**

**Action on the Pulmonary Circulation in Animals with Open Chests.** Injection of BW 45/50 (0.5 to 2 mg./Kg. into the pulmonary artery or intravenously) caused a fall in pulmonary arterial pressure of 1.5 to 17 per cent, in 5 cats and 7 dogs. In 2 cats there was a very slight rise in pulmonary arterial pressure after injection of BW 45/50 into the pulmonary artery. However, in both cats and dogs the lowering of the pulmonary arterial pressure after BW 45/50 was invariably accompanied by a decline in blood flow in the left pulmonary artery, ranging from 12 to 47 per cent (fig. 1A). There was usually a diminution in tidal air, a prolonged rise in systemic pressure (+12 to 66 mm. Hg in cats, and +16 to 48 mm. Hg in dogs), bradycardia, and slight changes in left atrial pressure in either direction. The electrocardiogram (lead I) showed no changes apart from those normally accompanying bradycardia in the 3 cats in which it was recorded. Section of the vagosympathetic trunks in the neck usually abolished the bradycardia, but all the other effects were unchanged. There was occasionally a slight residual slowing of the heart, which may have been a direct effect on the heart muscle, since slowing was also observed in two isolated perfused rabbits' hearts.

In cats there was invariably an increase in pulmonary vascular resistance after BW 45/50 (mean increase 31 per cent, range...
+7 to +65 per cent). This was not simply a passive change due to the decline in blood flow, because when pressure flow curves were constructed before and after BW 45/50 it was found that higher pressures were required for the same flow after administration of the drug. After an interval, the values for pressure and flow approached the normal curve again, but recovery was rarely complete. In dogs the resistance changes were variable and were sometimes in different directions in successive tests in the same animal. These differences between cats and dogs were noted also in perfusion experiments.

**Action on Isolated Perfused Lungs.** In seven isolated cats' lungs perfused by the constant pressure method, and in three perfused by the constant flow method there was an increase in pulmonary vascular resistance after BW 45/50. There was a decrease in flow at constant pressure or an increase in pressure at constant flow, the left atrial pressure remaining constant (figs. 2 and 3). One to 2 mg./Kg. BW 45/50 usually produced this effect, but sometimes bigger doses were required. The tidal air was reduced (fig. 3). In six isolated lungs there was no effect, but most of these had already been given theophylline ethylene diamine, which causes a sustained reduction in pulmonary vascular resistance. In only 1 cat was there any evidence of a reduction in pulmonary vascular resistance after BW 45/50, and this was only after repeated doses of theophylline ethylene diamine and BW 45/50. At first BW 45/50 caused an increase in resistance, later a biphasic effect, and finally a decrease. We thought this curious result possibly depended on a combination of two drugs recirculating in the perfusing fluid in large amounts.

In eight isolated dogs' lungs perfused by the constant flow method the effect of BW 45/50 varied in the same way as it did when the circulation was relatively intact. In three there was a slight fall in pulmonary arterial pressure, in two there was no change, and in three there was an increase.

**The Effect on Cardiac Output in Intact Dogs.** The effect of BW 45/50 on the total cardiac output was measured in 3 anesthe-

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**Fig. 1 Top.** Dog, 18.5 Kg. chloralose. At A, 30 mg. BW 45/50; at B, 25 mg. theophylline ethylene diamine. Both drugs given into tubing of flowmeter in left pulmonary artery. From above down: left pulmonary arterial blood flow (density flowmeter), carotid arterial pressure, left pulmonary arterial pressure distal to flowmeter.

**Fig. 2 Middle.** Cat, 3.8 Kg. Constant flow lung perfusion. At A, 5 mg. BW 45/50; at B, 3 mg. BW 45/50; at C, 8 mg. BW 45/50; at D, 3.8 mg. theophylline ethylene diamine; at E, 12.5 mg. theophylline ethylene diamine. From above down: pulmonary blood flow (Gaddum outflow recorder), pulmonary arterial pressure, left atrial pressure. Between C and D there was a momentary interruption of flow.

**Fig. 3 Bottom.** Cat, 2.1 Kg. Constant pressure lung perfusion. At A, 15 mg. BW 45/50; at B, theophylline ethylene diamine 2.5 mg. From above down: pulmonary blood flow (density flowmeter), pulmonary arterial pressure, changes in tidal air (increase in height indicates a decrease in tidal air).
The effect of BW 45/50 on the cardiac output of intact anesthetized dogs (chloralose). Dog 1 breathing naturally, dogs 2 and 3 receiving artificial respiration. The separate curves for each dog represent successive injections of the drug. Arrows represent time of injection. Axes: vertical, cardiac output; horizontal, time after injection. Note that the control value for cardiac output is lower for later injections because of incomplete recovery from earlier injections. Dog 3 had a third injection between the two shown here, that accounted for the very low control before the final injection.

The Effect on Respiration and the Isolated Heart. In 5 anesthetized dogs and 4 anesthetized cats BW 45/50 (1 mg./Kg.) led to a profound fall in cardiac output (−34 to −48 per cent), an increase in the arteriovenous oxygen difference, and a decrease in oxygen consumption, followed in the naturally breathing animal by a compensatory increase in oxygen consumption. After large doses (2 to 4 mg./Kg.) there was incomplete recovery. The right intraventricular pressure fell slightly in the 2 dogs being artificially ventilated, and rose slightly in the dog breathing naturally.

Theophylline Ethylene Diamine: Action on the Pulmonary Circulation in Animals with Open Chests. The administration of theophylline preparations in 14 cats (0.1 to 2.5 mg. into the pulmonary artery or intravenously) and 4 dogs (7.5 to 100 mg. into the pulmonary artery) almost invariably effected an increase in blood flow in the left pulmonary artery (+8 to +64 per cent in cats, and +11 to +61 per cent in dogs; figure 1B). The left pulmonary arterial pressure was frequently slightly lowered in the cat but in the dog there was sometimes a rise and sometimes a fall, depending upon a balance between increased pulmonary blood flow and reduced pulmonary vascular resistance. The left atrial pressure often fell slightly and the calculated value for pulmonary vascular resistance diminished (−14 to −46 per cent in cats, −4 to −18 per cent in dogs). That this was more than a passive effect due to the increase in blood flow was shown by the fact that values for pressure and flow after theophylline preparations nearly always fell nearer to the flow axis than the normal pressure flow curve. Figure 5 shows part of a pressure flow curve after theophylline ethylene diamine in a cat compared with a normal curve for the same animal. The values for pressure and flow were measured when the effect of the drug was at its maximum. There was usually a fall in
systemic pressure after theophylline ethylene diamine, but the reduction in pulmonary vascular resistance was sometimes observed when the systemic effect was very small. The action on pulmonary blood flow and resistance could be repeated many times, and it was very striking how a sustained improvement in blood flow and reduction in resistance could be achieved in an animal in poor condition at the end of an experiment. A few animals were insensitive to theophylline preparations insofar as they showed no change in the pulmonary circulation and only a very small diminution of systemic blood pressure. Section of the vagosympathetic trunks in the neck and atropine (1 to 2 mg./Kg.) had no effect on the action of theophylline preparations in cats.

**Action on Isolated Perfused Lungs.** In the isolated lungs of 8 dogs and 15 cats perfused by the constant flow and constant pressure methods, theophylline preparations caused a decrease in pulmonary vascular resistance (figs. 2 and 3). This effect was also observed when the pulmonary vascular resistance had been increased by 5-hydroxytryptamine (fig. 6), BW 45/50, and diphenhydramine, an anti-histamine which has also been shown to increase pulmonary vascular resistance (Barer and Niisser, 1958). The tidal air was increased, probably by bronchodilatation, but the time relations of this change were quite different from those of the resistance change, and the two effects varied independently (fig. 3).

**Effect of Theophylline Preparations after Pulmonary Embolism.** When the suspension known as Chlorbismol is given intravenously or into the pulmonary circulation, its suspended particles form emboli that obstruct the pulmonary vessels, leading to an increase in pulmonary arterial pressure and a reduction in pulmonary blood flow, and, in the intact animal, to rapid shallow respiration. We found that after embolism theophylline preparations increased the pulmonary blood flow and reduced the pulmonary arterial pressure in a dog with an open chest (fig. 7), reduced the pulmonary vascular resistance in isolated perfused lungs (2 cats), increased the depth of respiration and reduced the raised right ventricular pressure in 2 intact anesthetized dogs.

**Effect of Ethylene Diamine.** Some of the properties of Aminophylline have been attributed to the ethylene diamine that it contains. The properties we have demonstrated are due to theophylline itself, since Silbephylbine (dihydroxypropyl theophylline) had the same action as did the preparations containing ethylene diamine. In 2 cats, ethylene diamine alone led to an increase in pulmonary vascular resistance.
DISCUSSION

Our results have shown that in the cat BW 45/50 is not a vasodilator but a vasoconstrictor of the pulmonary vessels. This action was demonstrated both with the circulation intact and in isolated perfused lungs. There is an accompanying decrease in tidal air which may be due to bronchoconstriction, and this in itself might increase pulmonary vascular resistance. However, the time relations of the two effects differed, so that we think there is probably also a direct effect on the pulmonary vessels themselves. In the dog, BW 45/50 may also lead to an increase in pulmonary vascular resistance, but at times a decrease has been observed both in intact animals and in perfused lungs. We have confirmed the results of Aviado et al.1 in that we observed a fall in pulmonary arterial pressure after BW 45/50 in both cats and dogs, but we ascribe this, entirely in the cat and at least partially in the dog, to a reduction in pulmonary blood flow. There was a decrease in total cardiac output in the intact anesthetised dog, and although we have not measured the total cardiac output in the cat it is a reasonable assumption that this was similarly reduced. The cause of the decline in cardiac output may be a reduction in venous return following systemic vasoconstriction, or a direct poisoning effect on the cardiac muscle. In favor of the latter factor being partly responsible is the fact that BW 45/50 diminished the contractions of two isolated rabbits’ hearts and also reduced the uptake of blood by the right heart of an animal whose right atrium was supplied with blood from a constant level reservoir. Also, bradycardia may in itself be a cause of temporary reduction in cardiac output.

We think, therefore, that BW 45/50 is not a promising drug for the treatment of pulmonary hypertension because of the means by which it lowers the pulmonary arterial pressure. We cannot think of any condition in which it would be justifiable to reduce pulmonary arterial pressure by reducing the cardiac output. We have also observed other undesirable effects on respiration and on tidal air.

We have confirmed the results of Quimby et al.2 in dogs, in finding that theophylline is a pulmonary vasodilator, or at least that it leads to a reduction in pulmonary vascular resistance. The same effect was observed in cats. This action is usually accompanied by an increase in tidal air and a decline in systemic pressure, but the effect on pulmonary arterial pressure depends upon whether the increased cardiac output or the pulmonary vasodilatation predominates.

Storstein, Helle, and Rokseth2 observed a fall in pulmonary arterial pressure after theophylline ethylene diamine in 21 patients suffering from various heart and lung diseases. Dulfano, Yahni, Toor, Rosen and Langer3 have used the effect on the pulmonary circulation of preoperative theophylline ethylene diamine to predict the effect of mitral valvotomy, with partial success. They claim that if the pulmonary vessels are irreversibly damaged there is less apt to be a fall in pulmonary arterial pressure. Our results suggest that theophylline might be a particularly useful drug in pulmonary embolism. Some of the benefit which asthmatics obtain from theophylline preparations may also be due to its pulmonary vascular effect, for it is known that raised pressure in the airway (which may occur during attacks) leads to a reduction in pulmonary blood flow, and an increase in pulmonary vascular resistance. A rise in pressure in the alveoli during asthma cannot be proved, but if the airway is constricted experimentally in animals to simulate bronchoconstriction there is a general rise in pressure beyond that point which may lead to a reduction in pulmonary blood flow.5

SUMMARY

\(\beta\)-(2,5-diethoxyphenyl)-\(\beta\)-hydroxy-isopropylamine reduces the pulmonary arterial pressure in cats and dogs but this is probably due to a reduction in pulmonary blood flow. In cats it causes an increase in pulmonary vascular resistance both in the intact animal and isolated perfused lungs. In dogs it has variable effects on pulmonary vascular resistance. In both animals it depresses respiration and in intact anesthetised dogs it causes a pro-
found fall in cardiac output. In doses of only 2 to 4 times those recommended it may lead to irreversible depression of the circulation. It is thought unlikely that it will prove useful for pulmonary hypertension.

Theophylline ethylene diamine causes a decrease in pulmonary vascular resistance in both cats and dogs. This is probably a direct action on the pulmonary vessels rather than an indirect effect following bronchodilatation. The effect on pulmonary arterial pressure depends on a balance between pulmonary vasodilatation and increased cardiac output. After experimental pulmonary embolism, theophylline ethylene diamine effected an increase in pulmonary blood flow and a reduction in pulmonary arterial pressure.

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SUMMARIO IN INTERLINGUA

Beta-(2,5-diethoxyphenyl)-beta-hydroxy-isopropylamina reduce le tension pulmono-arterial in cattos e canes, sed isto es probabilemente le consequentia de un reduction del fluxo de sanguine pulmonar. In cattos, illo causar un augmento del resistencia pulmono-vascular, tanto in animales intacte como etiam in isolate pulmones perfusione. In canes, illo ha variabile effectos super le resistencia pulmono-vascular. In ambe species illo deprime le respiratio, e in intacte anesthesiaste canes, illo causar un marcate reduction del rendimento cardiaco. In doses de solmente 2 a 4 vices le quantitate recommendate, illo pote effectuar un irreversibile depression del circulation. Es opinate que il es pouco probable que illo va provar se utile in le tractamento de hypertension pulmonar.

Theophyllina-ethylene-diamina causa un reduction del resistencia pulmono-vascular in cattos si ben como in canes. Isto es probablemente un action directe super le vasos pulmonar plus tosto que un effecto indirecte secundari a bronchodilatation. Le effecto super le tension pulmono-arterial depende de un balancia inter le vasodilatation e le augmentate rendimento cardiaco. Post embolismo pulmonar experimental, iste agente effectuava un augmento del fluxo de sanguine pulmonar e un reduction del tension pulmono-arterial.

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