Dissociation of Tracheobronchial and Cardiac Effects of Some Beta-adrenergic Stimulants

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The effects of three beta-adrenergic stimulating agents, isoproterenol, salbutamol, and terbutaline, were studied in the cat. In animals receiving halopropane, the dose of salbutamol or terbutaline necessary to produce ventricular arrhythmias was 100–500 times greater than the dose of isoproterenol needed. In cats receiving nitrous oxide, a dose of carbachol which increased airway pressure 50–135 per cent for a preset tidal volume was given. This action of carbachol was blocked by 2 μg/kg of salbutamol or terbutaline. The large differences between bronchodilating and arrhythmia-producing doses of salbutamol and terbutaline suggest that these agents might be of value in the treatment of bronchoconstriction in conscious and anesthetized patients. (Key words: Cardiac beta-adrenergic receptors; Tracheobronchial beta-adrenergic receptors; Cardiac arrhythmias; Bronchoconstrictors; Bronchodilators; Isoproterenol; Salbutamol; Terbutaline.)

Isoproterenol has been given by inhalation and intravenously for the treatment of bronchospasm occurring during anesthesia. Although this agent is effective, complications have often been seen. The β-adrenergic stimulating activity of isoproterenol, which produces relaxation of tracheobronchial smooth musculature, has also been held responsible for cardiac arrhythmias and arrest.[1] Salbutamol and terbutaline are new β-adrenergic stimulating agents that have been introduced for the treatment of asthma. The purpose of the present study was to determine the ability of these agents to 1) produce ventricular arrhythmias, and 2) inhibit carbachol-induced bronchoconstriction.

Methods

Twenty healthy, nonpregnant cats weighing 3–4 kg were studied. Anesthesia was induced with pentobarbital, 36 mg/kg, intraperitoneally. Either a tracheostomy was done or the trachea was intubated with an uncuffed Portex tube 4.0–5.0 mm in internal diameter. A constant-volume animal respirator with a nonrebreathing valve was used to control ventilation at $V_T = 10$ ml/kg + 10 ml at a rate of 20/min. In prior experiments in cats this ventilation was found to maintain arterial *p*H and P_{CO_2} at control levels of 7.3 and 30. Anesthesia was maintained with either nitrous oxide or halopropane (see below). The femoral vessels were cannulated and arterial pressure was measured with a Statham transducer and recorded on a Grass polygraph. The femoral vein was used for all injections. Rectal temperature was monitored with a Yellow Springs thermometer and maintained above 36 F in most cats by a heating blanket.

Group I: Arrhythmia Studies

Twelve cats were anesthetized with halopropane, an agent known to sensitize the heart to the arrhythmic effect of catecholamines.[1, 2] In these animals the arrhythmia thresholds of salbutamol and terbutaline were determined and compared with that of isoproterenol. These cats were prepared as described above and lead II of the ECG was recorded on the Grass polygraph. The Vernitrol vaporizer was used to deliver 0.5–1.0 per cent halopropane in 99.5–99 per cent O_2. Incremental doses of salbutamol, terbutaline, and isoproterenol were given until a ventricular arrhythmia was re-

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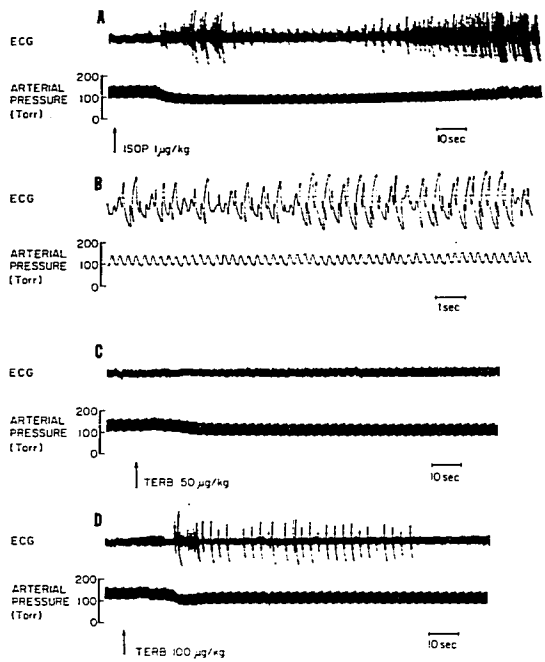


FIG. 1. Comparison of the abilities of isoproterenol and terbutaline to produce arrhythmias in the halopropane-anesthetized cat. *A*, at the arrow isoproterenol (ISOP), 1 μg/kg, was injected and produced cardiac arrhythmias. Panel *B* is a continuation of panel *A*, at a speed of 25 mm/sec. *C*, at the arrow terbutaline (TERB), 50 μg/kg, was injected and did not produce cardiac arrhythmias. *D*, a dose of 100 μg/kg of terbutaline produced an arrhythmia, but the number of ectopic beats was less than seen with 1 μg/kg of isoproterenol.

corded. An arrhythmia was judged to be either five consecutive ventricular beats or a persistent ventricular irregularity such as bigeminy. Doses used (μg/kg) were:

Isoproterenol	0.05	0.1	0.5	1.0				
Salbutamol }	0.5	1.0	5.0	10	25	50	100	
Terbutaline }								

Six cats received isoproterenol and salbutamol, and six, isoproterenol and terbutaline. Once the arrhythmic threshold dose of isoproterenol had been determined, salbutamol or terbutaline was given. The interval between doses of isoproterenol was 15 minutes and that for salbutamol and terbutaline, 15–30 minutes.

TABLE 1. Doses of Isoproterenol, Salbutamol, and Terbutaline Causing Arrhythmias in 12 Cats*

	Arrhythmic Dose (μg/kg)					
Isoproterenol (I)	0.1	0.5	0.5	0.1	0.5	1.0
Terbutaline (T)	>50	50	>50	25	>50	100
Dose ratio I:T	>1:500	1:100	>1:100	1:250	>1:100	1:100
Isoproterenol (I)	0.1	0.1	0.1	0.5	1.0	1.0
Salbutamol (S)	25	10	>50	>50	>50	100
Dose ratio I:S	1:250	1:100	>1:500	>1:100	>1:50	1:100

* When > appears, the dose listed was the largest given and did not produce arrhythmias.

TABLE 2. Effectiveness of Salbutamol and Terbutaline in Blocking Carbachol-induced Bronchoconstriction

	Carbachol Dosage (μg/kg)	Increase in Airway Pressure (Per Cent)			Per Cent Block		Duration (Min)	
		Carbachol only	Carbachol after Terbutaline (2 μg/kg)	Carbachol after Salbutamol (2 μg/kg)	Terbutaline	Salbutamol	Terbutaline	Salbutamo
Cat 1	2.5	60	13	6	78	90	50*	>120
Cat 2	2.0	50	13	20	74	60	50*	15
Cat 3	1.25	57	17	14	70	75	>120	60*
Cat 4	2.0	60	20	21	67	65	> 40	97*
Cat 5	2.5	135	14		90		75	
Cat 6	1.75	54	12		80		>150	
Cat 7	2.0	60		10		83		>60
Cat 8	2.0	100		44		56		>100
MEAN	2 μg/kg	72	15	19	76	68		

* Indicates whether salbutamol or terbutaline was given first.

GROUP II: TRACHEOBRONCHIAL STUDIES

In eight cats, anesthesia was maintained with 75 per cent N_2O and 25 per cent O_2. The inspiratory airway pressure necessary to deliver a fixed tidal volume was measured with a Statham low-pressure transducer and recorded on the Grass polygraph. Bronchoconstriction was induced with carbachol, given intravenously. The initial dose of 1.0 μg/kg was increased by 0.25 μg/kg-increments until the inspiratory airway pressure had increased 50 per cent or more. After at least three constant responses to this dose of carbachol had been obtained, salbutamol or terbutaline, 2 μg/kg, was given intravenously. The carbachol dose was repeated every 15–20 minutes until the original increase in airway pressure had been reproduced or until at least 45 minutes had elapsed. Two cats received salbutamol only, two cats, terbutaline only, and four cats, both salbutamol and terbutaline. The second drug was administered only after the response to carbachol had returned to the control level. In the four cats receiving both drugs, salbutamol was given first in two and terbutaline first in the other two.

Results

GROUP I: ARRHYTHMIA STUDIES

In all 12 cats the dose of salbutamol or terbutaline needed to produce arrhythmias far exceeded that of isoproterenol (fig. 1, table 1). The dose of isoproterenol needed to cause a ventricular arrhythmia was 0.1 μg/kg in five

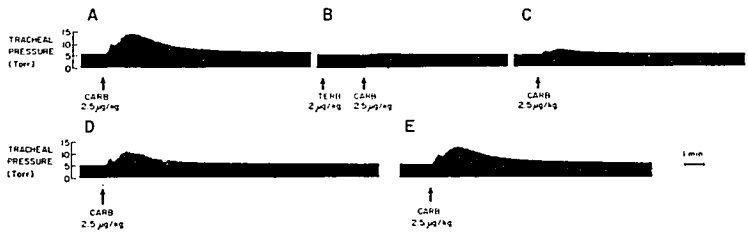
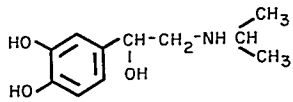
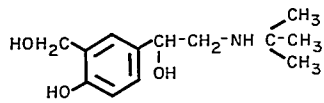


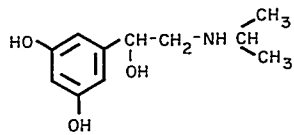
FIG. 2. Ability of terbutaline to prevent the increase in airway pressure produced by carbachol. *A*, injection of carbachol (CARB), 2.5 μg/kg, at the arrow increased airway pressure. *B*, injection of terbutaline (TERB), 2 μg/kg, prior to carbachol virtually abolished the effect of carbachol. *C*, *D*, and *E* show the recovery of carbachol response 45, 60, and 75 minutes after injection of terbutaline.



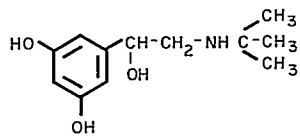
ISOPROTERENOL



SALBUTAMOL



ORCIPRENALINE



TERBUTALINE

FIG. 3. Structural formulas of isoproterenol, orciprenaline, salbutamol, and terbutaline.

animals, 0.5 μg/kg in four, and 1.0 μg/kg in three. Among the six cats given salbutamol, one had an arrhythmia at 10 μg/kg, one at 25 μg/kg, and one at 100 μg/kg. The remaining three cats had had no arrhythmias after 50 μg/kg, and no further salbutamol was given. Of the six cats given terbutaline, one had an arrhythmia at a dose of 25 μg/kg, one at 50 μg/kg, and one at 100 μg/kg, while the other three developed no arrhythmias at 50 μg/kg, the largest dose given.

GROUP II: TRACHEOBRONCHIAL STUDIES

In all eight cats salbutamol or terbutaline blocked the increase in airway pressure produced by carbachol (fig. 2, table 2). The doses of carbachol varied from 1.25 to 2.5 μg/kg and increased airway pressures 50–135 per cent. Terbutaline, 2.0 μg/kg, blocked the carbachol response by 76 per cent, while salbutamol, 2 μg/kg, blocked the response by 68 per cent.

Discussion

The results of the present study demonstrate that the dose of salbutamol or terbutaline needed to produce ventricular arrhythmias is usually 100–500 times greater than that for isoproterenol. Furthermore, although the arrhythmic dose of salbutamol or terbutaline was between 10 and 100 μg/kg, bronchoconstriction induced by carbachol could be markedly inhibited by 2 μg/kg.

Our interest in alternatives to isoproterenol was stimulated by recent reports linking isoproterenol to the annual increase in mortality of asthmatics in England and Wales.[3-6] These deaths associated with isoproterenol have been attributed to: 1) alterations in viscosity of tracheal secretions resulting in bronchial plugging; 2) decreased arterial oxygen tensions; 3) increased ventricular irritability resulting in arrhythmias.[4, 7, 8]

Two types of β-adrenergic receptors have been described by Lands *et al.*[9] Those responsible for cardiac stimulation and lipolysis were termed "β_1" and those responsible for bronchodilation and vasodepression, "β_2." The optimal molecular configurations for cardiac and bronchial β-adrenergic receptor stimulation differ. The presence of a cyclopentyl group on the terminal nitrogen increases cardiac stimulation, whereas a —CH_2OH at the meta position on the benzene ring increases bronchial dilation.[10] Englehardt *et al.*[11] have shown that the catecholamine structure is not essential for β-adrenergic stimulation. Modification of the isoproterenol molecule led to the

production of several compounds with bronchial effects more potent than those of isoproterenol, but producing less cardiac stimulation (fig. 3). The first of these was orciprenaline.[11] Salbutamol, a more recent selective β-adrenergic stimulator, proved to be longer-acting than orciprenaline and to cause still less cardiac stimulation.[12, 13] A similar drug, terbutaline, has been shown to have twice the activity of orciprenaline on the isolated guinea pig trachea and to produce less cardiac stimulation at equipotent doses.[14] The results of the present study of salbutamol and terbutaline demonstrate the difference between their tracheobronchial and cardiac effects *in vivo*.

Isoproterenol, in addition to its potential for producing ventricular arrhythmias, has other drawbacks, which include: 1) short duration of action; 2) rapidly developing tachyphylaxis; 3) ineffectiveness orally; 4) tachycardia.[15–17] The short duration of action of isoproterenol is due to its rapid O-methylation by catechol-o-methyltransferase (COMT) to 3-methoxy isoproterenol.[18] The presence of a $-CH_2OH$ at the meta position in salbutamol is thought to prevent its breakdown by COMT,[19] thus prolonging its duration of action to at least twice that of isoproterenol.[12, 13] Terbutaline's duration of action is also at least twice as long as that of isoproterenol.[14] Tachyphylaxis to isoproterenol has been shown to be due to one of its metabolites, 3-methoxy isoproterenol, which is a β-adrenergic blocker.[17, 18] Although preliminary studies suggest that salbutamol and terbutaline do not produce tachyphylaxis like that seen with isoproterenol, further studies are necessary. Although isoproterenol is ineffective orally, salbutamol in large doses can be effective,[12] while in preliminary studies terbutaline has seemed to be orally effective.[14]

Finally, tachycardia, which is common with isoproterenol, is rarely produced by therapeutic doses of salbutamol or terbutaline.[5, 13, 14] In view of these considerations and the large differences between bronchodilating and arrhythmia-producing doses of salbutamol and terbutaline shown by this study, it seems likely that these drugs will be of value in the treatment of bronchoconstriction in both conscious and anesthetized patients. They are clearly safer and more effective than isoproterenol for this purpose.

References

1. Katz RL, Bigger JT Jr: Cardiac arrhythmias during anesthesia and operation. ANESTHESIOLOGY 33:193–213, 1970
2. Katz RL: Neural factors affecting cardiac arrhythmias induced by halopropane. J Pharmacol Exp Ther 152:88–94, 1966
3. Speizer FE, Doll R, Heaf P: Observations on recent increase in mortality prone asthma. Brit Med J 1:335–339, 1968
4. Speizer FE, Doll R, Heaf P, *et al.*: Investigation into use of drugs preceding death from asthma. Brit Med J 1:339–343, 1968
5. Greenberg MJ, Pines A: Pressurized aerosols in asthma. Brit Med J 1:563, 1967
6. Pickvance W: Pressurized aerosols in asthma. Brit Med J 1:756, 1967
7. Kundson RJ, Constantin HP: An effect of isoproterenol on ventilation–perfusion in asthmatic versus normal subjects. J Appl Physiol 22:402–406, 1967
8. Palmer KNV, Legge JS, Hamilton WFD, *et al.*: Comparison of effect of salbutamol and isoprenaline on spirometry and blood–gas tensions in bronchial asthma. Brit Med J 2: 23–24, 1970
9. Lands AM, Arnold A, McAnliff JP, *et al.*: Differentiation of receptor systems activated by sympathomimetic amines. Nature 214: 597–598, 1967
10. Lands AM, Brown TG: Comparison of cardiac stimulating and bronchodilator actions of selected sympathomimetic amines. Proc Soc Exp Biol Med 116:331–333, 1964
11. Englehardt A, Hoefke W, Wick H: Zur Pharmakologie des Sympathomimeticums 1-(3, 5-Dihydroxyphenyl)-1-hydroxy-2-isopropylaminoathan. Arzneimittelforschung 11:521–525, 1961
12. Cullum VA, Farmer JB, Jack D, *et al.*: Salbutamol: A new selective β-adrenoceptive receptor stimulant. Brit J Pharmacol 35: 141–151, 1969
13. Choo-Kang YFJ, Simpson WT, Grant IW: Controlled comparison of the bronchodilator effects of three β-adrenergic stimulant drugs administered by inhalation to patients with asthma. Brit Med J 2:287–289, 1969
14. Covino B: Personal communication
15. Ross SB: In vivo inactivation of catecholamines in mice. Acta Pharmacol Toxicol 20:267–273, 1963
16. Exon PD: Pressurized aerosols in asthma. Brit Med J 2:178, 1967
17. Paterson JW, Conolly ME, Davies DS: Isoprenaline resistance and the use of pressurized aerosols in asthma. Lancet 2:426–429, 1968
18. Sjoerdsma A: Relationships between alterations in amine metabolism and blood pressure. Circ Res 9:734–748, 1961
19. Editorial. Nature 219:861–862, 1968