Pressurised Aerosols
A NEW LOOK

M. H. DÜRR

SUMMARY

Data available on the increase in sudden asthma deaths during 1964 to 1967 in a number of countries do not allow for the condemnation of pressurised aerosols.

It appears that highly β_2-selective pressurised aerosols (fenoterol and salbutamol) do not have cardiovascular actions. Doses 12 times those required for bronchodilation do not affect heart rate. It is assumed that selective-β_2 adrenoceptor stimulants have a topical action on receptors in the mouth and pharynx. As this assumption does not explain the immediate action on bronchospasm and on uterine motility in preterm labour, the existence of a still unknown and hypothetical reflex mechanism cannot be excluded.

The topical actions and the minute doses absorbed render the inhalation of selective β_2-adrenoceptor stimulants very safe treatment.

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It has become customary to associate the increase in asthma mortality — which was observed in England, Wales and some other countries between 1964 and 1967 — with the administration of pressurised aerosols.[1-4] The sales of pressurised bronchodilator aerosols increased during the period from 1964 to 1967 almost throughout the world. The increase in asthma mortality, however, was confined to a small number of countries. The decline in asthma mortality after 1967 is contrary when compared with the still increasing sales of pressurised aerosols.

A very recent article by Girdwood,[5] reviewing deaths after the taking of medicaments from June 1964 to October 1971, gives the number of patients in England and Wales who presumably died after an overdose of isoprenaline as 17; the same figure for orciprenaline was 6. During the same period there were more than 11 million prescriptions made out for isoprenaline and more than 6 million for orciprenaline. These figures do certainly not confirm the impression of pressurised aerosols being dangerous drugs.

Stolley[6] offered an explanation for the phenomenon by condemning the higher concentration of a particular brand of isoprenaline. There might be some coincidental relationship between the sales of this particular product and the incidence of asthma deaths, but this relationship does not exist in all countries where isoprenaline forte was on the market. Higher concentration of an aerosol means primarily a greater number of particles per puff since the pressurised aerosols are dry aerosols. The same effect is, however, achieved by excessive doses of lower concentrated aerosols.

Most authors believe that death was caused by adverse cardiovascular effects of the bronchodilator aerosol resulting in fatal ventricular fibrillation. Since death was sudden in most cases, fibrillation could not be recorded on an electrocardiograph. In addition, in those patients who died in hospital, fibrillation either did not occur or was not recorded or, when recorded, could not conclusively be interpreted as having been caused by the administration of a bronchodilator aerosol. Read and Rebuck[7,8] found a high percentage of ECG abnormalities in severe asthma, irrespective of bronchodilator pretreatment.

Animal experiments have shown that extremely high doses of a bronchodilator can be administered without causing arrhythmia.[9] Arrhythmia and fibrillation can, however, be seen in acidosis after fairly low doses. This may indicate that patients in respiratory failure should not be given bronchodilators. It is doubtful whether bronchodilating effects can be obtained during acidosis. As soon as pO_2 and pCO_2 values approach normality in previously acidotic patients, sympathomimetic bronchodilators seem to again become effective.[7,8]

Tachycardia in status asthmaticus is a regular finding.[7,8] In most cases it is impossible to assess whether tachycardia was caused by the administration of pressurised aerosols or whether tachycardia was a symptom inherent to the condition. The circumstances under which sudden asthma deaths occurred, and the lack of tangible cardiovascular data, do not permit one to reach valid conclusions as to whether, or to what degree, pressurised aerosols contributed towards the aetiology of those deaths.[10]

Taylor and Harris,[11] after experimenting with mice, associated asthma deaths with fluorocarbon propellants used in asthma inhalers. Dollery *et al.*[12] investigated 4 different fluorocarbons in 4 volunteers and 2 patients. They concluded that more work is needed to establish the significance, if any, of the blood concentrations in relation to catecholamine-induced arrhythmia. Azar *et al.*[13] refuted the findings by Taylor and Harris. Their experiments with mice and dogs indicated that concentrations of propellants in inhalers are not sufficient to cause cardiac sensitisation to catecholamines. Paterson *et al.*[14] felt that chronic blood levels in overusers of pressurised aerosols are unlikely to sensitise the heart to adrenergic compounds. In a recent paper, Fabel *et al.*[15] found that 16 puffs of propellants in healthy volunteers and 10 puffs of propellants in patients suffering from hypoxic conditions did not affect ECG recordings. From the foregoing it appears

Boehringer Ingelheim, Randburg, Tvl
M. H. DÜRR, *Director of Medical Services*

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safe to conclude that fluorocarbon propellants used in pressurised aerosols did not contribute towards the asthma deaths.

Sympathomimetic bronchodilators are now grouped according to their β_2-adrenoceptor selectivity, which expresses the degree of dissociation between their action on β_1- and β_2-adrenoceptors. Isoprenaline has about equal actions on β_1- and β_2-receptors in all dosage forms and is therefore considered non-selective. Orciprenaline and hexoprenaline are β_2 selective as aerosols, and the more recent introductions—salbutamol, terbutaline and fenoterol are considered highly β_2-selective.[16]

The fact that selectivity appears to be different with different dosage forms or routes of administration, gives rise to speculation. Parenteral and oral administration of the selective and highly selective agents result in varying degrees of β_1-action which correlates with bio-availability, i.e. with plasma levels, indicating that absorption is required for β_1-action. After inhalation of 7-^{3}H-fenoterol, Seyberth and Rahn[17] found measurable blood levels after 1 hour and maximal blood levels after 3 hours. Leblanc,[18] on the other hand, could show that bronchodilating action commences 2 minutes after inhalation and that maximal effects are seen after 10 minutes. The discrepancy between blood levels and bronchodilator action could also be demonstrated by Walker *et al.*[19] for salbutamol. With the highly selective bronchodilator aerosols (salbutamol and fenoterol) in doses up to 12 puffs, no changes in heart rate could be observed, while 1 puff resulted in adequate bronchodilation.[18] The conclusion that bronchodilating action after inhalation does not depend on systemic absorption is unavoidable. Cardiovascular actions after inhalation — if these occur at all — correspond with blood levels now thought to be caused by that part of the dose which reaches the plasma.[19,20]

So far, it is not possible to measure the exact amount of aerosol reaching the lung and being absorbed there. It is agreed that a proper inhalation technique is required to transport the aerosol with the inhaled air into the lungs. Since it is also obvious that the majority of patients do not administer the aerosol in the prescribed manner, it can be assumed that only a very small amount of the aerosol actually arrives somewhere in the lung, the better part being deposited on the jet-nozzle of the inhaler apparatus or in the mouth. Herzog[21] feels that about 90% of the released dose does not get further than the mouth. Steen[22] believes that 12% of an aerosol actually reaches the lung.

In all probability the bronchodilating action of an aerosol thus originates in the mouth. If that is so, then a sophisticated technique for administration is not required. Investigation into this problem has confirmed the above views, and observations by Shore and Weinberg[23] imply that the mouth and pharynx are the site of β_2-adrenoceptors. This would explain the missing action on β_1-receptors, since only very small amounts would, following absorption, reach β_1-receptor sites via the bloodstream.

The local action on — still hypothetical — receptors in the mouth raises the question of how to explain the bronchodilating action originating further down in the respiratory tract. The rather rapid onset rules out an absorption mechanism, but would point to a reflex mechanism which is as yet not understood. This view is supported by recent findings by Baillie and Dürr[24] who found a reduction in uterine activity following fenoterol inhalations comparable to that achieved with intravenous administration. Although inhalation did cause an identical reduction in uterine motility, it did not cause a significant increase in heart rate as was observed after parenteral administration.

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