Resistance to β-adrenoceptor stimulants and death from bronchial asthma

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A sharp rise in unexpected sudden death from bronchial asthma occurred in the 6 years following the introduction of pressurized aerosols of β-adrenoceptor agonists (chiefly isoprenaline), for the treatment of this condition (Speizer, Doll & Heaf, 1968). Although the death rate has fallen considerably since the recognition of this danger (Inman & Adelstein, 1969) it remains important to establish the mechanism underlying this phenomenon since isoprenaline is still in use.

In eight humans, intravenous infusions of isoprenaline at an average rate of (0·007 μg base/kg)/min for 34 min, which produced no response in any of these subjects, reduced the chronotropic response of the heart to rapid injections of more isoprenaline (0·1–10 μg) by a factor of 3·93 times ($P<0·001$).

In thirteen mongrel dogs, infused with isoprenaline at an average rate of (0·042 μg base/kg)/min for 36 min the chronotropic response of the heart to rapid injections of more isoprenaline was reduced by an average factor of 2·80 times ($P<0·001$). The fall in diastolic blood pressure in response to rapid injections of isoprenaline (0·1–30 μg) after these infusions was reduced on average 2·36 times ($P<0·001$). Rapid injections of isoprenaline up to 35 times the size of the infused dose did not alter the animals' responsiveness to isoprenaline. Single injections of long acting β-adreneceptor agonists such as isoetharine (150 μg) or terbutaline (100 μg) caused a reduction in isoprenaline sensitivity similar to that following prolonged isoprenaline infusions.

Guinea-pigs were each given 10 injections of saline or isoprenaline (4 μg base/kg) salbutamol (4 μg base/kg), or terbutaline (15 or 20 μg base/kg) spaced out over 4–5 hours. Two hours later, the animals were challenged with a dose of histamine which had been shown to produce a low mortality in control animals. In all groups which received β-adrenoceptor stimulants the mortality from bronchospasm was increased. This effect failed to achieve statistical significance in the isoprenaline treated animals and just failed to do so in one of the terbutaline groups. However, a significant increase in mortality occurred in the other groups.

Prolonged exposure to isoprenaline even in subthreshold doses produces a reduced sensitivity to isoprenaline in a way not seen after large single injections of this drug. In contrast, single injections of long acting β-adrenoceptor stimulants will produce such resistance.

The guinea-pig data suggest that this resistance is characterized by cross-resistance to the adrenergic nerve excitation of β-receptors, rendering the animal more susceptible to the bronchoconstricting effects of histamine. It seems to occur more readily with the long acting β-adrenoceptor stimulants.

It is suggested that a similar phenomenon occurs in asthmatic patients taking excessive doses of β-adrenoceptor stimulants and this may explain the rise in asthma deaths. Further, it is possible that under conditions of overdose the newer long acting agents may be more hazardous than isoprenaline in this respect.

REFERENCES

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