THE INFLUENCE OF HYPOXIA AND HYPERCAPNIA ON THE CARDIOTOXICITY OF ISOPRENALINE IN DOGS

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Circumstantial evidence (Speizer et al, 1968) has pointed strongly to an association between the excessive use of pressurized aerosols of sympathomimetic drugs, in particular isoprenaline, and the observed rise in asthmatic mortality in the British Isles between the years 1959-1966. The following investigation was carried out to see if changes in arterial blood oxygen tension (PaO_2) and carbon dioxide tension ($PaCO_2$), similar to those known to have occurred during asthmatic attacks, could alter the cardiovascular effects of isoprenaline in anaesthetized dogs.

Four groups of 5 greyhounds were anaesthetized with pentobarbitone (30 mg/kg i.v.) and then artificially respired (see Table 1). Arterial pressure and heart rate were recorded on a Devices M19 recorder. Samples of arterial blood were analysed for PaO_2, $PaCO_2$ and pH using a digital pH/blood gas analyser. Following a control period of hypoxia and/or hypercapnia, doses of isoprenaline (2.5 µg/kg i.v.) were administered at 6 minute intervals until a fatal response ensued. Arterial samples were taken 3 minutes after each dose of isoprenaline.

Table 1.

Group number	Arterial blood gas tensions PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Number of doses required to attain fatal response
1	30-40	30-40	7.6
2	50-55	30-40	15.6
3	30-40	55-65	2.6
4	50-55	55-65	13.2

Repeated equipotent doses of isoprenaline increased heart rate and decreased blood pressure in all dogs. The magnitude of the cardiovascular response to isoprenaline was similar for each group and for each dose within a group. Hence, neither the degree of hypoxia nor the presence nor absence of hypercapnia influenced the changes in heart rate and blood pressure. With increasing number of doses, the PaO_2 and pH fell in all experiments. Considering the mean values of PaO_2, $PaCO_2$ and pH for each group immediately prior to giving what proved to be the fatal dose, the most striking feature to emerge was the uniformity of PaO_2 values in all dogs. The number of doses required to attain this fatal level of hypoxaemia, however, varied from group to group (see Table 1). These results infer (a) that the initial level of hypoxaemia may be a crucial factor in determining the number of doses of isoprenaline a dog can survive and (b) that only in the presence of a severe hypoxaemia would co-existing hypercapnia augment the toxicity of isoprenaline. In the clinical situation, therefore, patients with very low PaO_2 values and raised $PaCO_2$ values could, through overuse of their isoprenaline aerosols, conceivably achieve sufficiently high blood levels of the drug to cause a fatal response.

Speizer, F.E., Doll, R. and Heaf, P. (1968). Brit. med. J., 1, 335-339,343.