Actions of the sympathomimetic bronchodilator, AQL208, on the cardiovascular, bronchiolar and skeletal muscle systems of the cat

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Trimetoquinol is a sympathomimetic bronchodilator first described by Yamato, Hirakura & Sugasawa (1966).

It was reported to be about 10 times more potent by weight than isoprenaline in producing relaxation of the guinea pig tracheal chain, but only one fifth as potent as isoprenaline in stimulating the perfused heart (Iwasawa & Kiyomoto, 1967). In preliminary experiments in this laboratory, the active (−)-isomer of trimetoquinol (AQL208) was found to be about half as potent as (−)-isoprenaline in decreasing fusion of incomplete tetanic contractions of the cat soleus muscle. These results, on tissues from different species, suggested that AQL208 might be relatively selective for β-receptors in the lung compared with those in the heart and in skeletal muscle. Such a drug would be valuable in the symptomatic relief of asthma because it would be less likely to produce muscle tremor and unwanted cardiac stimulant effects.

Further experiments have now been performed in order to assess the effects of AQL208 on the cardiovascular and bronchial systems and on skeletal muscle of the chloralose-anaesthetized cat under identical *in vivo* conditions. Effects on myocardial blood flow and general haemodynamics were studied by the methods described by McInnes & Parratt (1969), and effects on lung compliance and resistance parameters by a modification (for the cat) of the method described by Amdur & Mead (1958). Effects on incomplete tetanic contractions of the soleus muscle were studied using the method described by Bowman & Nott (1970) (reference to which is made in the previous abstract).

Intravenous infusions of AQL208 (0·05 to 0·25 μg/kg min) were found to be about equipotent with (−)-isoprenaline in lowering general arterial blood pressure and in increasing left ventricular pressure, left ventricular dp/dt, myocardial blood flow, pulmonary artery pressure and heart rate. Intravenous injections of AQL208 were found to be about half as potent as (−)-isoprenaline in decreasing fusion of soleus contractions. In their abilities to antagonize 5-hydroxytryptamine-induced bronchospasm, AQL208 and (−)-isoprenaline again did not differ markedly in potency, although the dose-response curve for AQL208 was shallower than that for (−)-isoprenaline and therefore accurate comparisons of potency could not be determined. In all tests, the effects of AQL208 were 2–5 times longer lasting than those of (−)-isoprenaline when responses of equal magnitude were compared.

Thus the results emphasize the obvious importance of determining the various effects of a drug in the same species, and they show that, at least in the cat, AQL208 does not exhibit any marked selectivity for β-receptors in particular tissues. The results, therefore, suggest that if the cat is a reliable test animal, AQL208 may not be devoid of side effects on the cardiovascular and skeletal muscle systems in man.

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The hyperglycaemic effect of the diuretic chlorthalidone

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Chlorthalidone, like the benzothiadiazine diuretics, has been reported to impair glucose tolerance in some patients (Reutter & Labhardt, 1961; Carliner, Schelling, Russell, Okun & Davis, 1965) and to produce hyperglycaemia in the rat following single large doses of the drug dissolved in alkali or administered as a suspension (Tabachnick, Gulbenkian & Yannell, 1965; Foy, 1967; Wales, Grant & Wolff, 1968). The work presented in this communication was performed in an attempt to elucidate the mechanism of the hyperglycaemic effect.