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

I. W. RODGER
Department of Pharmacology, University of Strathclyde, Glasgow, C.1, U.K.

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

B. L. FURMAN
Department of Pharmacology, University of Strathclyde, Glasgow, C.1, U.K.

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.

Chlorthalidone, administered intraperitoneally in single doses up to 200 mg/kg, exerted no significant effect ($P > 0.05$) on rat blood sugar at 1 or 2 h after injection when compared with an alkaline saline control. The low solubility of chlorthalidone necessitated the use of high concentrations of alkali (pH 12) to dissolve the drug in sufficient concentration to administer the large doses employed. A similar control solution was shown to produce a statistically significant ($P < 0.05$) hyperglycaemic response when injected intraperitoneally. Two hours after injection of chlorthalidone (200 mg/kg, i.p.) the intravenous glucose tolerance, as measured by the rate of disappearance of an intravenous glucose load (1 g/kg), was not significantly different from that of the controls ($P > 0.05$). In concentrations up to 200 μg/ml, chlorthalidone did not diminish glucose uptake by rat diaphragm muscle or epididymal adipose tissue incubated *in vitro*. Oral treatment with chlorthalidone (100 mg/kg day) for 28 days produced no deterioration of intravenous glucose tolerance when compared with pair-fed controls.

It is concluded that chlorthalidone is not hyperglycaemic in the rat in single, large doses when compared with a suitable alkaline control solution and does not influence the glucose tolerance of rats so treated, or treated orally for 28 days with large doses of the drug.

I wish to thank Dr. D. F. Ingham, Geigy Pharmaceuticals, for generous supplies of chlorthalidone, and Mr. John Boswell for excellent technical assistance.

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Mechanism of action of neostigmine at the neuromuscular junction

SANDRA N. WEBB
Department of Pharmacology, University of Strathclyde, Glasgow, C.1, U.K.

A study has been made, in cats under chloralose anaesthesia, of the relative abilities of a number of acetylcholine antagonists (hexamethonium, benzoquinonium, tubocurarine, gallamine and pancuronium) to inhibit the various facets of neostigmine's activity at the neuromuscular junction of the soleus muscle.

Neostigmine (150 μg/kg intravenously) increased the amplitude of the maximal twitch and gave rise to muscle fasciculations that were independent of the nerve stimulation. These effects were associated with repetitive action potentials both in the muscle and in the motor nerve, the latter being recorded antidromically in the soleus ventral rootlets (L7 and S_1).

Although, in large enough doses injected close-arterially into the muscle, all of the acetylcholine antagonists abolished all the effects of neostigmine, it was possible, by careful dosage with the different drugs, to dissociate muscle fasciculations and repetitive firing in the nerve from twitch augmentation and repetitive firing in the muscle. Hexamethonium depressed muscle fasciculations and repetitive firing in the nerve in doses slightly smaller than those necessary to diminish the augmented twitches and muscle repetition. On the other hand, gallamine and pancuronium depressed the augmented twitches and the muscle repetition in doses that allowed fasciculations and nerve repetition to continue. With both benzoquinonium and tubocurarine, it was not possible to demonstrate selectivity for any aspect of neostigmine's action, all effects being depressed simultaneously. The results indicate that muscle fasciculations and nerve repetitive firing are related events, as are twitch augmentation and muscle repetition. It is now known that acetylcholine can depolarize motor nerve endings as well as the post-junctional membrane of the muscle endplate (Hubbard, Schmidt & Yokota, 1965). Hexamethonium is relatively more active as a ganglion blocking drug than as a neuromuscular blocking drug, indicating its selectivity for neuronal receptors. Gallamine and pancuronium, however, have little ganglion blocking activity and are relatively selective for muscle receptors. Tubocurarine and benzoquinonium block both ganglionic and muscle receptors in comparable doses. It is concluded that muscle fasciculations and repetitive firing