β -ADRENOCEPTOR ANTAGONISTS AND RESPIRATORY FUNCTION

Whilst agreeing with many of the assertions made by Dr McDevitt in his editorial on adrenoceptor antagonists and respiratory function (McDevitt, 1978), may I draw attention to certain inconsistencies and related issues.

In dealing with the paper by Perks, Chatterjee, Croxson & Cruickshank (1978), he notes their inability to demonstrate significant tachycardia with inhaled isoprenaline and so dismisses their ability to infer that the antagonists being tested were having equivalent cardiac effect. In point of fact inhaled isoprenaline is recognized to be a poor cardiac (direct and reflex) stimulant as its systemic availability is so low (Martindale, 1977). Using isoprenaline, it is only possible to confirm equivalence of cardiac β blocking activity (with certain limitations for reflex effects) when it is given intravenously. Thus workers making use of inhaled β adrenoceptor agonists have to infer cardiac equivalence of different doses of antagonists from independent studies. Secondly, he does not point out that the dose of inhaled agonist which can be delivered is affected by the pre-existing degree of airway obstruction, so that this too is a reason for preferring the i.v. route for pharmacological agonisms. Thirdly, he fails to appreciate that in asthmatics the measured response to isoprenaline is affected by the degree of pre-existing airway obstruction (Hume & Gandeia, 1957), in that there is an optimal range of obstruction associated with the greatest response. Hence, it is not entirely surprising that in the presence of pre-existing obstruction (after taking atenolol) the change in FEV₁ after isoprenaline could indeed appear to be enhanced. Finally, and surprisingly he has not criticized their decision to assign patients into 'labile' and 'non-labile' groups retrospectively rather than prospectively or according to any fixed predetermined criteria.

While the results obtained by Oh, Kaye, Warrington, Taylor & Wadsworth (1978) may be perplexing and contrary to our present concepts they should not be entirely dismissed on the grounds that their technique (using vigorous exercise in healthy subjects) has not previously been shown to distinguish decisively at all times between a known selective and known non-selective drug. On the contrary the use of vigorous exercise has helped to emphasize that selectivity is not such a cut and dried property, and at least in the airways of non-asthmatics, unlike much earlier work merely revealing significant differences in response between propranolol and placebo and not between practolol and placebo, this technique showed a significant difference between the responses of the two active drugs (Kumana, Kaye, Leighton, Turner & Hamer, 1975; Kumana, Marlin, Kaye & Smith, 1974). Criticisms concerning variations of exercise peak flow rates before either form of treatment are

well taken and it is also true that exercise peak flow rates are not highly reproducible. Regardless of the inferences made by Oh *et al.* (1978), it is hard to understand the different pattern in exercise peak flow rate response with oral and with i.v. practolol (a drug which is virtually unmetabolized in man). This admittedly calls into question the comparability of subjects and/or details of technique between their various studies. More disturbing still, is the comparison of responses following i.v. doses from two different investigations involving different sets of subjects on different occasions, which surely invalidates statistical analysis of differences in response between either oxprenolol or metoprolol and propranolol and practolol.

In defence of vigorous exercise as a means of achieving sympathetic agonism to test antagonistic drugs in normal subjects it should be realized that (a) the risk of precipitating asthma is extremely small, (b) the agonism is physiological, (c) it is possible to directly confirm the degree of cardiac agonism and antagonism from the heart rate (the heart rate response to i.v. agonists is subject to modification by antagonist through reflex as well as direct action), (d) spontaneous changes in airway function are unlikely to be as great as in asthmatics and (e) it does not require i.v. infusions (pharmacological agonists are known to have toxicity and have to be delivered i.v. to ensure consistent dosing). A concerted approach utilizing all the available methods of assessing selectivity is likely to give us the most information.

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β -ADRENOCEPTOR ANTAGONISTS AND RESPIRATORY FUNCTION

With reference to the leading article by Prof. D.G. McDevitt and the paper by Dr W.H. Perks and co-workers (McDevitt, 1978; Perks, Chatterjee, Croxson & Cruickshank, 1978) we wish to raise the following points:

(1) *Differentiation of non-selective and cardioselective β -adrenoceptor antagonists*

Although McDevitt (1978) argues that early studies using exercise in normal subjects failed to distinguish clearly between non-selective and cardioselective β -adrenoceptor antagonists, all our more recent studies have enabled this distinction to be made when the drugs are administered intravenously (Oh, 1977; Oh, Kaye, Warrington, Taylor & Wadsworth, 1978). When practolol 200 mg was given orally the plasma concentrations of drug obtained were similar to those at which cardioselectivity can no longer be shown (Bodem, Bramwell, Weil & Chidsey, 1973; Oh, 1977).

(2) *Peak expiratory flow rate (PEFR)*

In each of the three studies we reported (Oh *et al.*, 1978) the variation in exercise PEFR within each study day was consistently less than that between days. The coefficients of within-day variation were 5.09, 18.6 and 16.8 for the first, second and third studies respectively; the coefficients of between-day variation were 5.79, 19.2 and 17.4. Therefore, comparison of PEFR values obtained at different times after treatment with those at 0 h on the same day made better sense than comparison with results obtained after placebo administration on a different day.

Although the variation in exercise PEFR is greater than that in exercise heart rate, this follows from the design of the study: the exercise loads are chosen to produce heart rates of 160–170 beats/min, and the resulting PEFR will inevitably vary between subjects.

(3) *Partial agonist activity*

We do not attribute the lack of effect on the airways of oxprenolol and pindolol to partial agonist activity; we discuss and largely reject this hypothesis. We do not suggest that drugs with partial agonist activity can safely be given to asthmatic subjects.

(4) *Volunteer studies*

Studies in healthy volunteers are more useful than patient studies for eliciting basic pharmacological mechanisms. Patients are a heterogeneous population, and their responses to drugs are likely to be more variable than those of healthy individuals (Skrabal, Czaykowska, Dittrich & Braunsteiner, 1976; Perks *et al.*, 1978).

Volunteer studies allow the use of severe exercise as a β -adrenergic stimulus, which is more physiological than isoprenaline by inhalation or intravenous infusion. Such strenuous exercise has the additional advantage of eliminating the effects of changes in vagal tone, a variable which is entirely ignored in most studies in patients (Glick & Braunwald, 1965; Robinson, Epstein, Beiser & Braunwald, 1966).

Volunteer studies can more satisfactorily meet McDevitt's (1978) important criterion that the dose of each β -adrenoceptor antagonist should be shown to produce an equivalent degree of cardiac β -adrenoceptor blockade, because the high heart rates which can be reached in normal subjects allow large reductions due to the drug. In the study by Perks *et al.* (1978) the β -adrenergic stimulus of inhaled isoprenaline caused a mean increase in heart rate of only 8.9 beats/min, which is clearly not adequate for the comparison of cardiac effects of different β -adrenoceptor antagonists.

Short-term laboratory investigations in patients can not be claimed to show that any β -adrenoceptor blocking drug can safely be given to subjects with airflow obstruction. Only studies in which large numbers of such patients are treated with different β -adrenoceptor antagonists in varying doses for prolonged periods can show whether one drug is safer than another. We regard our studies in healthy volunteers as complementary to this type of investigation.

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