The effect of pindolol on creatine kinase is not due to β_2-adrenoceptor partial agonist activity

We read with interest the recent article (Tomlinson *et al.*, 1990) which demonstrated that an increase in serum creatine kinase (CK) activity occurs during treatment with the β-adrenoceptor blocking drug pindolol. As a possible explanation for this phenomenon the authors postulated that the β_2-adrenoceptor partial agonist activity (PAA) of pindolol on skeletal muscle was responsible for this effect. Known effects of β_2-receptor stimulation on skeletal muscle include finger tremor and hypokalaemia (Lipworth & McDevitt, 1989a). However, the effect of of β_2-adrenoceptor stimulation on creatine kinase has not to our knowledge been previously reported in the literature. We therefore investigated the effects of inhaled terbutaline (a known selective β_2-adrenoceptor agonist) on serum creatine kinase activity in 34 normal volunteers (mean ± s.e. mean age, 25 ± 3 years).

All subjects attended the laboratory at the same time of day (09.00 h) and were rested supine on arrival for a period of 30 min. Following this, subjects were given inhaled terbutaline 5 mg delivered via a 750 ml pear-shaped spacer device, in order to eliminate individual differences in inhaler technique. Thirty minutes after inhalation, venous blood was taken for estimation of serum potassium and creatine kinase activity. Serum potassium was analysed by flame photometry (IL943, Instrumentation Laboratory, Warrington, UK) with a coefficient of variation (CV) for analytical imprecision of 0.4%. Creatine kinase activity was assayed by an ultraviolet method using a Cobas Fara centrifugal analyser and CK NAC kit (Hoffman-La Roche & Do., AG Basel, Switzerland) with a C.V. value for analytical imprecision of 2.1%.

Statistical comparisons before and after treatment were made by two-way analysis of variance. Paired Student's *t*-test was used to assess the significance of the percentage change in CK activity. All values are given as means and 95% confidence intervals. The critical difference value for total variability in measuring CK activity was calculated from the formula $1.65 \times (CV_A^2 + CV_I^2)^{1/2}$, where CV_A represents the analytical imprecision and CV_I the intra-individual biological variability calculated from values derived from the world literature for healthy subjects (Costongs *et al.*, 1985; Fraser, 1986). It has previously been shown that there is no difference in biological variability between healthy individuals and patients with chronic stable disease (Fraser, 1988). The critical difference value represents the change required to exclude analytical and biological variability with 95% confidence, and is calculated at 36.5% for creatine kinase. Thus, an increase in CK in response to terbutaline should be greater than the critical difference value in order to represent a true drug effect. The reference ranges for our laboratory are K (3.5–5.0 mmol l^{-1}) and CK (up to 150 u l^{-1}).

Terbutaline produced a significant fall in serum K from 3.83 (3.73 to 3.91) mmol l^{-1} to 3.42 (3.34 to 3.50) mmol l^{-1} ($P < 0.001$). There was no significant change in CK activity: 99 (94 to 103) u l^{-1} before terbutaline, 104 (99 to 109) u l^{-1} after terbutaline. Furthermore, the percentage change (post-pre) in CK activity was 11 (−2 to 25)% and this was not statistically significant.

These results clearly show that terbutaline administration caused hypokalaemia, which is a known β_2-adrenoceptor-mediated effect on skeletal muscle (Brown *et al.*, 1983; Lipworth *et al.*, 1989a,b), but in contrast the same dose of terbutaline had no significant effect on serum CK activity. Indeed, the percentage change was less than the critical difference value required to exclude biological variability. Our results suggest that the effect of pindolol on serum CK activity is not due to stimulation of skeletal muscle β_2-adrenoceptors as a consequence of its PAA. This of course does not exclude the possibility that pindolol may cause direct non β_2-mediated effects on skeletal muscle resulting in release of CK, in chronic rather than single dosing. Studies are therefore indicated to assess the effects on creatine kinase of other β-adrenoceptor blocking drugs with PAA.

N. M. WHEELDON, D. M. NEWNHAM, G. C. FRASER, D. G. McDEVITT & B. J. LIPWORTH
Departments of Clinical Pharmacology and Biochemical Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland

Received 29 January 1991,
accepted 4 February 1991

ADONIS 030652519100132X

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Correspondence: Dr N. M. Wheeldon, Department of Clinical Pharmacology, Ninewells Hospital and Medical School, Dundee DD1 9SY

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