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Antagonism by INPEA of isoprenaline-induced tachycardia in man

The compound (±)-1-(*p*-nitrophenyl)-2-(isopropylamino) ethanol (±-INPEA) has been shown to have β-adrenoceptor blocking properties in animals (Murmann & Gamba, 1966) and to differ from many existing β-adrenoceptor blocking agents in its associated pharmacological actions. Due to the lack of data on the β-adrenoceptor blocking actions of (±)-INPEA in man, a study was undertaken of its effects on isoprenaline-induced tachycardia in healthy volunteers.

Five fully informed healthy volunteers whilst lying down, had a cannula placed in the antecubital vein for infusion of isoprenaline and injection of (±)-INPEA. The electrocardiogram was monitored and recorded continuously from the CR5 lead; heart rate was counted from the recording. The subjects received initially an injection of physiological saline and the heart rate response to this injection was observed for 5 min. At least 5 min after the injection of saline, isoprenaline was infused by means of a mechanically-driven syringe at a rate of 3 μg/min for 4 min and the heart rate response was recorded during and after the infusion until basal conditions had been re-established. Thirty min after the infusion of isoprenaline a single dose of (±)-INPEA was administered and approximately 5 min later the infusion of isoprenaline was repeated.

Isoprenaline sulphate B.P. was dissolved in isotonic sodium chloride injection containing 0·003% ascorbic acid to yield a final concentration of 1·5 μg per ml. A fresh solution was made for each subject. (±)-INPEA was used as an aqueous solution containing 25 mg per ml.

The subjects received 10, 25 and 45 mg of (±)-INPEA. The only side effect was peripheral paraesthesiae which was noted by one subject after intravenous administration of 45 mg.

Infusion of isoprenaline 3 μg/min for 4 min increased the heart rate in all five subjects, (increased rate control: 29·0 ± 2·4, after (±)-INPEA: 10 mg, 22·6 ± 4·3; 25 mg, 13·6 ± 1·4*; 45 mg, 12·2 ± 2·0* means ±s.e. of 5 subjects).

The increase had stabilized between the third and fourth minute of the infusion and this increase at the end of the fourth minute was taken as the response to isoprenaline. The mean response to the infusion of isoprenaline for the five subjects was an increase of 29 beats/min (±2·4 s.e.).

* Significantly different from control $P<0·001$

Pre-treatment with (±)-INPEA 10, 25 or 45 mg, intravenously, reduced the chronotropic effect of isoprenaline but this reduction did not become statistically significant until 25 or 45 mg (±)-INPEA had been administered.

The inhibition of the chronotropic action of isoprenaline was dose-related, the dose response curve showing a rather shallow gradient. The increase in heart rate (as % of control) was (±)-INPEA 10 mg, 77·9%; 25 mg, 46·8%, 45 mg, 42·0%. Pre-treatment of the subject with doses of (±)-INPEA which effectively attenuated isoprenaline-induced tachycardia had no effect on resting heart rate.

Thus, (±)-INPEA is capable of effectively attenuating, in a dose-related manner, the chronotropic effect of isoprenaline in man and thus complies with the main criterion for a β-adrenoceptor blocking agent.

(±)-INPEA, in doses that reduced isoprenaline-induced tachycardia, did not result in changes in resting heart rate. This is in contradistinction to the action of propranolol, sotalol, (Ekue, Lowe & Shanks, 1970) practolol (Brick, Hutchinson & others, 1968) and oxyprenolol (Reale, Imhof & Motolese, 1967).

Animal studies have shown that in addition to a pronounced β-adrenoceptor blocking action, (±)-INPEA also possesses some intrinsic β-sympathomimetic activity. This concomitant sympathomimetic activity may result in obviation of any negative chronotropic action the drug may possess by virtue of its β-adrenoceptor blocking activity. This may explain the shallowness of the dose/response curve found. Other drugs of this type with intrinsic sympathomimetic activity have also been reported to have very little effect on basal heart rate (Ablad, Johnson & others, 1967).

(±)-INPEA differs pharmacologically from many other β-adrenoceptor blocking drugs; e.g. Davis (1970) has shown that (±) INPEA has very little local anaesthetic or "quinidine-like" activity. Hahn, Pendleton & Wardell (1968) demonstrated a number of differences between propranolol and (±) INPEA on the cardiovascular system of the dog. The administration of β-adrenoceptor blocking doses of propranolol resulted in a significant increase in coronary vascular resistance and mean left atrial pressure. (±)-INPEA, on the contrary, had no significant effect on these parameters. These data suggest that (±)-INPEA may differ from other β-adrenoceptor agents in its liability to induce myocardial depression.

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