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The effect on experimental cardiac arrhythmias of a new anticonvulsant agent, Kö 1173, and its comparison with phenytoin and procainamide

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There has been renewed emphasis on the treatment of ventricular extrasystoles and other cardiac arrhythmias since the introduction of intensive coronary care. At present there is no drug which is completely satisfactory for the long-term control of arrhythmias. Quinidine, procainamide, propranolol and phenytoin all have undesirable side-effects. We have studied the effects on experimental cardiac arrhythmias of a new compound, Kö 1173 (1-(2',6'-dimethyl-phenoxy)-2-amino-propane; Boehringer, Ingleheim), whose actions on the central nervous system are similar to those of phenytoin (Danneberg & Giesemann, personal communication). The effect of Kö 1173 on these arrhythmias is compared with those of phenytoin and procainamide.

Ventricular tachycardias or ventricular extrasystoles were produced in anaesthetized dogs by the intravenous injection of ouabain (Allen, Shanks & Zaidi, 1970). The test compound was given as a continuous intravenous infusion at the rate of 0·2 mg/kg per min. Kö 1173 was given to ten dogs. In eight dogs sinus rhythm was restored after a mean dose of 1·37 mg/kg. The remaining two dogs died with ventricular fibrillation 5 min and 13 min after starting the infusion of Kö 1173. Phenytoin was given to three dogs and sinus rhythm was restored at a mean dose of 2·37 mg/kg. Procainamide was given to three dogs and sinus rhythm was restored at a mean dose of 16·6 mg/kg. Three dogs were given procainamide at the rate of 1 mg/kg per min; one dog reverted to sinus rhythm after 2·5 mg/kg.

Ventricular extrasystoles were produced by the intravenous injection of increasing doses of adrenaline in dogs anaesthetized with morphine and pentobarbitone and respired with 1% halothane and room air (Allen *et al.*, 1970). The adrenaline challenge was repeated after increasing doses of the test compound. Kö 1173 was given to five dogs and phenytoin and procainamide to four dogs each. The arrhythmia was abolished in all dogs. The mean dose required to abolish the arrhythmia was 0·65 mg/kg for Kö 1173; 1·12 mg/kg for phenytoin and 4·12 mg/kg for procainamide.

These studies indicate that Kö 1173 is as effective as phenytoin in experimental cardiac arrhythmias. As Kö 1173 does not possess local anaesthetic activity or block β-adrenoceptors (Danneberg & Giesemann, personal communication) its action on cardiac arrhythmias may be similar to phenytoin (Bernstein, Gold, Lang, Pappelbaum, Bazika & Corday, 1965; Bigger, Bassett & Hoffman, 1968).

REFERENCES

ALLEN, J. D., SHANKS, R. G. & ZAIDI, S. A. (1970). *Br. J. Pharmac.*, in the Press.

BERNSTEIN, H., GOLD, H., LANG, T., PAPPELBAUM, S., BAZIKA, V. & CORDAY, E. (1965). Sodium diphenylhydantoin in the treatment of recurrent cardiac arrhythmias. *J. Am. med. Ass.*, **191**, 695–697.

BIGGER, J. T., BASSETT, A. L. & HOFFMAN, B. F. (1968). Electrophysiological effects of diphenylhydantoin on canine Purkinje fibers. *Circulation Res.*, **22**, 221–236.

Observations on the sub-division of β-adrenoceptors in the circulation of the dog

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The concept that β-adrenoceptors can be divided into β_1, exemplified by those which stimulate the heart, and β_2, which lower vascular resistance in skeletal muscle, is gaining wider acceptance (Lands, Arnold, McAuliff, Luduena & Brown, 1967). This paper describes a study of various drugs reputed to have a predominant effect on one or other of these receptors, in order to see whether this concept of two distinct types of β-adrenoceptor is justified.

Observations were made in dogs anaesthetized with morphine sulphate and pentobarbitone. The effects of the intravenous injection of isoprenaline, orciprenaline, isoetharine and salbutamol on heart rate were compared. The effects of the injection into the femoral artery of these four drugs on blood flow to the hind limb, measured by an electromagnetic flow probe around the artery, were also compared. All four drugs increased heart rate and femoral blood flow. The order of activity for increasing heart rate was isoprenaline>orciprenaline>isoetharine=salbutamol. The order for increasing femoral blood flow was isoprenaline>isoetharine=salbutamol>orciprenaline.

The effects of the intravenous injection of isoprenaline on heart rate and of the injection of isoprenaline into the femoral artery on hind limb blood flow were recorded before and after the intravenous injection of increasing doses of I.C.I. 50172 (practolol) and butoxamine which block the responses produced by β_1- and β_2-adrenoceptors respectively (Dunlop & Shanks, 1968; Levy, 1966). Large doses of both drugs reduced cardiac and peripheral vascular effects of isoprenaline but practolol produced