J. Pharm. Pharmacol. 1985, 37: 276–277
Communicated June 18, 1984

The effect of nifedipine and verapamil on the pendular movements of the rabbit isolated ileum

D. B. BELESLIN*, RANKA SAMARDŽIĆ, BRANKA TERZIĆ, DANICA JOVANOVIĆ-MIĆIĆ, *Department of Pharmacology, Medical Faculty, P.O. Box 662, 11000 Belgrade, Yugoslavia*

The inhibitory effect of calcium antagonists such as nifedipine and verapamil on the pendular movements of the rabbit isolated ileum was investigated. Nifedipine and verapamil depressed or abolished the pendular movements. The inhibitory effects of nifedipine and verapamil were concentration-dependent. Nifedipine is about 1000 times more potent than verapamil. Calcium ions failed to reverse the inhibitory effects of nifedipine and verapamil. Calcium antagonists which influence the motor activity of the digestive tract, therefore, could have therapeutic use independent of their action on the cardiovascular system.

The requirements of calcium ions for the pendular movements of the guinea-pig (Gerhards et al 1964) and the rabbit (Beleslin 1974) isolated ilea have already been described. The effect of nifedipine, a calcium antagonist, on the contractions of the guinea-pig isolated ileum caused by nicotine, acetylcholine, histamine, 5-hydroxytryptamine, bradykinin and hypertensin has also been investigated (Vater et al 1972). On the other hand, data about the effects of calcium antagonists on the pendular movements of the isolated intestine are still scarce. Therefore, the present experiments were undertaken to study the effects of calcium antagonists, such as nifedipine and verapamil, on the pendular movements of the rabbit isolated ileum.

Method

Rabbits of either sex, 1·9–2·6 kg, were killed by cervical dislocation and the terminal ileum excised at least 15 cm from the caecum. The segments were set up in an isolated 20 ml organ bath in Tyrode solution gassed with 95% O_2 and 5% CO_2 at 37 °C and placed under a load of about 1 g. The segments were left for about 30 min by which time spontaneous activity and tone had developed. Recordings were made on a smoked drum with a frontal writing isotonic lever and a vibrator was used to overcome the friction. The longitudinal muscle movements were magnified about 10 times. The bath fluid was renewed every 10 min. The drugs were allowed to act from the serosal surface of the intestine.

Calculations of the mean effective concentrations (ED50, i.e. the concentration required to reduce to 50% the pendular movements by the calcium antagonists) and their 95% confidence limits were calculated using linear regression according to the method of least squares.

Nifedipine, 0·8 mg, was dissolved in 1 ml of ethanol and thereafter adequate dilutions were made in 0·9% NaCl solution. In control experiments the adequate aqueous dilutions made from ethanol without nifedipine had no significant effect on the pendular movements of the ileum. The following substances were used: nifedipine, verapamil chloride and calcium chloride. All drug concentrations refer to the salts, except those of nifedipine which refer to the drug.

Results

In the first series of experiments the effect of nifedipine and verapamil on the pendular movements of the ileum was investigated. Nifedipine and verapamil depressed or abolished the movements (Figs 1A, B; 2A, B). As shown in Fig. 1A, B the inhibitory effect of nifedipine ($r = 0·99$; $P < 0·01$) and verapamil ($r = 0·96$; $P < 0·01$) on the pendular movements are concentration-dependent. The ED50 with 95% confidence limits for nifedipine is $2·1 \pm 8·5 \times 10^{-12}$ M, whereas that for verapamil is $2·0 \pm 4·5 \times 10^{-9}$ M. It appears, therefore, that nifedipine is approximately 1000 times more potent than verapamil.

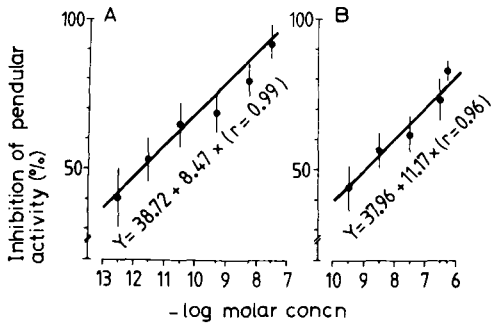

FIG. 1. Log concentration-response relation of nifedipine (A) and verapamil (B) on the pendular movements of the rabbit isolated ileum. Inhibitory responses are expressed as percentage of the maximum of pendular movements. Each point represents the mean of 6 different experiments ± s.e.m.

* Correspondence.

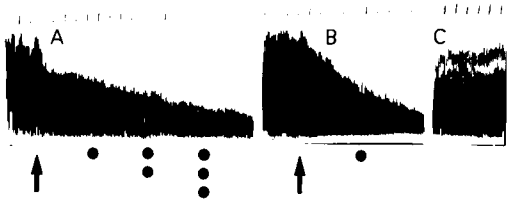

FIG. 2. Intractions of nifedipine (A) and verapamil (B) and calcium ions on pendular movements of the rabbit isolated ileum. A, at the arrow nifedipine was 1×10^{-8} M added to Tyrode solution. At one, two and three dots in A, calcium chloride in excess was added to Tyrode solution at 1×10^{-11}, 1×10^{-7} and 1×10^{-5} M respectively. B, at the arrow verapamil was added to Tyrode solution at 1×10^{-7} M. At the dot in B, calcium chloride in excess was added into Tyrode solution at 1×10^{-6} M. Records B and C are 20 min apart; during this time the ileum was kept in normal Tyrode. Time marker in min.

In the second series of experiments the interaction between calcium ions in excess and nifedipine or verapamil on the pendular movements on the rabbit isolated ileum was studied. Calcium ions added into the organ bath in concentrations from 1×10^{-11}–1×10^{-3} M failed to reverse the inhibitory effects of nifedipine (1×10^{-12}–1×10^{-9} M; n = 6) and verapamil (1×10^{-11}–1×10^{-6} M; n = 6). Such an experiment for nifedipine is illustrated in Fig. 2A, and for verapamil in Fig. 2B. The inhibitory effects of nifedipine and verapamil persisted in spite of the presence of calcium ions in excess, but after washing out calcium antagonists and calcium ions in excess, a full recovery of pendular movements took place within 20 min (Fig. 2B, C).

Discussion

As shown in these experiments, the pendular movements of the rabbit isolated ileum are sensitive to the inhibitory effects of nifedipine and verapamil. The finding that nifedipine is more potent than verapamil is in good agreement with the results of Taira (1979), although the relative efficacies of calcium antagonists are different in particular tissues (Kazda et al 1983). Of gastrointestinal motor disturbances, constipation is the most common side effect of many calcium antagonists, especially of verapamil (Simon & Bloomfield 1983). Accordingly, the constipation produced by calcium antagonists could be related to an action on motor activity of the gastrointestinal tract. Conceivably, calcium antagonists which influence the motor activity of the digestive tract could have a therapeutic use independent of their action on cardiovascular system.

The present experiments further revealed that calcium ions in excess could not reverse the inhibitory effects of nifedipine and of verapamil on the pendular movements of the ileum. The movements are also depressed or abolished either by omitting the calcium ions from Tyrode solution or by adding calcium ions in excess to the Tyrode solution (Beleslin 1974). In this context, the sensitivity of the contractile response of the longitudinal muscle of the guinea-pig isolated ileum to acetylcholine, muscarinic drugs, nicotine, histamine and 5-HT is reduced or even abolished when the bathing fluid contains increased calcium ions (Burgen & Spero 1970; Beleslin & Samardžić 1976). This inhibitory effect of calcium ions was obtained when the amount of calcium chloride was raised from several to ten times the normal amount in Tyrode and Krebs solution (Burgen & Spero 1970; Beleslin 1974; Beleslin & Samardžić 1976). It appears therefore, that the possible explanation is that calcium ions in excess cannot reverse the inhibitory effects of calcium antagonists simply because their presence in excess reduces the sensitivity of the smooth muscle to respond to signals evoking pendular movements.

This work has been supported by Pharmaceutical Industry 'LEK', Ljubljana, Yugoslavia.

REFERENCES

Beleslin, D. B. (1974) Iugoslav. Physiol. Pharmacol. Acta 10: 421–425

Beleslin, D. B., Samardžić, R. (1976) Neuropharmacology 15: 565–569

Burgen, A. S. V., Spero, L. (1970) Br. J. Pharmacol. 40: 492–500

Gerhards, K. P., Röttcher, M., Straub, R. W. (1964) Pflügers Arch. ges. Physiol. 279: 251–264

Kazda, S., Garthoff, B., Towart, R. (1983) in: Merrill, G. F., Weiss, H. R. (eds) Ca^{2+} Entry Blockers, Adenosine, and Neurohumors. Urban & Schwarzenberg, Baltimore-Munich, pp 93–107

Simon, H., Bloomfield, D. A. (1983) Cardioactive Drugs. Urban & Schwarzenberg, Baltimore-Munich

Taira, N. (1979) in: Bing, R. J. (ed.) New Drug Therapy with a Calcium Antagonist. Diltiazem Hakone Symposium '78. Excerpta Medica, Amsterdam, pp 91–103

Vater, W., Kroneberg, G., Hoffmeister, F., Kaller, H., Meng, K., Oberdorf, A., Puls, W., Schlossman, K., Stoepel, K. (1972) Arzneim.-Forsch. (Drug Res.) 22: 1–14