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The calcium channel antagonist, verapamil, potentiates the inhibitory action of morphine on intestinal and biliary motility

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The effects of morphine and verapamil have been assessed on the gastrointestinal propulsion of charcoal meal and egg yolk-induced gall bladder emptying in mice. Each drug significantly inhibited these functions. In combination, an additive effect was seen on the inhibition of gastrointestinal transit, whilst verapamil potentiated the morphine-induced inhibition of gall bladder emptying. It is concluded that calcium ion channel antagonists may potentiate the activity of opiate drugs.

It has been suggested that calcium antagonizes the antinociceptive action of opiates as well as the development of tolerance and physical dependence upon them (Harris et al 1975). Subsequently, it has been demonstrated that calcium channel antagonists can potentiate morphine-induced analgesia and hypothermia (Ben-Sreti et al 1983; Shah et al 1987). The present work was conducted to assess the effect of verapamil, a calcium channel blocker, on the peripheral actions of morphine on gastrointestinal and biliary tract activity in mice.

Materials and methods

The effects of verapamil and morphine were observed on gastrointestinal propulsion in intact animals as described by Janssen & Jageneau (1957). Adult Swiss (inbred) mice of either sex 20–25 g, were kept fasting for 24 h. They were divided into four groups of 12 animals each. The first group served as control and received 0·9% NaCl (saline) (1 mL kg^{-1}, i.p.). Second and third groups were given morphine (5 mg kg^{-1} i.p.) or verapamil (15 mg kg^{-1} i.p.) respectively. The fourth group was treated with verapamil 5 min before the administration of morphine. All animals received orally 0·3 mL of an aqueous suspension of a 10% charcoal meal in 5% acacia gum 15 min after the drug administration. Subsequently, animals were killed by ether inhalation 20 min after the charcoal meal and the intestines and stomach removed. The pyloric end of the stomach was tied to a glass rod and suspended with a 3 g weight at the ileo-caecal junction for 20 s. The total length of the intestine from pylorus to ileo-caecal junction as well as the length travelled by the charcoal meal was measured. The length travelled by the meal was calculated as a percent of the intestine length and the results were analysed by Student's *t*-test.

The effects of verapamil and morphine on gall bladder motility were determined by the method of Valsecchi & Toson (1982) which is based on the fact that the presence of egg yolk in the duodenum releases cholecystokinin which causes contraction and emptying of the gall bladder and reduces its weight. Thus, it is the weight of the gall bladder at death which serves as a measure of its earlier motility. Female mice 20 ± 1 g, were kept fasting for 24 h. They were divided into five groups of ten animals each. The first group received saline by both oral and i.p. routes to establish the normal weight of gall bladder. In animals of all other groups, gall bladder emptying was induced by the oral administration of 1 mL of a 30% suspension of lyophilized egg yolk in saline. The second group served as control and was given saline (i.p.) 8 min before the oral administration of egg yolk. The third and fourth groups were similarly treated with morphine (20 mg kg^{-1} i.p.) or verapamil (15 mg kg^{-1} i.p.) respectively. The last group received a combined treatment of morphine and verapamil. Animals were killed by ether inhalation 15 min after oral administration of normal saline or egg yolk. Gall bladders were removed by sectioning the cystic duct and weighed. The average weight of gall bladder was calculated for each group. Percent inhibition of emptying was calculated with the formula % inhibition of emptying = $(Ti - C) \times 100/(B - C)$ where B = mean weight (mg) of gall bladder in saline group, C = mean weight (mg) of gall bladder in egg yolk (control) group and Ti = weight of gall bladder (mg) in each mouse in the drug-treated group. Dunnett's *t*-test was used for statistical evaluation.

Results

As shown in Fig. 1, the length of intestine travelled by a charcoal meal was significantly reduced in animals pretreated with morphine or verapamil. The degree of reduction was greater for morphine. When both the drugs were given in combination the maximum reduction observed was almost equal to the sum total effect of the two drugs given individually.

Similarly, results of experiments on gall bladder motility showed (Table 1) that pretreatment with morphine or verapamil caused a significant inhibition of the egg yolk-induced gall bladder emptying. The degree of inhibition was marginally greater in morphine-treated animals. When both the drugs were given in combination, the emptying of gall bladder was preven-

* Correspondence.

Table 1. Inhibition of egg yolk-induced gall bladder emptying in mice.

Treatment	Dose (mg kg^{-1})	Gall bladder wt (mg; mean ± s.e.; n = 10)	% inhibition of emptying
Saline (i.p. and orally)	—	17·90 ± 2·14	—
Saline (i.p.)	—	1·81 ± 0·28	—
Morphine	20	6·45 ± 0·81	28·83*
Verapamil	15	5·66 ± 0·50	23·92*
Verapamil + morphine	15 20	17·60 ± 1·76	98·13*

In comparison with group 2 control animals (normal saline and egg yolk p.o.).
* $P < 0·05$ (Dunnett's t-test).

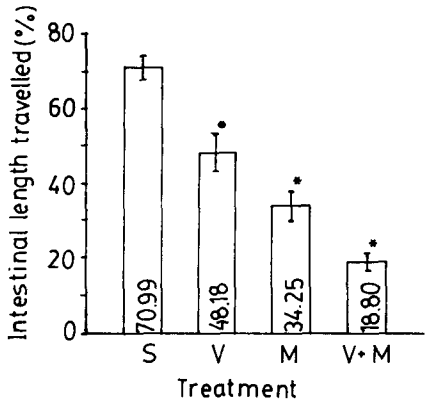

FIG. 1. Intestinal transit of a charcoal meal in control and drug-treated mice. Mean ± s.e. of 12 animals has been shown. S = Saline, V = verapamil (15 mg kg^{-1}), M = morphine (5 mg kg^{-1}), V + M = verapamil and morphine (in similar doses). Statistically significant difference from the normal saline-treated control group, * $P < 0·01$ (Student's t-test).

ted, the inhibition being greater than the sum total effect of the two drugs given individually.

Discussion

A number of reports have indicated that the actions of narcotic drugs are modified by calcium ions (Kakunaga et al 1966; Kaneto 1971). In addition, the calcium ion chelators and recently some calcium channel antagonists have also been shown to potentiate the central actions of morphine (Kakunaga et al 1966; Ben-Sreti et al 1983). In the present work we have observed that verapamil, a calcium channel antagonist, exerts a synergistic effect on the inhibitory effect of morphine on the gastrointestinal and biliary tracts. Morphine reduced the gastrointestinal transit of a charcoal meal and this is consistent with its ability to produce constipation by causing a spasm of the intestinal smooth muscle (Vaughan Williams & Streeten 1950). Verapamil alone also inhibited the gastrointestinal transit and with morphine it exhibited a strong synergism on this effect. It is possible that verapamil reduces the intestinal motility by relaxing the smooth muscles by a blockade of the entry of calcium through the slow channels in the plasma membrane (Stone 1980; Castell 1985).

Morphine is also known to prevent gall bladder emptying by causing a spasm of the sphincter of Oddi (Crema et al 1965). The present study has shown that verapamil also inhibits the gall bladder emptying, probably due to a relaxation of the biliary smooth muscle. But when both drugs are given together the inhibition of gall bladder emptying is potentiated and complete. This observation could also mean that verapamil relaxes the smooth muscle of gall bladder but fails to antagonize the spasmogenic effect of morphine on the sphincter of Oddi.

Although the exact mechanism of the interaction between calcium channel antagonists and the opiate drugs remains to be elucidated, the present evidence suggests that a synergism may exist between these drugs.

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