Effects of guanoxan on intestinal smooth muscles

SIR,—Guanoxan has adrenergic neuron blocking properties (Augstein & Green, 1964) and combines the chemical structure of both guanethidine and benzodioxan in one molecule. Introduced as an antihypertensive agent, one of its reported side-effects is an urgency to defaecation, some minutes after its administration (Peart & MacMahon, 1964), or diarrhoea (Frohlich, Dustan & Page, 1966).

We have previously noticed that the administration of guanoxan to our anaesthetized animals often induced defaecation (Bueno, de Castro & Sollero, 1967).

In 20 dogs anaesthetized with pentobarbitone sodium (30 mg/kg), the intestinal contractions were examined *in situ* by means of an extensible balloon filled with saline which was intraluminally inserted in the small intestine and connected to a water manometer. After intravenous administration of guanoxan, and paralleling the fall in blood pressure, an immediate and short-lasting contraction was seen.

With the isolated ileum of the guinea-pig suspended in Tyrode solution at 37·5°, guanoxan evoked contractions in doses beginning with 2 μg/ml. Repeated administration did not induce tachyphylaxis and a direct dose-effect relation was also seen (Fig. 1). The contractions were not blocked by an antihistamine drug (promethazine 0·5 μg/ml), a 5-hydroxytryptamine-blocking agent (BOL 8 μg/ml) or a ganglion blocking drug (hexamethonium 8 μg/ml).

On the rabbit isolated duodenum suspended in Tyrode solution at 37·5°, guanoxan also evoked contractions in doses starting with 1 μg/ml. These contractions are not blocked by atropine sulphate (2 μg/ml) or hexamethonium (8 μg/ml).

It seems that there is a direct action of guanoxan on the smooth muscle fibres and since one of the most common side-effects during antihypertensive therapy is diarrhoea this mechanism should also be re-evaluated for those drugs having a guanidine nucleus in their molecules.

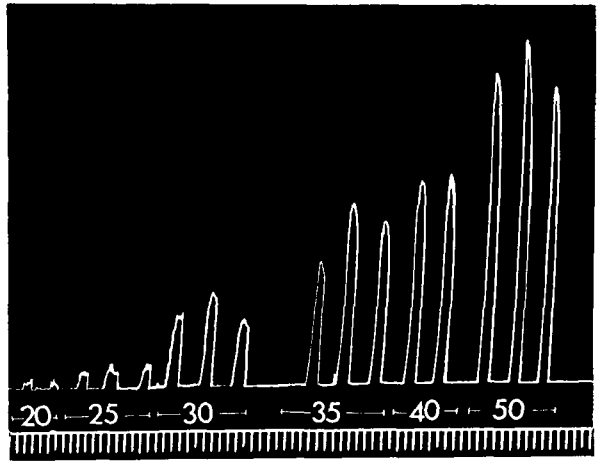

FIG. 1. Guinea-pig isolated ileum. Bath volume: 20 ml. Temperature: 37·5°. Contractions evoked by guanoxan (20, 25, 30, 35, 40 and 50 μg—total doses) added to the bath. The interval between each contraction was 60 sec. Note the dose-effect relation and the absence of tachyphylaxis.

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The effect of the chronic administration of sodium barbitone on the exploratory behaviour of rats

SIR,—Contrary to previous experience with rats (Leonard, 1967) it now appears that the chronic administration of sodium barbitone affects the reward-motivated rather than fear-motivated behaviour, and therefore it was of interest to investigate the action of the barbiturate on unlearned behaviour, for example, exploratory activity. The Y-box test of Steinberg, Rushton & Tinson (1961) appeared to provide a simple, quantifiable method for the determination of exploratory activity.

Female rats (initially 45–55 g) originally of the Wistar strain were housed singly throughout the experiment. Sodium barbitone was added to the drinking water in increasing concentrations over a period of 5 weeks and then withdrawn. The initial dose of barbitone was 100 mg/kg/day and this was increased by increments of 100 mg/kg/day every week. Sodium saccharin (20 mg/100 ml) was added to the drinking water to disguise the bitter taste of the barbiturate and also to the drinking water of the untreated animals. To ensure maximal activity all animals were kept on reversed (12 hr) lighting. The experimental and untreated rats were individually put into the Y-box during the period of barbiturate administration and after its withdrawal as shown in Fig. 1. The total number of entries into the arms of the Y-box in 3 min was recorded. The exploratory activity was measured on the second day after withdrawal of the barbiturate from the experimental rats, as it has been shown previously that this coincided with the period of maximal withdrawal hyperexcitability (Leonard, 1967). All rats were allowed free access to food and water apart from the time during which they were in the Y-box. They were disturbed as little as possible and the experiment was conducted in the room in which they were housed. A diffuse red light enabled the animals to be observed during the time in which they were in the Y-box.

The results (Fig. 1) show that sodium barbitone does not affect the exploratory behaviour and that familiarity with the Y-box does not lead to a noticeable reduction in exploratory activity since the mean response of the untreated animals did not change appreciably during the course of the experiment. When the barbiturate was withdrawn the mean number of entries was reduced by about 70% and was still significantly reduced 4 weeks later. This post-withdrawal depressant effect is surprising because apart from the hyperexcitability and occasional spontaneous convulsions that occurred during the first few