The Effect of Terbutaline (PINN) 1-(3.5-Dihydroxyphenyl)-2-(t-Butylamino)-Ethanol on the Choledochoduodenal Sphincter

Experimental evidence has been reported in favour of the existence of β-adrenergic receptors in the terminal part of the common bile duct (BENZI et al.[1], CREMA et al.[2], DARDIK et al.[3]). When these β-receptors are stimulated with isoprenaline, a relaxation of the sphincter of Oddi takes place. According to LANDS et al.[4,5], different kinds of β-receptors can be distinguished, β-1 (active in cardiac acceleration, small intestine relaxation) and β-2 (active in bronchodilatation). A selective β-2 stimulating compound, terbutaline (PINN) 1-(3, 5-dihydroxyphenyl)-2-(t-butylamino)-ethanol has been shown to have marked bronchodilating activity in doses that produce minimum effects on the heart, whereas isoprenaline, active on both β-1 and β-2 receptors, shows strong cardioactivity in bronchodilating doses (BERGMAN et al.[6], PERSSON and OLSSON[7], PERSSON and JOHNSON[8]). The question of the nature of the β-receptors in the terminal part of the common bile duct prompted the present study on the effect of terbutaline on the sphincter of Oddi.

Young healthy cats weighing at least 2.0 kg were used. After being deprived of food, but not water, for 24 h, they were anaesthetized with pentobarbital 40 mg/kg i.p. The terminal portion of the common bile duct was isolated and cannulated towards the duodenum. The hepatic part of the bile ducts was drained to prevent distension. The pressure was continuously recorded during constant rate saline perfusion through the choledochoduodenal junction. Duodenal pressure was simultaneously recorded by the open tip technique. Details of the experimental set-up have been published elsewhere (LIEDBERG and HALABI[9]). Heart rate was recorded in all experiments, and blood pressure by arterial cannulation in some.

A rhythmic activity independent of duodenal motility was found in the unstimulated sphincter. The i.v. injection of terbutaline constantly depressed the sphincter activity and decreased the resistance to flow through the sphincter. Of 25 cats, 20 responded in this way to terbutaline in the dose range 0.5–4.0 µg/kg, the other 5 responded similarly to 5–10 µg/kg. Isoprenaline 0.5–5.0 µg/kg had a similar effect on the sphincter, but differed markedly from terbutaline in the effects on heart rate and intestinal activity (Figures 1 and 2).

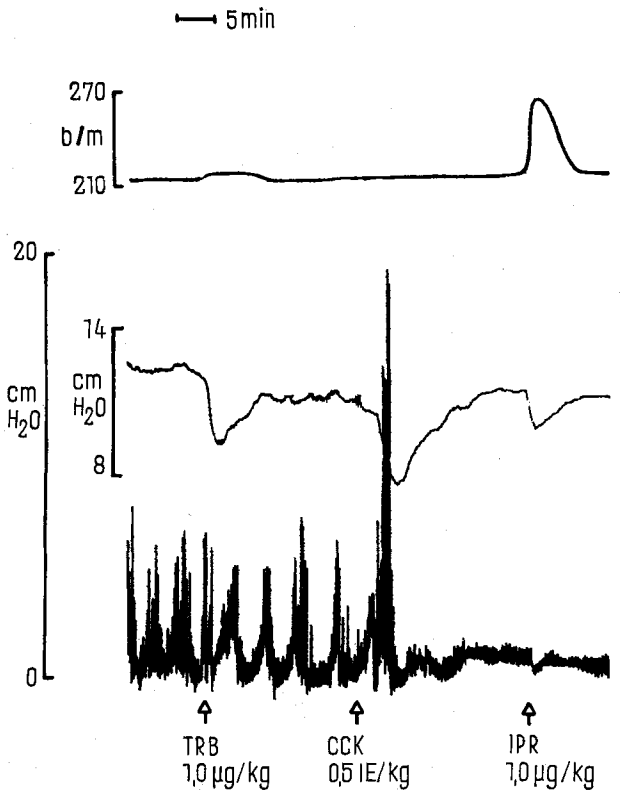

Fig. 1. Cat, 2.0 kg. Upper curve heart rate (beats/min), middle curve common duct pressure during constant rate infusion of saline 0.2 ml/min, lower curve duodenal pressure. Terbutaline (TRB) 1.0 µg/kg relaxes the sphincter with minimum effect on heart rate and duodenal pressure. CCK relaxes the sphincter and stimulates the duodenum. Isoprenaline (IPR) 1.0 µg/kg relaxes the spincter and produces marked tachycardia.

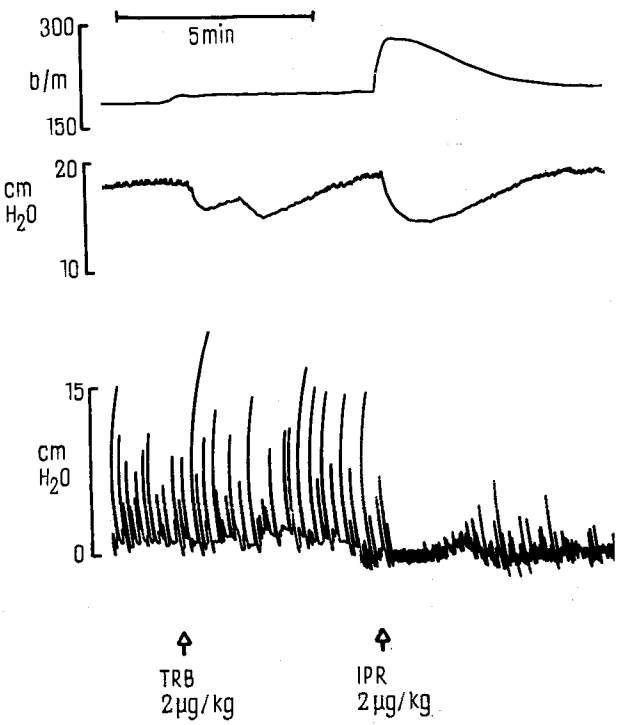

Fig. 2. Cat, 3.3 kg. Terbutaline (TRB) 2.0 µg/kg relaxes the sphincter (middle curve) with minimum effects on heart rate (upper curve) and duodenal motility (lower curve), whereas isoprenaline (IPR) 2.0 µg/kg produces both tachycardia and inhibits duodenal motility.

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Cholecystokinin (CCK) in most cats increased the intestinal activity and relaxed the sphincter (Figure 1). Isoprenaline relaxed both sphincter and intestine, whereas terbutaline relaxed the sphincter with negligible effects on the intestine (Figures 1 and 2). These results support the conception of a choledochoduodenal junction operating independently of the intestine. The effect of terbutaline on the sphincter of Oddi, compared to its slight effect on the heart and the small intestine, indicates that these organs contain β-receptors that differ from those found in the sphincter of Oddi[10].

Zusammenfassung. Die β-Rezeptoren vom Sphinkter von Oddi werden durch Terbutalin selektiv stimuliert.

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[10] Work partly supported by grants from Svenska Sällskapet för Medicinsk Forskning.

Adriamycin: Toxicity Data

Adriamycin is a new antibiotic possessing both in vivo and in vitro antitumoral activity[1], obtained in these laboratories by cultivation of *Streptomyces peucetius var. caesius*; it has a structure similar to that of daunomycin being in fact 14-hydroxydaunomycin[2,3]. The initial clinical tests[4], which are now in progress, confirm the antitumoral activity in humans affected by leukemia or by malignant neoplasia of various types.

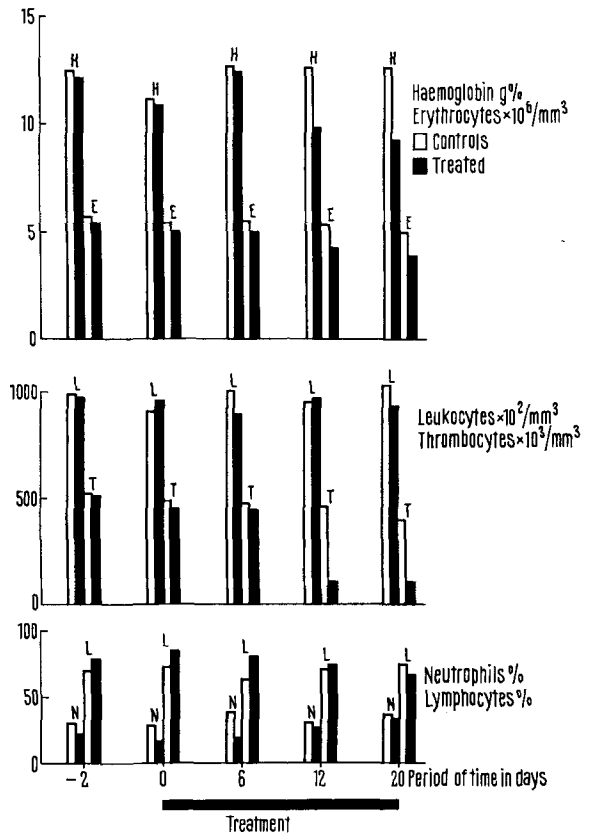
The acute toxicity has been determined in albino mice (Swiss strain) by means of i.v. injections of doses of adriamycin hydrochloride, increasing by a factor of 1.25, the doses being given to each of a group of 10 mice (5 males + 5 females).

The mortality rate, constant after 30 days from treatment, and the effect on body growth are reported in Table I; the statistical analysis of the death-rate, calculated by the method of the probits[5], gives a DL_{50} of 20.8 mg/kg. Mortality begins a few days after injection and is complete within 20 days; during this period the animals lose weight, show signs of anorexia and eventually of haematic diarrhea.

The subchronic toxicology has been studied in the rabbit; in a group of 6 animals (3 males + 3 females) adriamycin hydrochloride was administered i.v. at doses of 1 mg/kg (in 0.25 ml of physiological solution) every other day, for 3 weeks. Another 6 rabbits, kept as controls, were treated analogously with physiological solution only.

During the course of the tests there were no deaths, cases of haematic diarrhea nor any signs of clinical toxicity. Even the ECG does not reveal evident alterations in cardiac pattern; only the frequency is slightly higher (316 pulsations/min in treated rabbits compared with 235 in the controls). Only in the males is there a slight reduction in body weight increase.

Adriamycin provokes a slight normochromic anaemia with thrombocytopenia (Figure) without variation of prothrombin and coagulation time and of the number of



Adriamycin. Subcronic toxicity in rabbits. Mean haematological values before and during treatment.

Table I. Adriamycin. Acute toxicity in mice

Dose[a] mg/kg	No. of mice	No. of dead	LD_{50} mg/kg	Fiducial limits for $P = 0.05$	Body weight after days: 0	8	16	30
Controls	10	0	–	–	21.8	23.1	25.3	27.4
16	10	2	21.1	18.48–24.00	21.4	18.5	22.2	27.0
20	10	3			21.7	18.0	20.5	24.3
25	10	8			21.7	14.9	18.1	22.0

[a] Adriamycin was injected i.v. in 0.5 ml of distilled water, over 15 sec.

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