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The Effect of Digitalis on Regional Ischaemia of the Rat Small Intestine

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ABSTRACT

Research in recent years has shown that under certain conditions digitalis has a strong vasoconstrictive effect in the splanchnic region. This may imply that in cases of mesenteric ischaemia, digitalization may inhibit a collateral circulation necessary for restoration of the intestinal function. In this investigation the effect of digitoxin on the exchange circulation of the small bowel mucosa was studied in rats with induced regional ischaemia of the intestine. On analysis 30 min after establishment of the ischaemia a statistically significant negative effect of digitoxin was observed.

INTRODUCTION

It has long been known that digitalis has an effect on peripheral blood vessels (6, 10). Until recently this has been considered of little clinical importance, but in the last few years it has received new interest. The constrictive effect of digitalis on arterioles and veins has been studied by several authors (15, 1, 2). That digitalis has a particularly marked effect on the splanchnic vessels has been pointed out by Ferrer et al. (8), Harrison et al. (9) and Danford (5). Cohn and collaborators (4) showed that the peripheral vascular effects of digitalis may be of greater clinical significance than has been previously believed. They found that digitalization could increase the mortality of patients in shock, and assumed this to be due to its peripheral vascular effects.

In acute mesenteric infarction, clearcut vascular occlusion is often not found, either angiographically or at pathology. In some clinical materials these cases comprise up to 50% of ischaemic intestinal catastrophes (14, 3). The origin of the probably causative vascular spasm may vary, but most of these patients seem to have received high doses of digitalis. It has therefore been suspected that in many cases the vasoconstrictive effect of digitalis may be the underlying mechanism of this often fatal mesenteric vascular spasm (17, 20).

The aim of the present investigation was to determine whether digitalization can be hazardous even in cases with more regional small bowel ischaemia. Does digitalis impair the collateral circulation necessary for restoration of the intestinal function, and thus prevent healing of the ischaemic damage?

MATERIAL AND METHODS

Male Sprague-Dawley rats weighing 200–250 g were used. The animals were strictly standardized as regards iodine metabolism and iodine was added to their drinking water both before and during the experimental period.

To produce standardized ischaemia of the small intestine a defined number of mesenteric end arcades (mes end arc) were ligated. The ligature material was 5–0 cardiovascular silk (Ethicon). The first ligature was applied on the 6th mes end arc counted from the ileocaecal angle, and a further 7 or 11 mes end arc, in the proximal direction, were then ligated. At the same time a central loop in the devascularized intestinal segment was marked with silk threads. These were placed around the intestine without affecting the terminal blood vessels. The length of the loop always corresponded to the extent of 2 mes end arc.

The mucosal circulation was assessed by a technique described by Nylander & Wikström (13), based on the fact that the passive absorption, i.e. the diffusion of a given substance from an intestinal loop of defined size, is an expression of the effective exchange circulation in the mucosa of the intestinal segment. A radioactive iodine isotope (NaI^{131}) was used as the test substance. At the time of analysis the previously indicated intestinal loop (2 mes end arc) was ligated and the test dose was deposited into its lumen by transmural injection. The pylorus was tied off to prevent gastric contents from passing into the small intestine. After 30 min the rat was killed with ether. The abdomen was opened and the stomach was ligated at the cardia and resected. The isolated intestinal loop into which the test substance had been deposited was also resected. The radioactivity in the stomach, the intestinal loop and the whole body (thus excluding the stomach and test loop) was recorded.

Table I. *Series I. Characteristics of the material and percentage distribution of the radioactive dose (NaI^{131}) 30 min after its deposition in the isolated loop*

Mean values with S.E. LC=laparotomy control group

Experimental group	*n*	Body weight (g)	Percentage of dose in		
			isol. loop	stomach	body
LC	20	231±3.8	26.1±2.2	12.0±0.8	61.9±1.9
11 mes end arc, untreated	20	253±0.8	50.3±2.4	4.9±1.0	44.8±2.7
11 mes end arc, digitoxin-treated	20	241±5.5	63.2±2.2	3.4±0.6	33.4±3.0

Two series of experiments were performed. In the first series (series I) an intravenous injection of digitoxin (0.1 mg/100 g body weight) was given and 2 h later small bowel ischaemia comprising 11 mes end arc was produced. The exchange circulation in the ischaemic intestinal segment was analysed 30 min after establishment of the ischaemia. This series also included two control groups, one with small bowel ischaemia but not treated with digitoxin (untreated controls) and one without ischaemia, in which the exchange circulation was analysed 30 min after a laparotomy (laparotomy controls).

In the second series (series II) the small bowel ischaemia comprised 7 mes end arc and following establishment of the ischaemia a subcutaneous injection of digitoxin (0.1 mg/100 g body weight) was given daily for 14 days, after which the exchange circulation was analysed. The series also included an ischaemic group (7 mes end arc) treated with physiological saline instead of digitoxin (untreated controls).

RESULTS

In series I (Table I) all animals survived. In the ischaemic animals (11 mes end arc) treated with digitoxin 50% of the given radioactive test dose remained in the isolated intestinal loop at the end of the analytical period. The animals treated previously with digitoxin showed diminished absorption of radioiodide from the intestine, 63% of the dose remaining in the isolated loop. In the laparotomy controls the absorption was considerably better, and only 25% of the radioactivity was found in the intestine at the end of the analytical period.

In series II (Table II) with the more moderate ischaemia (7 mes end arc) 4 of 22 animals in the digitoxin-treated group died. All untreated controls survived. Two weeks after the ischaemia had been produced the untreated group had increased their body weight by 10%, whereas the weight of the digitoxin-treated animals was unchanged. In the untreated group 37% of the test dose remained in the isolated intestinal loop. In the group with the same degree of ischaemia but treated with digitoxin for 2 weeks the corresponding amount was 42%.

DISCUSSION

The observed deterioration of the exchange circulation in the acute experiments and on analysis two weeks after establishment of the intestinal ischaemia is in agreement with previously reported findings (13, 18). The exchange circulation of the intestinal wall is a function of the mucosal circulation and of the permeability of the mucosa and vessel walls (21). Wikström (18) assumed that the

Table II. *Series II. Characteristics of the material and percentage distribution of the radioactive dose (NaI^{131}) 30 min after its deposition in the isolated loop*

Mean values with S.E.

Experimental group	*n*	Mortality	Body weight (g)		Percentage of dose in		
			Initial	Final	isol. loop	stomach	body
7 mes end arc, untreated	20	–	252±4.6	271±2.6	37.3±4.3	8.5±1.1	54.2±3.6
7 mes end arc, digitoxin-treated	22	4	243±3.6	243±5.0	41.6±3.7	10.7±1.0	47.4±3.2

impaired exchange circulation in the acute stage is due mainly to a reduction of the mucosal circulation, whereas two weeks after the ischaemic damage has been produced secondary fibrosis in the intestinal wall also plays an important role. A decisive factor for the degree of disturbance of the intestinal wall function following intestinal ischaemia is the availability of a collateral circulation immediately after establishment of the ischaemia (12). In view of the fact that digitalis has been reported to have a marked vasoconstrictive action in the splanchnic region in severe intestinal ischaemia (5), we considered that digitalization might have a deleterious effect on the so essential collateral circulation to the ischaemic small bowel segment.

The result of the acute experiment in the digitalis-treated group indicates that the mucosal circulation was, in fact, impaired. In the digitalis-treated group analysed 2 weeks after establishment of the ischaemia, however, there was no such impairment that might suggest that digitalis inhibited restoration of the intestinal circulation. The extent of the ischaemic damage was smaller, however, in the latter group than in the acute experiments, and it cannot therefore be excluded that with more extensive ischaemia digitalization might have this effect.

The acute experiments indicate that digitalis can impair a collateral circulation arising from adjacent healthy intestine, by constricting the central mesenteric vessels, or that it can have a direct constrictive effect on the small vessels in the ischaemic intestinal tissue. Our observations correspond to findings in dog experiments (16) in which ouabain caused extremely high mesenteric vascular resistance in disturbed metabolic conditions such as shock.

In a smaller study the immediate effect of high doses of digitoxin on the systemic circulation was examined. No change in the arterial blood pressure was noted 2 hours after the digitoxin injection. This speaks against the possibility that the observed impairment of the mucosal circulation could have been caused by a toxic effect of digitoxin on the myocardium.

In the long-term experiments there was some increase in mortality among the digitalis-treated animals. Lefer et al. (11) demonstrated in dogs that digitalis markedly reduced the arterial blood flow in the splanchnic region in haemorrhagic shock. They considered that this ischaemia could lead to a release of a myocardial depressant factor with a serious effect on the myocardial function. Such an indirect depressive effect of digitalization on the myocardium in intestinal ischaemia could explain the increased mortality in the digitalis group in our experiments. However, it cannot be excluded that the increased mortality and the absence of a body weight increase in the digitalis group represent toxic effects of long-term treatment with high digitalis doses such as were used in these experiments. In long-term rat experiments with the same digitalis dosage as was used here, however, Williams & Braunwald (19) demonstrated a positive inotropic effect on the myocardium and at the same time found that this dose gave no mortality or loss of weight in intact, non-operated animals. Falkenhahn (7) used the same high digitoxin doses with a good effect in tolerance experiments in rats.

The present acute experiments on rats support previous observations in both clinical studies (17) and animal investigations (16) that digitalis can aggravate an acute mesenteric ischaemia and indicate that discontinuation of digitalis therapy should be considered in the presence of both regional and more extensive intestinal ischaemia.

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