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Influence of chronic bisacodyl treatment on the effect of acute bisacodyl on water and electrolyte transport in the rat colon

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Excessive or unnecessary taking of laxatives leads to a vicious circle with perpetuation of laxative abuse and increase of laxative dosage, accompanied by severe clinically evident disturbances. It was investigated in rats whether chronic administration of bisacodyl reduces the effects of *acute* bisacodyl administration on net water and electrolyte flux in the rat colon transport in-vivo. After chronic pretreatment with bisacodyl had been given for 21 days (3 mg and 10 mg kg^{-1} day^{-1}), net water and sodium absorption was found to be decreased whereas potassium secretion was increased. After 21 days of pretreatment, the effect of *acute* bisacodyl (10 μg ml^{-1} intraluminal) on net water and sodium transport was reduced whereas the effect on potassium secretion remained unchanged. Serum and erythrocyte levels of sodium and potassium remained unchanged in chronically pretreated rats. Serum aldosterone levels were enhanced two fold. It is concluded that under the experimental conditions described, chronically administered bisacodyl leads to elevated serum aldosterone which counteracts the effect of bisacodyl on net water and sodium transport but acts synergistically with bisacodyl on the effect on potassium loss.

The diphenolic laxative bisacodyl inhibits absorption of water, sodium and chloride and at higher concentrations, it converts absorption to secretion. Potassium secretion is enhanced by bisacodyl. These effects result in an increased intestinal fluid volume (Forth et al 1966; Nell et al 1971; for further references see Binder 1977; Gaginella & Bass 1978).

Several mechanisms are supposed to be involved in the laxative effect of bisacodyl. Inhibition of the Na^+-K^+-activated adenosine-triphosphate (Na-K^+-ATPase) indicates an inhibition of the active sodium absorption (Chignell 1968; Schreiner et al 1980; Rachmilewitz et al 1980). Stimulant laxatives like bisacodyl also have been shown to increase mucosal permeability (cf. Binder 1977; Gaginella & Bass 1978). Like other laxatives, bisacodyl stimulates PGE-release. The effect on fluid secretion is inhibited by indomethacin, indicating an involvement of PGE-release in the generation of active fluid secretion (Beubler & Juan 1978a, b; Beubler & Juan 1979; Rachmilewitz et al 1980). Finally, morphological changes induced by bisacodyl may also contribute to the effect of bisacodyl on fluid secretion (Saunders et al 1977; Meisel et al 1977). The laxative effect declines after laxative abuse in humans and several morphological and functional alterations are reported following the abuse of laxatives (Cummings 1974; Meisel et al 1977; Riemann et al 1980; Schreiner et al 1980).

In the present investigation the effect of bisacodyl on fluid, sodium and potassium transport in the colon in-vivo was studied in chronically bisacodyl-treated rats.

Methods

Animals. Female Sprague Dawley rats (Himberg, strain OFA, S.D. SPF, 200 ± 10 g) deprived of food 24 h before the experiment, but with free access to water, were fed with normal diet or diet containing different amounts of bisacodyl for 21 days. From the amount of food taken, an average bisacodyl-dose of 3 mg kg^{-1} day^{-1} and 10 mg kg^{-1} day^{-1} was calculated.

Preparations. In rats under urethane anaesthesia (1·25 g kg^{-1}), the entire colon was rinsed with 20 ml warm 0·9% NaCl (saline) solution in-situ. After an interval of 30 min, the colon was filled in-situ with 2 ml Tyrode solution or Tyrode solution containing bisacodyl (10 μg ml^{-1}) and tied off (Forth et al 1966). After 60 min, the colon was removed and weighed (weight A). The fluid remaining in the loop was drained and analysed for sodium and potassium (Flame photometer, Lange). The remaining tissue was also weighed (weight B). Net water transport was obtained from the difference between weight A and weight B after subtraction of the 2 ml Tyrode solution with which the colon was filled. A negative value denotes net absorption and a positive value net secretion.

Net water transport was expressed as μl per g wet weight of colon h^{-1}. Net transport of sodium and potassium was expressed as μmol per g tissue h^{-1}. After the colon had been removed, blood samples were taken from the carotid artery. Whole blood and serum were analysed for sodium and potassium. Sodium and potassium in erythrocytes was calculated from the concentration in whole blood and in the serum, taking the haematocrit into account. Aldosterone was determined in the serum by radioimmunoassay (CIS-radioactive products, France–Belgium–Italy).

The drugs used were: bisacodyl (Boehringer, Ingelheim, FRG; Urethane (Merck, Darmstadt, FRG).

Statistics. Statistical significance of the differences of the means was evaluated by the two sample Student's *t*-test; all the values given are means ± s.e.m.

Results

Fluid and electrolyte transport. In normal rats, acute

bisacodyl (10 μg ml^{-1}, intraluminal) reversed net absorption of fluid and sodium to net secretion and enhanced potassium secretion (Fig. 1). In rats pretreated with bisacodyl 3 mg kg^{-1} day^{-1} for 21 days net fluid and sodium absorption were reduced compared with normal rats and potassium secretion was enhanced ($P < 0.05$). The effect of acute bisacodyl on net transport of fluid and sodium in absolute terms was the same as in normal rats. The effect of acute bisacodyl on potassium secretion was enhanced in pretreated rats compared with the effect in normal rats ($P < 0.05$) (Fig. 1).

In rats pretreated with 10 mg kg^{-1} day^{-1} bisacodyl for 21 days, net fluid and sodium absorption again were reduced compared with normal rats ($P < 0.05$) and potassium secretion was enhanced ($P < 0.05$). The effect of acute bisacodyl on net transport of fluid and sodium in absolute terms was reduced and the effect of potassium secretion was enhanced compared with normal rats ($P < 0.05$) (Fig. 1).

Electrolytes and aldosterone in the blood. Sodium and potassium were measured in the serum and in the erythrocytes of normal rats and of rats chronically pretreated with bisacodyl (10 mg kg^{-1} day^{-1}, 21 days). No differences were found in bisacodyl pretreated rats compared with normal rats (Table 1).

Aldosterone was measured in the serum of normal rats and in rats pretreated with bisacodyl (10 mg kg^{-1} day^{-1}, 21 days). Chronic bisacodyl pretreatment induced a more than two fold increase in serum aldosterone (Table 1).

Table 1. Sodium and potassium in serum and erythrocytes (ery) and aldosterone in serum of normal rats and in rats pretreated with bisacodyl (10 mg kg^{-1} day^{-1}, 21 days).

	Normal	Pretreated	P
Na^+ (μmol ml^{-1} serum)	142 ± 0·43 (20)	143 ± 0·92 (20)	n.s.
Na^+ (μmol ml^{-1} ery)	34 ± 1·63 (20)	33 ± 1·88 (20)	n.s.
K^+ (μmol ml^{-1} serum)	3·8 ± 0·15 (20)	3·9 ± 0·07 (20)	n.s.
K^+ (μmol ml^{-1} ery)	110 ± 1·11 (20)	110 ± 1·34 (20)	n.s.
Aldosterone (ng ml^{-1} serum)	1208 ± 45 (12)	2572 ± 244 (12)	$P < 0.01$

x̄ ± s.e.m., n.s. = not significant, ( ) = number of experiments.

Table 2. Summary of acute bisacodyl-induced changes (difference between the mean of the control values and the effect of acute bisacodyl) in normal rats and in rats pretreated with bisacodyl (3 mg kg^{-1} day^{-1}; 10 mg kg^{-1} day^{-1}, 21 days).

	H_2O μl g^{-1} h^{-1}	Na^+ μmol g^{-1} h^{-1}	K^+ μmol g^{-1} h^{-1}
Normal rats	1372 ± 55	206 ± 32	6·7 ± 1·2
Bisacodyl (3 mg kg^{-1} day^{-1})	1030 ± 89*	138 ± 20*	9·1 ± 2·7
Bisacodyl (10 mg kg^{-1} day^{-1})	706 ± 60**	118 ± 13**	10·3 ± 3·3

x̄ ± s.e.m., *$P < 0.01$ and **$P < 0.001$ compared with the effect in normal rats.

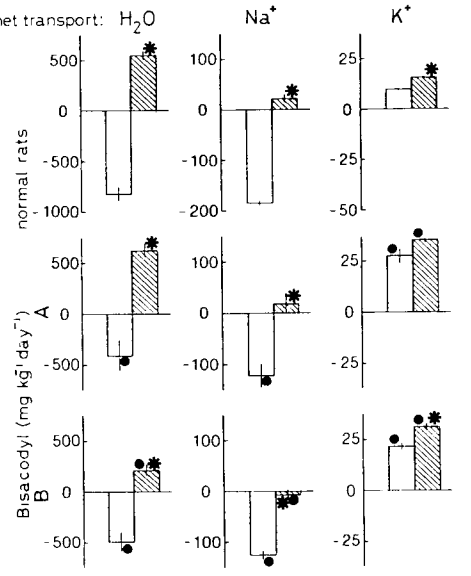

FIG. 1. Effects of acute bisacodyl (10 μg ml^{-1}, intraluminal) on net transport of fluid (μl g^{-1} h^{-1}) sodium and potassium (μmol g^{-1} h^{-1}) in the colon in vivo in normal rats (n = 30) and in rats pretreated for 21 days with bisacodyl (A, 3 mg kg^{-1} day^{-1}, n = 20, and B, 10 mg kg^{-1} day^{-1}, n = 10). Negative values denote net absorption, positive values net secretion. Open columns: controls. Cross hatched columns: acute bisacodyl. The values represent the mean ± s.e.m. *$P < 0.05$ compared with controls; •$P < 0.05$ compared with the corresponding value in normal rats.

Discussion

The aim of the present study was to obtain more information about the pathophysiological principles of altered intestinal fluid and electrolyte transport during chronic laxative administration.

The effects of bisacodyl on net transport of fluid, sodium and potassium in normal rats in the present study are similar to the results obtained earlier (Forth et al 1966; Beubler & Juan 1978a, b; Schreiner et al 1980).

Table 2 shows a summary of bisacodyl induced changes of fluid, sodium and potassium transport in normal rats and in rats pretreated with bisacodyl. Each value represents the difference between the mean of the control values and the effect of acute bisacodyl in the corresponding group. Pretreatment with bisacodyl significantly reduced the effect of acute bisacodyl on fluid and sodium transport in both groups of pretreatment. The reduction was more pronounced in the group pretreated with 10 mg kg^{-1} day^{-1} than in the group pretreated with 3 mg kg^{-1} day^{-1}, indicating a dose-dependency of pretreatment on the depressed effect of acute bisacodyl. The effect of acute bisacodyl on potassium secretion in the two groups was not significantly different from the effect in normal rats but tended to be enhanced.

To find out whether sodium and potassium loss during chronic bisacodyl pretreatment causes redistri-

bution of electrolytes between intracellular and extracellular fluid spaces, sodium and potassium were measured in serum and erythrocytes of normal and chronically pretreated rats. Sodium and potassium levels in the serum and in the erythrocytes were not changed in rats pretreated with bisacodyl for 21 days (10 mg kg^{-1} day^{-1}, Table 1).

In man, hypokalemia and elevated aldosterone serum levels have been observed after several years of laxative abuse (Wolff et al 1968). Continuous administration of aldosterone for several days did not cause extrarenal potassium loss nor was there any indication that potassium was redistributed between the intracellular and extracellular fluid spaces (Dawborn 1969). In the present experiments, serum aldosterone was elevated two-fold in chronically bisacodyl-treated rats compared with normal rats.

These elevated aldosterone serum levels may be the result of the sodium loss during pretreatment (Wolff et al 1968). This secondary hyperaldosteronism is not accompanied by hypokalemia in our experiments, probably due to the short time of treatment with bisacodyl compared with secondary hyperaldosteronism in man, which occurs after years of laxative abuse. Furthermore, potassium in the laboratory chow may compensate potassium loss caused by bisacodyl.

The elevated aldosterone levels are expected to enhance sodium absorption in the colon (Dolman & Edmonds 1975; Edmonds 1976; Frizzell & Schultz 1978). This effect cannot be seen in the present experiments, because fluid, sodium and potassium transport in the control experiments in bisacodyl-pretreated rats are probably still influenced by the slowly eliminated bisacodyl (Ferlemann & Vogt 1965). However, it is quite likely that the elevated levels of aldosterone were responsible for the diminished effect of acutely administered bisacodyl on sodium transport in rats pretreated with bisacodyl. Concerning potassium, elevated serum aldosterone acts synergistically with bisacodyl in increasing potassium secretion (Edmonds 1976).

In conclusion, chronic administration of bisacodyl reduces the effect of acute bisacodyl on net water and sodium secretion but not on net potassium secretion, which tends to be enhanced. In man, chronic abuse of laxatives leads to hypokalemia (Cummings 1974; Riemann et al 1980), an effect which cannot be observed in the rat after relatively short treatment with bisacodyl. The experiments suggest, however, that the vicious circle, which causes man to take higher and higher doses of laxatives, starts with enhanced aldosterone serum levels.

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