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EFFECT OF THE ANTIBIOTIC, NORFLOXACIN ON BILE FLOW IN GUINEA PIGS

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SUMMARY

In the present study, the effect of the antibiotic, norfloxacin on the bile flow was investigated in anaesthetized guinea pigs. Intramuscular administration of the drug in a dose of 5 mg/kg body weight resulted in a 28% decrease in the bile flow. The cholestatic effect ofnorfloxacin was not counteracted by administration of the choleretic drug, clanobutin sodium. Meanwhile administration of caffeine citrate significantly counteracted the cholestatic effect of norfloxacin. Moreover, norfloxacin has an inhibitoryeffect on the motility of isolated rabbit duodenum and induced relaxation ofthe isolated guinea pig ileum.

INTRODUCTION

Norfloxacin, a fluoroquinolone carboxylic acid, is a recently introduced antibiotic with a broad spectrum antibacterial activity commonly used in human and all animal species. It is commonly used in poultry for treatment of colibacillosis and samlonelosis (Ito et. al., 1980). Its efficacy for treatment of several problems as urinary tract infections, gonorrhea, and respiratory tract infections was described (Banerfeind and Ullman, 1984 and Wolfson and Hooper, 1985). The pharmacokinetic properties and side effects of norfloxacin were reported by Saito et. al., (1981) and Christ et. al., (1988). Norfloxacin inbibit gastric acid secretion in rats (Blandizzi et. al., 1991).

Several antibiotics such as erythromycin, actinomycin and nalidixic acid induced a state of cholestasis (Gumucio et. al., 1972 and Goodman and Gilman, 1975). No available data was abtained about the effect of norfloxacin on the bile flow. So the objective of the present work was to investigate the effect of norfloxacin on the bile flow in guinea pigs. Moreover, the effect of the choleretic drug, clanobutin sodium (Bykahepar®) and caffeine citrate administered after norfloxacin was investigated also.

MATERIALS AND METHODS

1- Effect of drugs on bile flow:

Fifteen mature male guinea pigs weighing 500-700 g were used. Animals were divided into 3 equal groups (5animals / group) and food water were provided ad libitum. Animals in group 1 were anaethetized by ethyl-carbamate (urethane, BDH) at a dose of 1.5 mg/kg intraperitonially the technique for studying the bile flow was performed according to the method described by Salib et. al., (1981). A median incision of 2-3 cm was below the chest, the duodenum was displaced from the abdominal cavity and the bile duct was exposed and cannulated by a polyethelene cannula. The basal bile flow was collected in glass watch every 15min for 90 min. The amount of bile was accuretly measured by a tuberculin syringe. Norfloxacin (5% solution, Cenavisa S/A,) was injected then the bile was collected every 15 min. for 90 min. Then, animals were injected with saline and the bile was collected for the same period.

Animals in group 2 were similarly trated as in group 1 except instead of saline injection, clanobutin sodium (Bykahepar®, Byk & Gulden konstan2, Germany) was administered i.m. in adose of 25mg/kg.

Animals in group 3 were similarly treated as group 1 and caffeine citrate (Sigma Chemical Company, USA) was administered S. C. in a dose of 50 mg/kg instead of saline.

All drug doses for man were calculated for guinea pigs according to Paget and Barnes, 1964. The percent change in biliary scretion (A) was calculated from the :formula

$$A = \frac{C_A - C_B}{C_B} \times 100$$

Where; C_B: is the mean value of bile collected every 90 min.

C_A: is the mean value of bile collected every 15 min.
for 90 min. after the test drug was administered.

II- Effect of norfloxacin on isolated smooth muscle preparations:

The effect of norfloxacin on the intestinal smooth muscle was studied on the rabbit duodenum and guinea pig ileum according to the method described by Magnus, (1904) using Tyrod's solution at 37°C.

Data were statisically analyzed by paired student t' test (Snedecor and Cochran, 1980).

RESULTS

1- Effect of drugs on bile flow:

A single i. m. injection of norfloxacin resuled in a significant ($P<0.05$) decrease in the mean bile flow compared to the basal value. Approximately 28% decrease in the bile flow was occured (table 1). Administration of clanobutin sodium after norfloxacin did not improve the bile flow and a further decrease was occured (table 2). Administration of caffeine citrate significantly improved the bile flow which was impaired by norfloxacin (table 3).

II- Effect of norfloxacin on isolated preparations:

Norfloxacin in a dose of 60 Ug/ml resulted in an inhibitory effect on duodenal motility of rabbit. A marked inhibition in the tone was induced by

Table (1): The Effect of norfloxacin (5 mg/kg) on the bile flow.

Guinea pig No.	Before treatment	After norfloxacin	Change %	After Na cl	Change %
1	1.15 ± 0.03	0.79 ± 0.08	-31.3	0.73 ± 0.07	-36.5
2	1.64 ± 0.03	1.24 ± 0.06	-24.4	0.87 ± 0.07	-46.9
3	1.42 ± 0.04	1.03 ± 0.04	-27.5	1.2 ± 0.06	-15.5
4	1.26 ± 0.04	0.87 ± 0.03	30.9	0.62 ± 0.04	50.7
5	1.08 ± 0.04	0.76 ± 0.05	29.6	0.70 ± 0.06	-35.2
	1.31 ± 0.10	0.94 ± 0.08*	-28.7 ± 1.3	0.82 ± 0.10*	-36.9 ± 6.1

* Significant difference ($p<0.5$) compared to the basal value (n=5)+ standard error of the mean.

Table (2): The Effect of clanobutin sodium (25 mg/kg) on the anticholeretic effect of norfloxacin

Guinea pig No.	Before treatment	After norfloxacin	Change %	After Clanobutin Na.	Change %
1	1.15 ± 0.03	0.79 ± 0.08	-31.3	1.64 ± 0.02	-44.3
2	1.64 ± 0.03	1.24 ± 0.06	-24.4	1.02 ± 0.05	-37.8
3	1.42 ± 0.04	1.03 ± 0.04	-27.5	0.92 ± 0.02	-35.2
4	1.08 ± 0.04	0.76 ± 0.05	29.6	0.60 ± 0.01	-44.4
5	1.36 ± 0.05	0.95 ± 0.07	30.1	0.80 ± 0.03	-41.2
	1.33 ± 0.10	0.95 ± 0.09*	-28.7 ± 1.2	0.80 ± 0.08*	40.6 ± 1.8

* Significant difference ($p<0.5$) compared to the basal value (n=5)+ standard error of the mean.

Table (3): The Effect of caffeine citrate (50 mg/kg b. wt) on the anticholeretic effect of norfloxacin.

Guinea pig No.	Before treatment	After norfloxacin	Change %	After Na cl	Change %
1	1.21 ± 0.06	0.81 ± 0.02	-33.3	1.30 ± 0.09	7.4
2	1.05± 0.02	0.73 ± 0.03	-30.5	1.05 ± 0.05	00
3	1.49 ± 0.07	1.09 ± 0.05	-26.8	1.58 ± 0.04	6.0
4	0.96 ± 0.02	0.69 ± 0.04	28.1	1.12 ± 0.07	16.6
5	1.20 ± 0.03	0.85 ± 0.04	29.2	1.36 ± 0.05	13.3
	1.18 ± 0.9	0.83 ± 0.07*	-29.5 ± 1.10	1.28 ± 0.09*	8.7 ± 2.9

* Significant difference ($p<0.5$) compared to the basal value (n=5)+ standard error of the mean.

doses of 100 and 200 Ug/ml (Fig. 1A). A marked relaxation of guinea pig ileum was observed after the addition of 100 and 200 Ug/ml of norfloxacin (Fig. 1B).

An attempt was made to explore the possibility of the muscarinic blocking effect of norfloxacin. It was noticed that norfloxacin (100Ug/ml) failed to evoke the contractile effect of acetylcholine (2Ug/ml) on the isolated guinea pig ileum and rabbit duodenum.

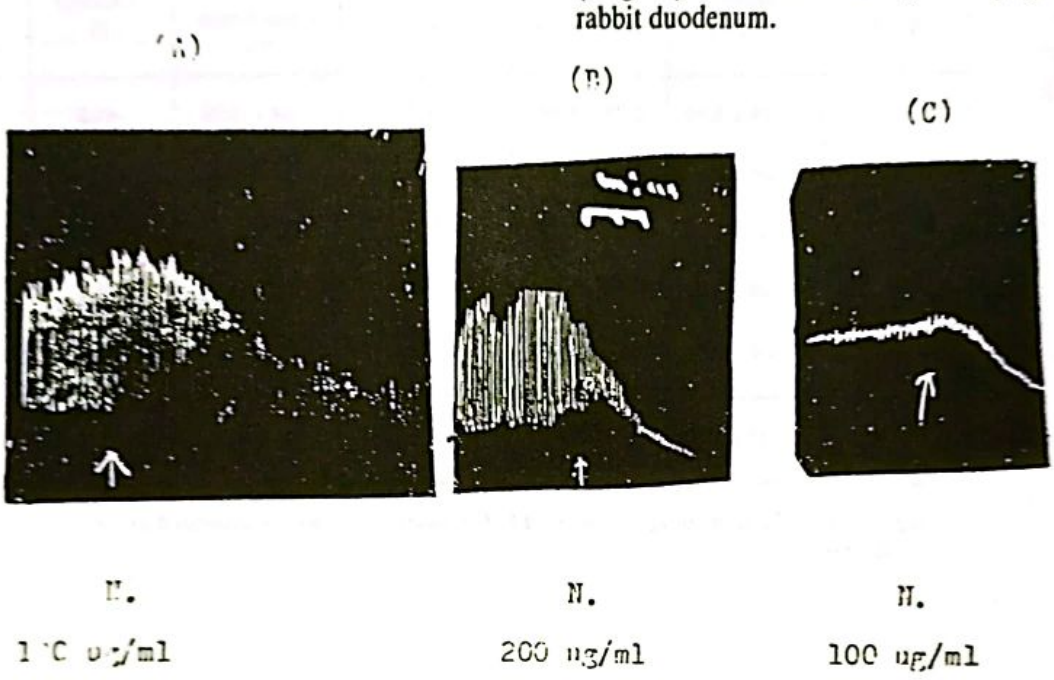

Fig (1 A, B and C): The effect of norfloxacin (N) on the isolated rabbit duodenum (A & B) and guinea pig ileum (C). Note the inhibitory effect of the drug, on the intestinal smooth muscles. Time interval: 1 minute.

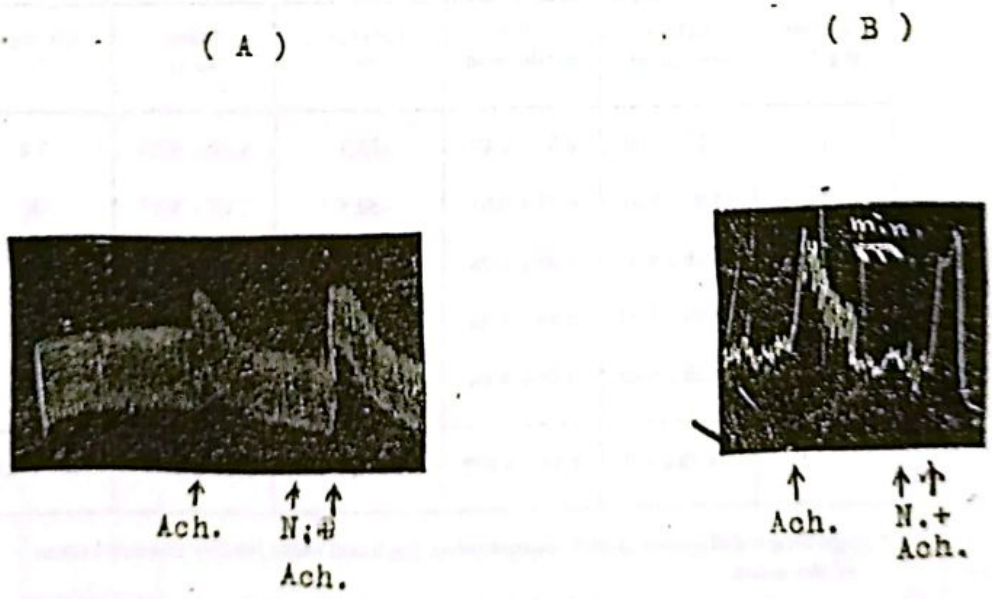

Fig 2(A, B): The effect of norfloxacin (100 Ug/ml) on the acetylcholine, Ach., (2 Ug/ml) induced contraction of the isolated rabbit duodenum (A) and guinea pig ileum (B). Time interval: 1 minute.

DISCUSSION

It is evident from the present study norfloxacin induced a singificant decrease in bile flow in guinea pigs. A decline in biliary secretion could be due to impairment of intrahepatic blood flow (Plaa et. al., 1960, Kendler et. al., 1971, Tavoloni, 1979 and Rene et. al., 1983). The effect of norfloxacin on intrahepatic hemodynamics is unknown. Norfloxacin inhibits the enzyme DNA gyrase in the microorganisms which appear to be essential for DNA replication and subsequently manufacturing of cellular proteins (Crumplen et. al., 1984, Kayser 1985 and Wolfson and Hooper 1985). Protein synthesis inhibitors pervent the stimulation of bile secretion (Simon et. al., 1979). Since the liver appears to be the primary site of norfloxacin metabolism (Christ et. al., 1988), it might possible that protein synthesis could be impaired and subsequently reduced the bile scretion.

The billary scretion controlled to some extent by the stimulation of muscarinic receptors (Fritz and Brooks 1963, Kaminski et. al., 1974, Rene et. al., 1983 and Garwacki et. al., 1988). The muscarinic blocking effect of norfoxacin could be excluded as indicated from this study and previously as observed by (Blandizzi et. al., 1991), they noticed that norfloxacin failed to affect guinea pig ileal contraction evoked by exogenously applied acetylcholine or transmural electrical stimulation.

The choleretic drug, clanobutin sodium failed to counteract the anticholeretic effect of norfloxacin. Clanobutin sodium has been found to cause bile stasis due to its relaxation effect on the gall bladder and constriction of sphincter oddi (Weiner and Taylor 1985). Moreover, administration of clanobutin sodium caused sever distension of gall bladder of guinea pigs, cattle and chickens (Ali et. al., 1987, Ahmed et. al., 1988 and El-Sawi et. al., 1989).

Administration of caffeine citrate significantly counteracted the cholestatic effect of norfloxacin. Xanthines (theophyline and caffeine) are known to increase the bile secretion due to increase CAMP production (Cyclic adenosine monophosphate) in hepatocytes (Javitt, 1976). Moreover elevation of CAMP on the gall bladder inhibits sodium choride reabsorption chloresis attributable to this mechanism may therefore imply an increase in the loss of sodium chloride and water in bile (Frizell et. al., 1974) or may by due to stimulation of secretin hormone release as increasing CAMP production stimulate this hormone (Kaminski and Deshpande 1983). It is not clear whether the cholestatic action of norfloxacin is due to the increase in the rate of sodium chloride and water reabsorption from the gall bladder and / or inhibiting secretin secretion which needs a further study.

It could be concluded that the antibiotic norfloxacin induced a significant cholestatic effect in male guinea pigs.

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