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Original Article

EFFECT OF VINCRISTINE ON MOTILITY AND HISTOLOGY OF GASTROINTESTINAL TRACT OF ALBINO RATS

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ABSTRACT:

Vincristine, an alkaloid of periwinkle plant (vinca) used in the treatment of various malignancies. The experimental group included 36 male wistar albino rats. The animals were divided into four groups of nine animals each. The animals received same dose of vincristine 1 mg/kg b.w. given intragastrically through a fine rubber catheter reaching lower third of oesophagus. Equal number of controls corresponding to each group was given vehicular fluid by the same route.

The animals of Group I, II, III and IV were used for the barium meal study after 1 hr, 5 hr, 12 hr and 24 hr respectively following the intragastric administration of the dose. The design of experiment was such that animal of Group I, II, III and IV were on fasting for 13 hr, 17 hr, 24 hr and 36 hr respectively before being used for the barium meal study.

The observation on animals studied after 1 hr, 5 hr, 12 hr and 24 hr of intragastric dose suggest that the drug initiate slowing down of motility within 1 hr (control group 64.13±11.36cm and experimental group 62.02±4.90cm) and increase motility within five hours of intragastric dose (control group 64.99±6.0 cm and experimental group 68.92±3.40cm).

The observation also shows that between 12-24 hours, the motility of small intestine was decreased. This decrease of intestinal motility in experimental animals as compared to control group was significant ($p<0.01$). The alkaloid reduces the rate of gastric emptying and slowed the transit of test substance through the small intestine.

INTRODUCTION

The vinca alkaloids are naturally occurring or semi synthetic nitrogenous bases extracted from the vinca rosea, a common flowering herb known as periwinkle plant.[1,2] Vincristine is a chemotherapeutic agent derived from Vinca rosea (Linn), which has been widely employed against hematological malignancies and solid tumors since the 1960.[3,4]

They are known to be neurotoxic and produce

severe gastrointestinal toxicity including diarrhea, constipation, and pain in abdomen and vomiting[5-8].

The toxicity of the alkaloids pertaining to the GIT indicates that the alkaloids affect GIT motility which is reflected in kinds of symptoms seen clinically[9-12].

Look in gat the pharmako dynamics a n d pharmacokinetic of vinca alkaloids It becomes clear that the vinca alkaloids are rapidly excreted in large percentage of the dose through the biliary system into the gut lumen.[13,14] This suggests that the vinca alkaloids could reach the GIT tract tissue via the blood stream on administration I/V or topically on excretion through the biliary system.[15] The possibility is that Vinca Alkaloid could influence gut motility while circulating in the circulation as has been shown earlier w h e n t h e a l k a l o i d s w e r e a d m i n i s t e r e d intraperitoneally in the experimental animals.[16]

Thus the objective of the present study was to determine the effect of vincristine on gastrointestinal motility of albino rats.

MATERIALS AND METHODS

Animal

The present study was conducted on 72 albino rats of wistar strain kept under standard laboratory conditions. Rats were caged with 4-5 rats per cage, in a well ventilated room at temperature ranging between 28oC to 32oC with normal day and light. They had free access to freshly prepared diet and water.

Experimental Protocol

The animals were divided in to 4 groups 18 each. Control group was given vehicular fluid while experimental group was given vincristine (dose 1mg/kg b.w.) by intragastric route.

The animals of either group were fasted for specified period ranging from 12-36 hrs before experimentation. The animals had free access to water during the period of fasting.

Barium meal study

Experimental Procedure

Seventy two rats were divided into 4 groups (Group I-

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Group IV) based on the time interval between administration of barium sulphate (GroupI-1hr, GroupII-5hrs, GroupIII-12hrs, GroupIV-24hrs). Each group was further divided into two subgroups, control group and Experimental group, containing 9 rats in each group. Rats in experimental group were administered vincristine intragastrically by the nasogastric tube reaching up to the lower 1/3rd of oesophagus, in the dose of 1mg/kg body weight suspended in normal saline. While rats in control group were given vehicular fluid (0.9%Nacl) in equal volume as that of vincristine suspension given to experimental group.

The fully conscious animal was intubated with firm rubber catheter reaching up to lower third of the oesophagus and 4ml of Barium sulphate suspension in isotonic saline (0.9%w/v) containing 3.2gm of BaSo4 was introduced into the stomach by 5ml syringe. The animals were used for the gastrointestinal motility 30 mins after feeding of the Barium meal.

The abdomen was opened by a midline incision and ligatures were rapidly applied at the esophagogastric, gastro duodenal and the ileocaecal junctions.

The intestine were removed from the abdomen and laid over a board fitted with a scale. The position of the Barium head had been located and measured from the point of gastro duodenal junction. The length of small intestine was measured by the method of Barry et al with some modification. A wooden block with a meter scale was used for the purpose, upper surface of the block was kept continuously wet with 0.9%, w/v, saline (37%). The small intestine extending from the gastro duodenal junction to the ileocaecal junction was laid out on the block closely along the meter scale and given manual stretch gently, on either of its ends, until it was just straight; thereafter the organ was left lying free on the block for one minute. At the end of the period, its total length was measured and then cut open lengthwise, to ascertain accurately the position of barium-head on scale.

Histological studies

Intestinal sample: Tissue sections from small intestine were immediately processed separately for histological study under light microscope.

For light microscopy: 4 samples were randomly selected, 2 from controls and 2 from 24 hours post intragastric Vincristine administration. Sample were fixed in a solution of formalin (10%) and stained with Hematoxylin & Eosin to be examined under light microscope at 40 to 100X magnification.

Statistical analysis

Mean and SE of all the observations were calculated and comparison were done between experimental and control groups by applying student's t test (unpaired).Comparisons of the effect of vincristine on intestinal motility among different experimental groups were done using one way ANOVA.

OBSERVATION AND RESULTS

The results are summarized in Table I and Table II.

After 24 hrs of intragastric dose of Vincristine, the animals showed toxic features with reduction in general activity and decreased appetite. On opening the abdomen, hyperemia of liver and mesentery, friable small intestine and stomach; with distention of stomach in some cases were present. After 2 hrs of drugs administration, histological examination of intestine in light microscopy (40X) showed some disruption of normal morphology and after 24 hrs the intestine revealed hyper activation of mucous secreting cells, intestinal glands and mononuclear cells infiltration & edema in lamina propria with multi hemorrhagic areas. (Fig. 1 and Fig. 2)

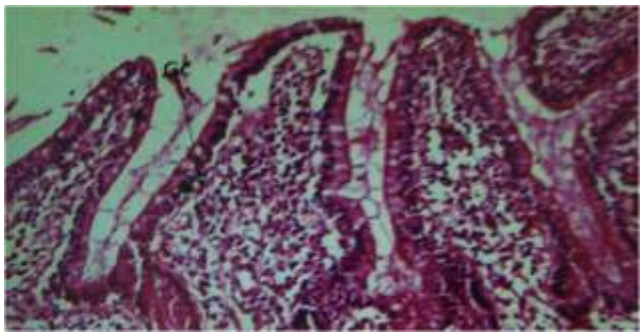

Fig. 1: Light Microscopy in control group.

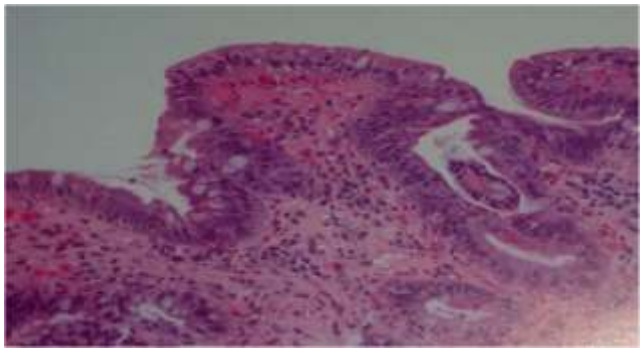

Fig. 2:Light Microscopy in drug group

The observation on animals studied after 1 hr, 5 hr, 12 hr and 24 hr of intragastric dose suggest that the drug

initiate slowing down of motility within 1 hr (control group 64.13±11.36cm and experimental group 62.02±4.90cm) and increase motility within five hours of intragastric dose (control group 64.99±6.0 cm and experimental group 68.92±3.40cm).

The observation also shows that between 12-24 hours, the motility of small intestine was decreased. This decrease of intestinal motility in experimental animals as compared to control group was significant ($p<0.01$). The alkaloid reduces the rate of gastric emptying and slowed the transit of test substance through the small intestine. (Table I)

Table I

Comparisons of effect of vincristine on intestinal motility following intragastric administration of single dose of vincristine (1 mg/kg b.w.) in different groups.

Groups	% length of small intestine (in cm) traversed by BaSO	
	Control (n=9)	Experiment (n=9)
Group I	64.13±11.36	62.02±4.9
Group II	64.99±6.0	68.92±3.4
Group III	71.68±8.49	58.22±6.94
Group IV	78.24±6.74	60.0±1.79

Table II

Comparisons of effect of vincristine on the length of small intestine following intragastric administration of single dose of vincristine (1 mg/kg b.w.) in different groups.

Groups	Length of small intestine (cm)	
	Control (n=9)	Experiment (n=9)
Group I	110.25±4.86	113.5±9.48
Group II	110.77±5.73	114.55± 6.83
Group III	109±7.85	104.77±5.84
Group IV	110±4.30	105± 6.94

DISCUSSION

Vincristine is an antineoplastic drug with a broad spectrum of activity against haematological malignancies and childhood sarcomas1,2 Many toxic effects of vinca alkaloids are now well known including neurological and those on the gastrointestinal tract.[5-7] The neurotoxicity commonly manifest as reduced motility of the intestine resulting in constipation and this neuropathy is predominantly sensory in nature.[12,13]

One of the important pharmacokinetic properties of the vinca alkaloids is their rapid accumulation by intestinal tissue, within minutes after injection intravenously or intraperitoneally. The aggregate concentration of the alkaloid in the tissue further increases rapidly, because of its entry into the intestinal lumen through the biliary route. Though the concentration of the alkaloid builds up quickly, the elimination of it from the intestinal tissue is comparatively a slow process, the drug may persist in the tissue at high concentration for more than 72 hrs. Nearly 60-70% of the administered drug gets excreted through bile into the gut lumen.[16] In some studies delayed feacal elimination of vincristine has been attributed to some degree of paralytic ileus. Enterohepatic circulation and subsequent elimination may also account for its prolonged elimination.

Present histological study shows disruption of normal morphology of intestine after first hour of vincristine administration. Then after 24 hours the intestine revealed hyper activation of mucous secreting cells, intestinal glands and mononuclear cell infiltration and oedima in lamina propria with multi haemorrhagic areas. Bairy KL et al[17] observed significant changes in histological picture of the intestine, where atrophy of villi demonstrating nests and cords of uniform small round cells were observed. Castle M C,et al[18] studied the antimitotic agent(vincristine)have been shown to bound rapidly by tissues rich in tubulin.Vincristine is a powerful inhibitor of mitosis which prevent the normal cellular proliferation from the crypts of the intestine. Mitolo-Chieppa D et al[19] observed marked changes in lamina propria (invasion by leucocytes)and an increase in the numbers of crypts cells arrested in mitosis.

Preliminary study shows that vinca alkaloid affects motor activity of the gastrointestinal tract 20-22 It reduces the rate of gastric emptying and also alters the passage of test meal through the small bowel. The drug showed an early enhancing effect over the intestinal transit rate which declines after 1hour. Perhaps the initial increase in the tone of gut musculature at the early phases of spasmogenic activity of the alkaloid, however, the intestinal transit rate fell significantly below the corresponding control values, obtained from animals fasted for 33-35 hrs. It appeared from these studies that the alkaloid finally rendered the motor system of the gut incapable of reaching to normal physiological stimuli like fasting.

The motility studies showed an initial rise and subsequent fall in the intestinal transit. The above finding combined with the observation of persistent

shortening of the length of the gut smooth muscle.

The present study also reported a dual action of vincristine. Vincristine decreases the intestinal motility probably through various mechanisms of actions.

CONCLUSION

The observations suggest that vincristine by its presence in gastric lumen or small intestine might influence gastrointestinal motility. The pattern of motility alteration by vincristine appear to be biphasic in the first hour following administration motility of small intestine was reduced and showed an increase five hours following the administration of the dose.

The results appear to suggest that vincristine might influence the motility of small intestine while in circulation and also its presence in gut lumen.

REFERENCES

1. Johnson IS. Historical background of vinca alkaloid research and areas of future interest. Cancer Chemother Rep 1968; 52:455-61
2. Johnson IS, Armstrong JG, Gorman M, et al. The vinca alkaloids: a new class of oncolytic agents Cancer Res 1963; 23: 1390-427.
3. Zhou X J, Placidi M, Rahmani R. Uptake and metabolism of vinca alkaloids by freshly isolated human hepatocytes in suspension. Anticancer Res 1994; 14:1017-22.
4. Zhoou X J, Martin M, Placidi M, et al. In vivo and in vitro pharmacokinetics and metabolism of vinca alkaloids in rats. II. Vinblastin and Vincristine. Eur J Drug Metab Pharmacokinetic 1990; 15:23.
5. Weiss Md, Walker MD, Wiernik PH. Neurotoxicity of commonly used antineoplastic agents N Engl J Med 1974; 291: 75-81
6. Watkins SM., Griffin JP. High incidence of vincristine induced neuropathy in lymphomas.Br Med J 1978; 1: 610-2.
7. Tormey DC. Neurotoxicity of vincristine. Lancet 1973; 1:1312.
8. Armstrong JG, Dyke RW, Foius PJ. Initial clinical experience with leurocristine, a new alkaloid from vinca rosea linn. Proc Amer Ass Cancer 1962; 3:301.
9. Rowinsky EK, Donehower RC. The clinical pharmacology and use of antimicrotuble agents in cancer chemotherapeutics. Pharmacol Ther 1992; 52: 35-84.
10. Owellen RJ, Root MA, Hains F O. Pharmacokinetic of vindesine and vincristine in humans.Cancer Res 1977; 37: 2603-7
11. Jordan A Hadfield JA, Lawrence NJ, et al. Tubulin as a target for anticancer drugs: agents which interact with the mitotic spindle. Med Res Rev 1998;18:259-96.
12. Jackson DV, Bender RA. Cytotoxic thresholds of vincristine in a murine and human leukemia cell line in vitro. Cancer Res 1979; 39:4346-9.
13. Jackson DV Jr, Castle MC, Bender RA Billiary excretion of vincristine. Clin Pharmacol Ther 1978; 24:101-7.
14. Gidding CE, Kellie SJ, Kamps WA, de Graaf SS. Vincristine revisited. Crit Rev Oncol Hematol 1999; 29: 267-87.
15. Owellen R J, Donigian DW. 3H vincristine: preparation and preliminary pharmacology. J Med Chem 1972; 15: 894-8.
16. Sharma RK. A Study of the effect of vinca alkaloid 'vinblastine' on gastrointestinal motility in rats. Archives Internationals de Pharmacodynamie et de therapie, 1979; 239: 331-9.
17. Bairy KL, Sanath S, Jagetia GC,et al. Evaluation of intraperitoneal Vincristine in malignant peritone a l effusion . indianjphysiol pharmacol. 2003; 47(3) : 270
18. Castle MC, Margileth DA, Oliverio VT. Distribution and excretion of (3H) vincristine in the rat and the dog. Cancer Res 1976; 36: 3684-9.
19. Mitolo-Chieppa D, Aprile L, Grasso G. Effects of vinblastine and vincristine on the innervated rat stomach. Boli Soc Ital Biol Sper 1976; 52: 806-811.
20. Sninsky CA. Vincristine alters myoelecctric activity and transit of the small intestine in rats. Gastroenterology 1987; 92: 472-8.
21. Lubitz L, Ekert H. Reversible changes in duodenal mucosa associated with intensive chemotherapy followed by autologous marrow rescue. Lancet 1979; 2: 532-3 Purdon RA, Bass P. Gastric AND intestinal transit in rats measured by radioactive test meal. Gastroenterology 1973; 64: 968-76.