EFFECTS OF ORLISTAT ON GASTROINTESTINAL SYSTEM OF ALBINO RATS – A HISTOLOGICAL STUDY

Thesis submitted to HIHT University

for award of

DOCTOR OF MEDICINE
IN
ANATOMY

2013

HIHT UNIVERSITY
SWAMI RAM NAGAR
DEHRADUN
UTTARAKHAND

Dr. NIDHI SINGH

CONTENTS

Summary

SUMMARY

Orlistat a hydrogenated derivative of lipstatin (tetrahydrolipstatin), is a potent irreversible inhibitor of gastric, pancreatic and carboxylester lipase thus promoting loss of weight by preventing the digestion and absorption of fat in the food. It blocks the action of lipase and thereby prevents the breakup and absorption of fat. It is used for the treatment of human obesity. Orlistat is commonly prescribed to the patients and can be purchased even without a prescription "over the counter". Orlistat blocks absorption of about 25% of the fat in a meal. This unabsorbed fat is excreted in the stool. Gastrointestinal side effects include oily spotting, flatus with discharge, fecal urgency, fatty or oily stool, oily evacuation, increased defecation, etc. There have been a lot of controversies on the side effects of the drug on the gastrointestinal system. The previous studies conducted showed decrease in the height of villi throughout the small intestine, loss of continuity of brush border epithelium, destruction of connective tissue in the core of villi associated with dilatation of intercellular spaces and lymphocytic infiltration in the lamina propria. Occurrences of aberrant crypt foci in the large intestine have been observed by various workers in the past which are the earliest identifiable neoplastic colonic lesions and precursors of colonic cancer. There has

been a dearth of past literature on the proximal portion of GI tract following Orlistat administration. Thus this present study was conducted to observe the deleterious effects of orlistat on the histology of the gastrointestinal tract.

60 albino rats were taken for the study which was conducted in 2 phases of 1 week (acute phase) and 3 weeks (subacute phase) duration consisting of 30 animals in each phase. The rats in phase I consisted of subgroups C1, A1 and B1 while the rats in phase II consisted of subgroups C2, A2 and B2 having 10 animals each. Experimental rats of A1and B1 subgroups of phase I were administered orally a dose of 5.14 mg and 10.28 mg of Orlistat per 100gms of body weight respectively for a duration of 1 week with the help of nasogastric tube. Experimental rats of A2and B2 subgroups of phase II were administered a dose of 5.14 mg and 10.28 mg of Orlistat per 100gms of body weight in a similar manner for a duration of 3 weeks. Control rats were administered an equal volume of normal saline in both the phases. At the end of 1 and 3 weeks, each group of rats was sacrificed after giving ether anesthesia. Tissues were processed and slides prepared. They were stained with H&E and PAS and examined under 100X, 200X and 400X magnification under a light microscope.

The oesophagus was observed to have a thickened epithelium with cellular proliferation and increased keratinisation with a horny

appearance. The stomach showed cellular degeneration in the form of cytoplasmic vacuolations and shrinkage of nuclei, degeneration of cells of the gastric glands specially parietal cells. Proliferation of mucosal neck cells leading to occlusion of the opening of the gastric glands into the gastric pits was also observed. There was slight widening of the gastric pits too. The small intestine revealed discontinuity of epithelium at multiple sites, increased thickness, degeneration and proliferation of the epithelial cells along with increase in the mean thickness of basement membrane. Lamina propria and submucosa showed increase in mononuclear cell infiltration associated with dilated and congested blood vessels. These were more prominent in the duodenum and ileum in comparison to jejunum. Similar changes were also observed in all the segments of large intestine. Additional observations noted included increased thickness of the epithelium along the margin of the crypts, thickening of its basement membrane and decrease in the number of the crypts/100μ field. Moreover, degeneration of crypts with increased pericryptal spacing was observed at a few places. Focal areas however, showed crowding of crypts. Type I aberrant crypts with a dilated lumen were seen in all the three segments of the large intestine which increased in frequency as the dosage and duration of drug increased. Few type II aberrant crypts with serrated margins were also observed. Numerous bilobed crypts and a few trilobed crypts were also seen. There was a

gradual increase in the number and size of goblet cells with change in their colour from pink to bluish hue at few places following PAS stain. These features of the large intestine progressively increased from its proximal to distal part.