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Improved Polymeric Contrast Agents for Roentgenologic Examination of the Gastrointestinal Tract

II. Preliminary Report on Animal Investigations

LARS BJÖRK, UNO ERIKSON, JOHN FALK, BJÖRN INGELMAN AND GERT LINDBLAD

From the Departments of Diagnostic Radiology and Clinical Chemistry, University Hospital, Uppsala, and Pharmacia AB, Uppsala, Sweden

ABSTRACT

A new improved water-soluble polymeric contrast agent has been studied in animal experiments. On oral and intraperitoneal administrations in mice, this polymer was found to have a very low toxicity. The contrast agent was used in connection with the roentgenologic examination of the gastrointestinal tract of dogs with good results. Further improvements are possible.

INTRODUCTION

The polymeric contrast agents described in our earlier publication in *Investigative Radiology* were found to have a very low toxicity in mice after oral and intraperitoneal administration.[1] The improved polymeric contrast agents described in the preceding part I of the present report also seem to have a very low toxicity and in addition possess favourable properties for roentgenologic examination of the gastrointestinal tract. In this report, some preliminary studies of toxicity in mice as well as some preliminary roentgenologic studies in dogs are described.

STUDIES OF TOXICITY IN MICE

A brief report is given below on som experiments on mice with the polymeric substance 730 E described in part I. (The weight average molecular weight $\bar{M}_w$ was about 5000.)

For the studies a neutral aqueous solution of the sodium salt of the substance 730 E was used. The solution contained 50 gram of substance per 100 ml of solution corresponding to an iodine content of about 180 mg per ml of solution. The solution was sterilized by autoclaving at 110°C for 30 minutes.

In these preliminary experiments very large doses were given orally and intraperitoneally in order to gain a general impression of the doses that should be used in future more detailed toxicity studies.

Ten mice were given a single oral dose of the solution, corresponding to 8 g of the substance per kg body weight. 5 mice were sacrificed after some hours and the other 5 mice were sacrificed after a week. None of the mice showed any toxic symptoms during the observation periods. At autopsy, no change were observed macroscopically. Histologic examinations performed on kidneys, liver, stomach and different parts of the intestines revealed no changes.

Ten mice were given a single intraperitoneal dose of the solution, corresponding to 8 g of the substance per kg body weight. 5 mice were sacrificed after some hours and the other 5 mice were sacrificed after a week. None of the mice showed any toxic symptoms during the observations periods At autopsy, no changes were observed macroscopically. Histologic examinations performed on kidneys, liver, stomach and different parts of the intestines revealed no changes.

Six mice were given an oral dose of the solution daily for 5 days, corresponding to 8 g of the substance per kg body weight per day. 3 mice were sacrificed after some hours and the other 3 mice were sacrificed after a week. None of the mice showed any toxic symptoms during the observation periods. At autopsy, no changes were observed macroscopically. Histologic examinations performed on kidneys, liver, stomach and different parts of the intestines revealed no changes.

Six mice were given an intraperitoneal dose of

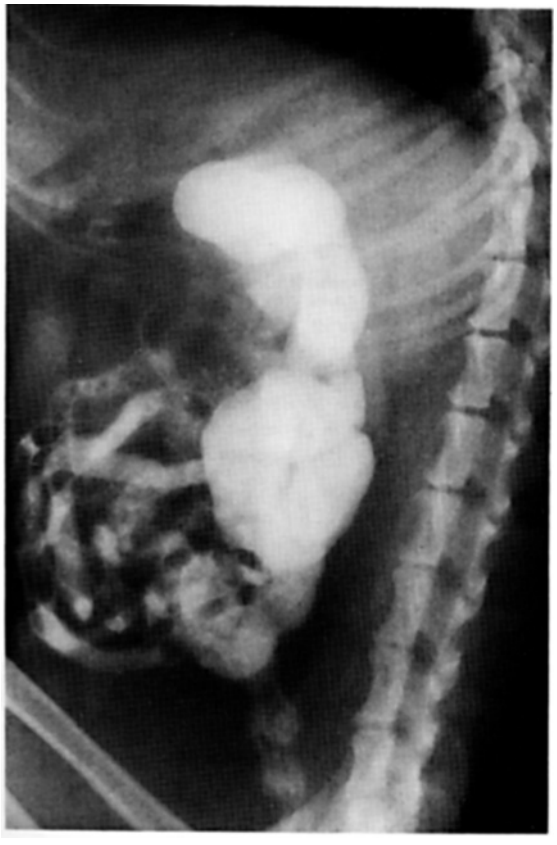

Fig. 1. Roentgenogram from a dog 1 hour after oral administration of 730 E.

the solution daily for 5 days, corresponding to 8 g of the substance per kg body weight per day. 3 mice were sacrificed after some hours and the other 3 mice were sacrificed after a week. None of the mice showed any toxic symptoms during the observation periods. At autopsy, no changes were observed macroscopically. Histologic examinations performed on kidneys, liver, stomach and different parts of the intestines revealed no changes.

ROENTGENOLOGIC STUDIES IN DOGS

The solution of substance 730 E which was used for studies of toxicity in mice was also used for roentgenologic studies of the gastrointestinal tract in dogs. Thus, the solution contained 50 g substance per 100 ml solution, corresponding to an iodine content of about 180 mg per ml.

Three dogs (beagles) weighing from 7–11 kg were fasted from the evening prior to the investigation. In the morning, 40 ml of the contrast solution was given orally to each dog through a gastric tube. Roentgenograms of the stomach and intestine were taken at 15–30 minute intervals.

One week later the same dogs were given 40 ml of Gastrografin (methyl-glucamine diatrizoate+ sodium diatrizoate; Schering AG, Berlin), which had been diluted with distilled water to the same iodine content as the solution of 730 E, i.e. to 180 mg/ml. The same roentgenologic procedure was followed as with 730 E.

With 730 E good visualization of the stomach and the intestines was obtained. No precipitation of the contrast medium was observed. The contrast medium was observed to mix well with the contents of the gastrointestinal tract. The contrast medium also coated the surface of the mucosa of the intestinal tract and a good double-contrast effect was observed in gas-filled parts of the intestines. The contrast filling of colon was good in all 3 dogs. Fig. 1. shows a roentgenogram from a dog 1 hour after oral administration of 730 E.

Good contrast filling of the stomach and the intestines was generally obtained with Gastrografin. However, in 2 of the dogs a considerable flocculation of the contrast medium was observed in the stomach and later precipitated contrast medium was seen as granular matter in the small intestine. The contrast filling of colon was somewhat poorer with Gastrografin than with 730 E, particularly in the two cases where flocculation of Gastrografin occurred. Fig. 2 shows a roentgenogram from a dog 2 hours after oral administration of Gastrografin.

There were no marked differences in the passage-time through the small intestine between the two contrast media.

No excretion of contrast medium in the renal pelvis or in the urinary bladder was observed roentgenologically on any occasion with either contrast media in these 3 dogs. No clinically manifest side effects were observed in any dog in these experiments.

DISCUSSION

The polymeric contrast agent used in the animal studies reported here has very high solubility in water even at low pH values. This contrast agent is not precipitated in acid gastric juices, whereas water-soluble iodine-containing contrast media in

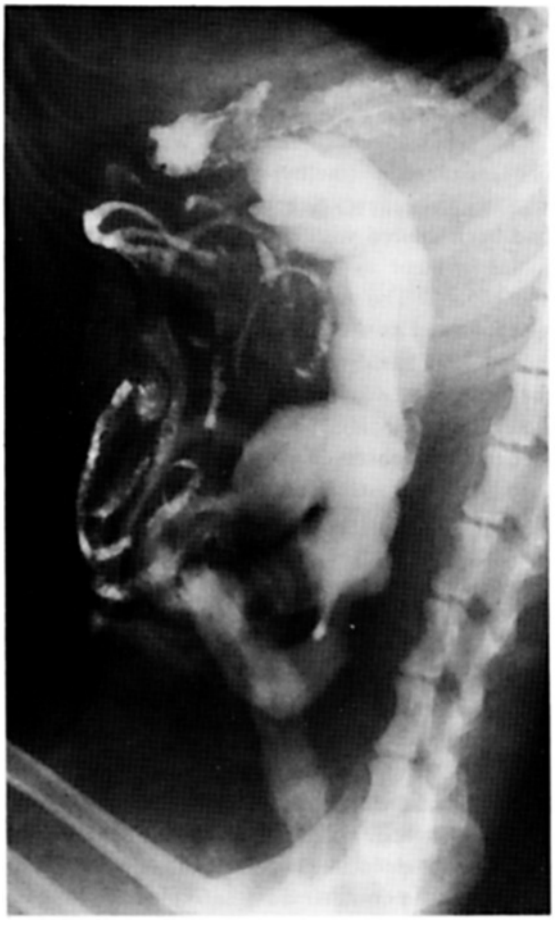

Fig. 2. Roentgenogram from a dog 2 hours after oral administration of Gastrografin.

current use are precipitated at low pH values and therefore can flocculate and precipitate in the stomach. (For example, diatrizoate preparations precipitate at about pH 3.) As this new contrast agent is a polymeric substance, it also has more favourable physical-chemical properties than those of the water-soluble contrast agents of comparatively low molecular weight used at present for this purpose. The preliminary toxicity studies as well as the preliminary roentgenologic studies in animals have shown that further investigations of this type of polymeric contrast agents are justified. The polymers can be further improved.

REFERENCES

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Address for reprints:
U. Erikson, M.D.
Department of Diagnostic Radiology
University Hospital
S-750 14 Uppsala
Sweden