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Preliminary Report on Angiography with Polymeric Contrast Agents in Rabbits and Dogs

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ABSTRACT

Polymeric, water-soluble, iodine-containing contrast agents have been synthesized and tested in renal angiography and thoracic aortography in rabbits and in femoral arteriography in dogs. Good filling of the arteries and also of the veins was obtained.

Polymeric, water-soluble, iodine-containing contrast agents of different types intended for use in, for example, angiography, lymphography, urography and hysterosalpingography have been prepared (1). Special polymeric contrast agents for the gastrointestinal tract which have a high solubility in water even at relatively low pH values, and therefore do not precipitate in the stomach, were also prepared. In earlier publications we have reported on animal investigations with such polymeric contrast agents in the radiological examinations of the gastrointestinal tract (2, 3, 4).

The polymers are of the type presented in the schematic Fig. 1*a*. In this figure *A* denotes iodine-substituted benzene derivatives (preferably 2,4,6-triiodobenzoic acid derivatives) and *B* denotes intermediate hydroxyl-bearing aliphatic bridges. Group *A*, for example, has the structure shown in Fig. 1*b* or in 1*c*. For contrast agents for oral use, long bridges (*B*) with several hydroxyl groups of the type shown in Fig. 1*d* were chosen (2), or such bridges in which the hydroxyl groups were partly replaced by glycerol ether groups (3, 4). For other uses (for instance for angiography and for urography) shorter bridges, for example of the type shown in Fig. 1*e*, were chosen. As iodine-substituted benzene derivative *A*, we have in most polymers preferred the structure shown in Fig. 1*c*.

Some of the angiographies performed in rabbits and dogs with the aid of some of the water-soluble, iodine-containing polymers synthesized will be described in this report.

MATERIALS AND METHODS

Polymeric contrast agents

The iodine-containing polymeric agents used in the animal investigations described in this report were given the code numbers 483, 549, 566, 599, 602, 616 and 727 E. They had been prepared by reacting 5-acetylamino-2,4,6-triiodo-N-methyl-isophtalic acid monoamide or 3-acetylamino-5-acetylamino-2,4,6-triiodo-benzoic acid in alkaline aqueous solution with 1,4-butandioldiglycide ether in molar ratios close to one to one according to the methods described in reference (1).

In all these polymers the bridge *B* was of the type shown in Fig. 1*e*. The iodine-substituted benzene derivative group *A* was in all these polymers of the type shown in Fig. 1*c*, with the exception of polymer 727E in which *A* was of the type shown in Fig. 1*b*. Polymers in which *A* has the structure shown in Fig. 1*b* are easily discoloured and the structure shown in Fig. 1*c* was therefore preferred.

Some data regarding these polymers are shown in Table I. The code numbers are given in the first column. In the second column, the weight average molecular weights $\bar{M}_w$ (determined by light scattering by Dr K. Granath) are shown. The $\bar{M}_w$ value of polymer 483 was never determined. However, polymer 483 was rather similar to polymer 566, to judge from some preliminary gel chromatography experiments. The iodine contents of the dry polymers are given in the third column. (All the polymers had been reprecipitated as polyacids after the synthesis, with the exception of 727 E which had been isolated as the sodium salt after several reprecipitations with acetone. The precipitated polymers had been dried at about 50°C under vacuum.) The type of the iodine-containing unit *A* and the type of the bridge *B* (cf. Fig. 1) are also shown in the table. The type of salts in the solutions used in the animal investigations described in this report are shown in the final column. These solutions contained 200–220 mgI/ml. Solutions of Conray Meglumine which had been diluted to the same iodine content were used for comparison.

The molecular weight distributions of these polymers are rather broad as, for the introductory animal tests reported here, the polymers were not fractionated in order to obtain products with narrow molecular weight distributions. For several of the polymers a low average degree of polymerization (and thus a relatively low average molecular weight) was chosen in order that the molecular weight distribution would be such that all of the material

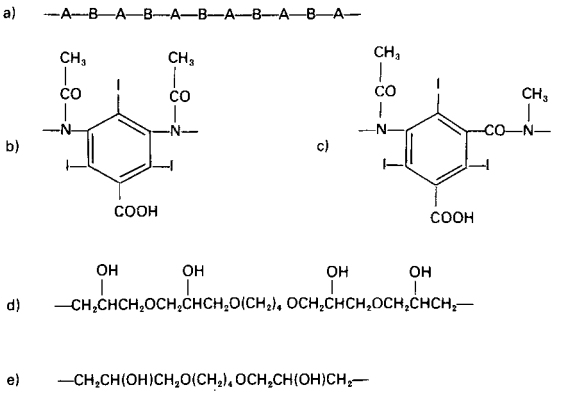

Fig. 1. (*a*) Basic structure of the polymeric contrast substances. *A* indicates iodine-substituted benzene derivatives, mainly 2,4,6-triiodobenzonic acid derivatives. *B* indicates hydroxyl-bearing aliphatic bridges. (*b*) Example of group *A*. (*c*) Example of group *A*. (*d*) Example of the bridge *B*. (*e*) Example of the bridge *B*. In the polymers described in this report the bridge *B* was of the type shown in Fig. 1*e* and the iodine-substituted benzene derivative group *A* was of the type shown in Fig. 1*c* with one exception.

would be well below the limit of permeability of the renal glomeruli. Analytical gel chromatography with polymer 599 (which in the animal tests has shown interesting properties) showed that about 15% by weight of this polymer product had molecular weights above 20000 and that about 20% by weight had molecular weights below 3000.

Renal angiography and thoracic aortography in rabbits

Female white New Zealand rabbits weighing approximately 2.5 kg were used as experimental animals.

The rabbits were anaesthetized with intravenous injection of phenobarbital, the iliac artery on one side was exposed and a fine polyethylene catheter was introduced into the artery and advanced with its tip immediately above the renal arteries. One of the kidneys, usually the left, was selected for the angiographic studies.

An X-ray tube with a 0.6 mm focal spot and a seven-inch cesium-iodine image intensifier and a 70 mm camera operated at 1 frame/s were used to record the angiograms.

The following polymeric contrast agents were tested and compared with Conray Meglumine: code numbers 483, 549, 566, 599, 602, 616 and 727 E. The iodine content of the solutions used was adjusted to about the same level (200–220 mgI/ml).

Each of the new compounds was tested in four rabbits in renal arteriography. In each rabbit four injections of the new compound were alternated with injections of similar amounts of diluted Conray Meglumine, 0.5 ml per kg body weight being injected on each occasion. In the absence of a suitable automatic injector for small volumes the injections were done manually. The injections were timed by a stop-watch and the average rate found to be 0.5 ml/s with only minor variations. The electrocardiogram was recorded continuously before, during and after the injections. The blood pressure was measured intermittently using the injection catheter.

In four rabbits the catheter was advanced to the ascending aorta and thoracic aortograms were performed in each animal with four polymeric contrast agents (549, 566, 602 and 616). One millilitre per kg body weight was injected on each occasion. The iodine content of the solutions was again 200–220 mg/ml.

Femoral arteriography in dogs

In four mongrel dogs (weighing approximately 25 kg each) the femoral artery on one side was exposed under general anaesthesia, and a catheter introduced and manipulated into the contralateral iliac artery and advanced until its tip was in the femoral artery.

Femoral arteriography in the dogs was performed with the same technique as described by Björk (5).

Comparative injections of polymeric contrast agents (483, 549, 566 and 616) and Conray Meglumine were made. The contrast solutions used had been diluted to about the same iodine content (200–220 mgI/ml).

The weight of the leg of each dog was estimated and the dose of contrast medium used was 1 ml per kg leg weight.

Full-size angiograms of the leg were obtained using a Frankling roll film changer.

Table I

M=methylglucamine, Na=sodium

Polymer code number	$\bar{M}_w$	Iodine content of dry polymer (1) as polyacid (2) as sodium salt	Type of iodine-containing unit *A*	Type of bridge *B*	Type of salt in test solution
483	–	46.1 (1)	c	e	M
549	4 000	45.5 (1)	c	e	M
566	5 000	46.1 (1)	c	e	M
599	14 000	44.7 (1)	c	e	M
602	41 000	44.7 (1)	c	e	Na
616	7 000	45.5 (1)	c	e	M
727 E	38 000	41.6 (2)	b	e	Na

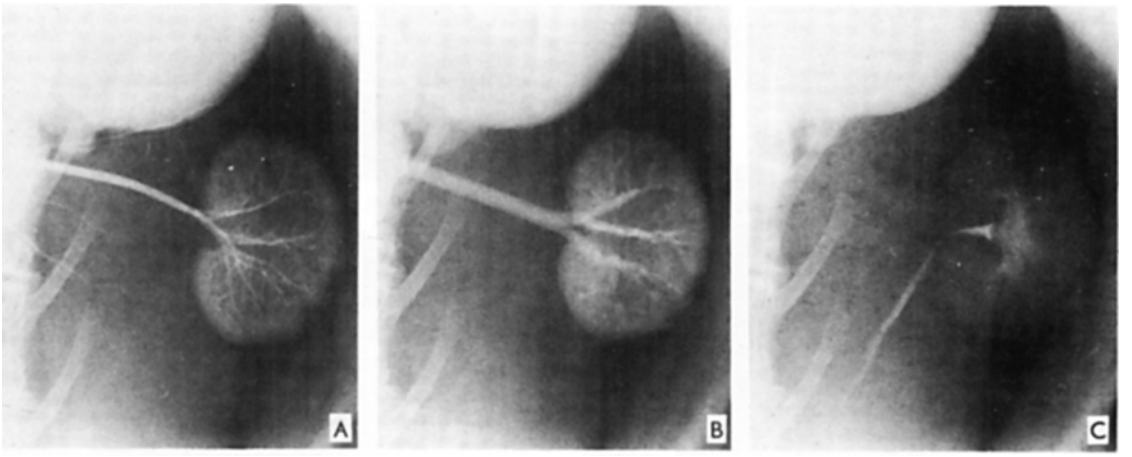

Fig. 2. Renal angiography in rabbit. Polymer 727 E. (A) Arterial phase. (B) 12 seconds after injection. Very good filling of intra renal veins. (C) 3 min after injection. Dense filling of collecting tubes in the papillae.

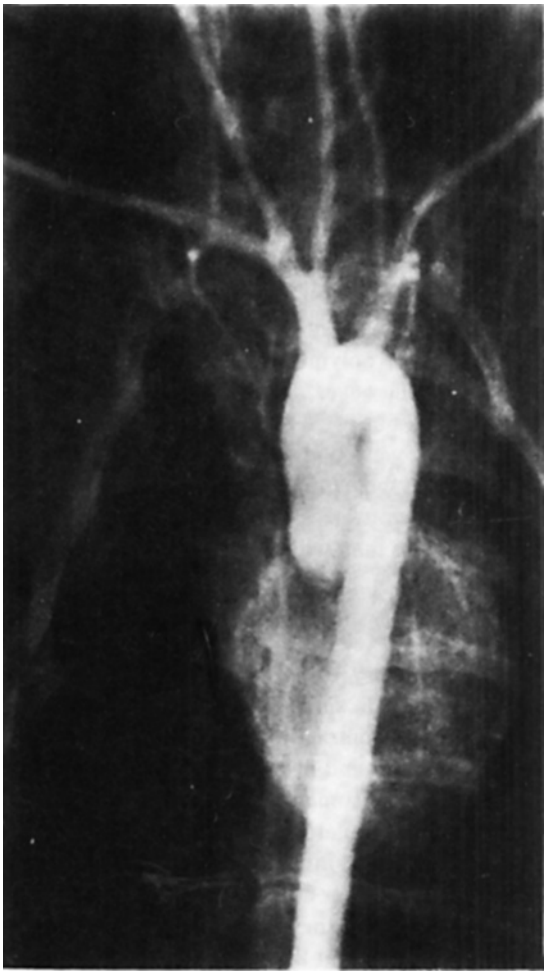

Fig. 3. Thoracic aortography in rabbit. Polymer 602.

RESULTS

Renal angiography and thoracic aortography in rabbits

Judging by experience at the injections, the viscosity of the solutions of code numbers 483, 549, 566, 599 and 616 was only moderately higher than that of the diluted Conray Meglumine solution used for comparison. The viscosity of the solutions of compounds 602 and 727 E was definitely higher than that of Conray Meglumine. However, with the small amounts used in the experiments no difficulty in injecting the contrast media was encountered.

The arterial filling was, as expected, similar with all contrast media used. The flow of the solutions of compounds 602 and 727 E in the vessels was slower than with the other compounds.

The venous filling was in all instances better with the new polymeric compounds than with similar injections of Conray Meglumine. This was particularly marked with the compounds 599, 602 and 727 E (Fig. 2. Polymer 727 E), with which a very marked filling of even small veins in the kidneys was seen.

The appearance time (i.e. the time from the start of the injection until contrast was visible in the veins) was on average 30% longer with the compounds 483, 549, 566 and 616 than with Conray Meglumine, and about 50% longer with compound 599. With the compounds 602 and 727 E the appearance time was on average twice as long as with Conray Meglumine.

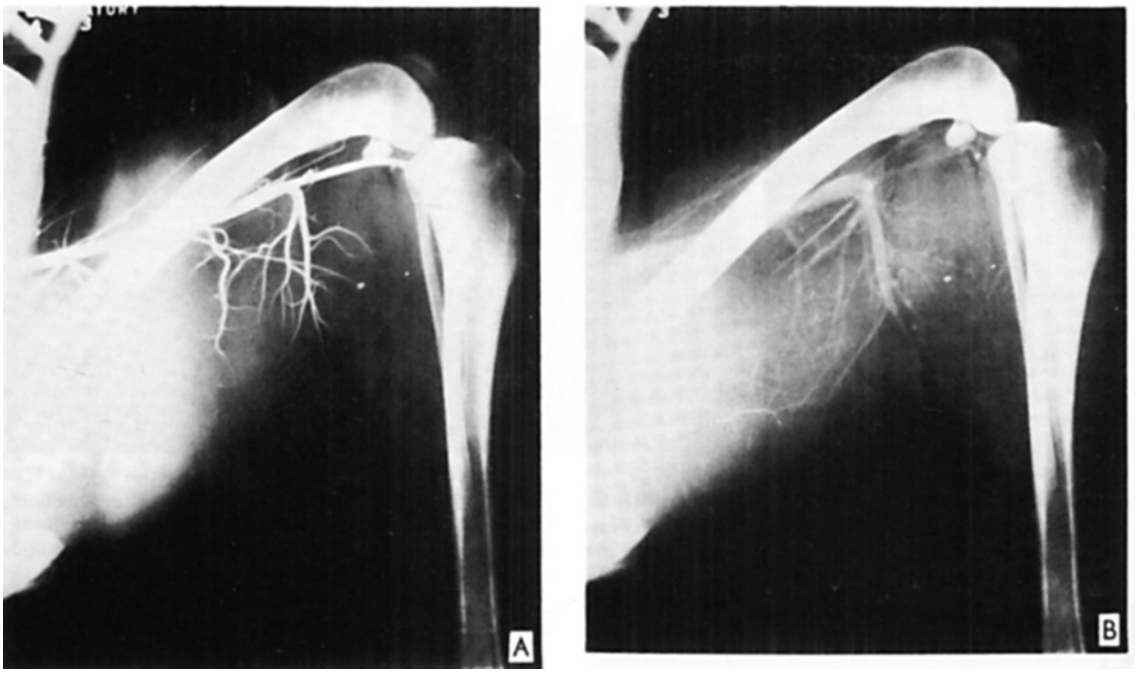

Fig. 4. Femoral arteriography in dog. Polymer 566. (A) Early arterial phase. (B) Very good filling of the veins in the leg.

The excretion of contrast medium into renal pelvis started at almost the same time with the compounds 483, 549, 566 and 616 as with Conray Meglumine. With the compound 599 there was some delay in the appearance in the renal pelvis and with the compounds 602 and 727 E there was a marked delay in appearance. With the latter three compounds there was also very dense filling, not only of the renal pelvis but also of the collecting tubes in the intrarenal papillae (Fig. 2. Polymer 727 E).

The changes in heart rate and blood pressure after injection of Conray Meglumine and the test compounds were usually slight. From these experiments it is difficult to draw any definite conclusions but there was a tendency towards less effect on the heart rate and blood pressure with the new compounds than with Conray Meglumine.

The four contrast agents (549, 566, 602 and 616) tested in thoracic aortography in four rabbits all gave satisfactory arteriograms with good filling of the arteries and also of the veins. The high viscosity of the solution of compound 602 proved to be no hindrance to rapid aortic injection for good filling of the thoracic aorta and its branches in these small animals (Fig. 3. Polymer 602).

Femoral arteriography in dogs

With Conray Meglumine there was good arterial filling, as expected. However, the filling of major veins was poor with all 16 injections.

With the four polymeric agents tested (483, 549, 566 and 616), however, good filling of the veins was seen 12 times out of 16 (Fig. 4. Polymer 566). The arterial filling was good in all animals.

The appearance time in the veins was always longer (on average 40% longer) with the polymeric contrast agents than with Conray Meglumine.

DISCUSSION

These preliminary experiments, as well as other experiments with similar polymers, have shown that polymeric contrast agents may be useful for, e.g. angiography and urography. The experiments also indicate that some of the expected advantages are present, particularly with agents of high molecular weight. These include better visualization of veins and also denser contrast excretion in the kidneys, provided that the sizes of the polymer molecules are not so great that they are unable to pass the renal glomeruli and easily be excreted with the

urine. The circulation time, as reflected by the appearance time in the veins following intra-arterial injection, was also longer with all polymeric contrast agents tested.

The differences observed between conventional contrast agents and polymeric contrast agents might be due to several factors, including larger molecular size (resulting in lower diffusion rate, higher viscosity, less osmotic activity etc.), less pronounced effects on the local vascular bed and less pronouned effects on the circulation.

The results of the studies performed give guidance in the choice of suitable molecular weights for these polymers. However, further experiments are needed to compare polymeric contrast agents with different and well-defined molecular weight distributions and to establish suitable molecular weight distributions of such polymers for various uses.

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