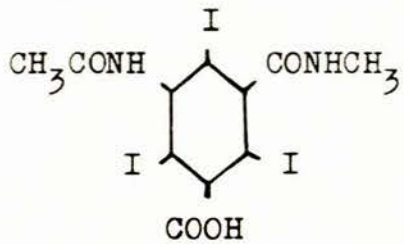
AN INVESTIGATION INTO A NEW CONTRAST MEDIUM

MEGLUMINE IOTHALAMATE INJECTION, 60% (CONRAY 60)

H. E. ENGELBRECHT, M.B., CH.B., D.M.R.D., *Senior Radiologist, King Edward VIII Hospital, Durban*

Iothalamic acid, a relatively new radio-opaque compound is, chemically, 5-acetamido-2.4,6-triiodo-N-methylisophthalamic acid and can be represented by the following structural formula:



Iodine content = 62%.

Iothalamic acid has low local and systemic toxicities, is pharmacologically inert, and its salts used in radiology are highly water-soluble even at low temperatures, giving clear solutions. The currently available injections of iothalamates have low viscosities, details of which are given along with iodine contents below:

Preparation	*Iodine content*		*Viscosity (centipoises)*	
	mg./ml.	*%*	*25°C*	*37°C*
Meglumine iothalamate injection 60% (Conray 280)	280	28	6·1	4
Sodium iothalamate injection 70% (Conray 420)	420	42	8·7	5·4
Sodium iothalamate injection 80% (Conray 480)	480	48	13·7	8

CLINICAL EXPERIENCES

Clinical experiences are discussed under 4 headings:

(*a*) Preliminary investigation in intravenous urography.
(*b*) Survey of large series of routine intravenous urograms.
(*c*) Use of Conray 60 in cranio-angiography.
(*d*) Experiences with Angio-Conray 80 (sodium iothalamate injection 80% w/v) in aortography.

A. Preliminary Investigation

Owing to the complete lack of experience of myself and colleagues in the use of Conray preparations, extreme caution and meticulous clinical and laboratory assessments were the keynotes of the preliminary investigation.

Method of Study

Intravenous pyelography was carried out in 100 consecutive inpatients at this hospital. Twenty ml. of Conray 60 were injected into the antecubital vein in all cases.

A careful history was taken of each patient with special reference to allergic and past sensitivity reactions; the psychological make-up of the patients was also assessed. Blood urea, complete urinalysis and creatinine clearance values were undertaken before and also 24 hours after each examination. The blood pressure and pulse rate were carefully monitored immediately before the administration of the contrast medium, during the examination and following the procedure. Sensitivity and toxic reactions were

carcinoma of the stomach in a man aged 77 years. Here again, the tumour was a mucinous adenocarcinoma.

Papavasiliou[4] in a general discussion on calcification of intra-abdominal tumours, reviewed Petersen's work and suggested that calcification in gastric masses is indicative of a mucinous adenocarcinoma.

Matthews *et al.*[5] reported 2 further cases of calcification in gastro-intestinal malignancy. The first was in a 59-year-old female who had a mucinous adenocarcinoma of the stomach. The second case was that of a 25-year-old male who exhibited calcification in a mucinous adenocarcinoma of the colon.

The case reported here has, in common with the above published reports, been proved to be a mucinous adenocarcinoma of the stomach. It seems that one is justified to make a radiological diagnosis of a mucinous adenocarcinoma in the presence of punctate and linear calcification in a gastric neoplasm.

Boyd,[6] in discussing mucoid carcinoma of the stomach, states that this is merely a degeneration of one of the varieties of carcinoma which occur in this region. Quoting a series of 2,516 cases of carcinoma of the stomach at the Mayo Clinic, where mucoid changes were found in 5·09% of cases, he states that the prognosis and fate of the patient did not appear to be affected by this degeneration. It would thus appear that although a fairly confident diagnosis of mucinous adenocarcinoma of the stomach can be made in the presence of punctate and linear calcification in relation to an infiltrative lesion of the stomach, it has little or no value in the assessment of prognosis.

SUMMARY

A case of calcification in a mucinous adenocarcinoma of the stomach is presented and the literature is reviewed.

The presence of punctate and linear calcification in an infiltrative lesion of the stomach almost certainly warrants the diagnosis of a mucinous adenocarcinoma. The preoperative knowledge is of no aid in the evaluation of the prognosis.

I am indebted to Mr. J. Wolfowitz and Dr. J. Gluckman, of Johannesburg, for the surgical and pathological reports.

ADDENDUM

Since this paper was written a further report on calcification in gastro-intestinal carcinoma has been reported by George Hermann and Roland Rozin,[7] and this was likewise a mucous-producing adenocarcinoma of the stomach. They quote their case as being the 13th in world literature, so presumably the case described in the above article is the fourteenth.

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assessed along the following lines: The patients were constantly observed during the complete examination, and clinical notes were made immediately after the injection, 5 minutes after and on completion of the examination. A circular note to the wards requesting information on any delayed reactions was issued in respect of each patient. These notes were completed on discharge of the patients and returned to the X-ray department. Careful interrogation in regard to subjective symptoms such as heat, cold, nausea, faintness, palpitations, headache, etc., was made during the examination. A test dose of 1 ml. of medium was administered to all patients, and an observation period of 2 - 4 minutes was allowed before proceeding with the remainder of the injection. The average time taken to inject 20 ml. was 3 minutes.

Hypaque 50% w/v was administered to a control series.

Assessment of Reactions to Conray 60

Only 4 patients reacted significantly to the contrast medium. The first patient complained of slight pain at the injection site. None of the other patients exhibited any evidence of local irritation or venospasm. The second patient vomited for 3 minutes during administration, with a moderate rise in blood pressure and pulse rate; this patient returned to normal within a few minutes. The third patient exhibited a fairly marked drop in body temperature with profuse sweating 10 minutes after the administration of the contrast medium. The blood pressure in this patient dropped from 120/80 to 90/70 mm.Hg, and the pulse rate increased from 80/min. to 100/min. This episode lasted for approximately 10 minutes when the patient returned to normal. In none of these 3 patients was there any history of allergy or sensitivity, but the general condition of the second and third patients was very poor; both had advanced carcinoma of the cervix. The fourth patient developed a moderately severe urticarial rash soon after injection. This patient had a positive history of drug allergy. Eight patients with a positive history of drug allergy did not react adversely to Conray 60 at all. A striking finding in all patients was the relative absence of nausea; the patients were carefully questioned about such an effect.

Toxic reactions with the use of Hypaque 50% were also insignificant, but more patients did admit to varying degrees of nausea.

Assessment of Contrast Quality

The radiographs of each examination were assessed on two different occasions and the following summary represents the mean qualitative values:

Resultant assessment	*No. of patients*
Excellent	15
Good	37
Adequate	34
Poor	10
Not diagnostic	4
Total	100

The categories 'poor' and 'not diagnostic' were retrospectively fully investigated in regard to technical factors, state of preparation of bowels, and clinical and laboratory data. The following transpired:

In the 'poor' category the bowels had been very poorly prepared in 8 patients. The remaining 2 patients showed slight elevation in blood urea and one patient was very obese. The 4 patients in the category 'not diagnostic' were also analysed. Two of these patients had a moderate elevation in blood urea. One patient was very obese with very poor preparation of the bowel, but no apparent explanation could be found for the remaining patient.

The control series, using Hypaque 50%, showed a slight shift of cases from the 'adequate' to 'good' categories. The 'excellent' and 'poor' categories were comparable.

Assessment of Excretion Rate

1. *The nephrographic effect.* In the majority of cases the nephrogram phase was best seen at 5 minutes and not at 1 minute. This was probably due to the fairly slow rate of injection. In a few patients maximum opacification of the renal parenchyma only occurred at 15 minutes. The quality of the nephrographic effect was good to average in most patients.

2. *The pyelographic effect.* Maximum opacification of the renal pelvis and calyces occurred in 52% of patients at 15 minutes, in 40% at 30 minutes and in 8% at 5 minutes. Adequate definition was present in 30% of patients at 5 minutes. These values were obviously to a large extent dependent on factors such as efficiency of compression, state of hydration, etc.

Assessment of Disease Index

Twenty-four percent of patients suffered from carcinoma of the cervix; many of these were advanced with consequent severe debility. Blood urea values were slightly or moderately elevated in 10%. Pathological changes in the kidneys, ureters or bladder were diagnosed in 43% of patients. Bilateral renal disease was present in 21%.

Assessment of Laboratory Data

Pre- and post-examination blood urea, complete urinalysis and creatinine clearance values demonstrated no significant changes.

Assessment of Pulse Rate and Blood Pressure

No significant variations in pulse rate were noticed, except in the patients who reacted. Some variation in blood pressure readings did occur in 40% of patients. These were analysed against the background of possible psychogenic factors and observer errors and variations. The only probably significant finding was a diastolic elevation of 5 - 20 mm.Hg in 21 patients, with the values returning to their normal levels after a varying period of time (usually soon after release of abdominal compression). This finding warrants further investigation under varying conditions of abdominal compression and also with the usage of different contrast media.

B. Analysis of 603 Cases with Routine usage of Conray 60 for Intravenous Urography

Having satisfied myself as regards its low toxicity and satisfactory contrast-producing qualities, Conray 60 was used as a routine for intravenous urography. Forty ml. was given by rapid injection with occasional quantity variations from 10 to 120 ml. according to age, weight and technical requirements. In 10 patients, employing the drip infusion technique, quantities of up to 180 ml. were

administered to patients with elevated blood urea values. Interrogation and observation of all patients were conducted by qualified medical personnel.

Details of the analysis of sensitivity reactions are as follows:

Manifestations	*No. of cases*
No reactions	501
Subjective symptoms	
Heat	25
Slight nausea	43
Moderate nausea	17
Severe nausea without vomiting	11
Faintness	4
Objective symptoms	
Vomiting	15
Skin rashes	2
Severe sensitivity e.g. anaphylactoid shock, oedema of glottis, etc.	0
Fatalities	0
Total	603

It is significant that 80% of patients did not react at all. There were no severe sensitivity reactions. In only 4 patients was it necessary to give drugs for reactions. No delayed reactions were brought to our notice. The over-all quality of contrast visualization was satisfactory and compared favourably with other contrast media.

C. The Use of Conray 60 in Cranio-Angiography

Sixty patients with suspected intracranial lesions were examined and, whenever feasible, the following routine was adopted: Conscious patients were examined under local anaesthesia and in any particular patient Conray 60 was alternated with Urografin 60%. 8 - 10 ml. of medium was delivered rapidly by manual injection into the cannulated common carotid artery. The patients were carefully observed and questioned after each injection. The qualities of the radiographs were analysed and compared. The number of injections totalled 199, 21 cases being bilateral investigations. The results of this investigation are as follows:

Manifestations	*Conray* 60 *injection*	*Urografin* 60% *injection*
No obvious reactions	82%	80%
Severe heat	10%	15%
Severe pain	6%	8%
Head movement owing to pain or heat	5%	6%
Serious reactions, e.g. convulsions, cranial nerve palsy and alteration in level of consciousness	0%	0%

Allowing for the many variable factors complicating an assessment of this nature, we did, however, conclude that no significant differences existed in the toxicity reactions between Conray 60 and the widely used Urografin 60%. On qualitative assessment of the radiographs obtained it was apparent that both media produced satisfactory contrast. The impression was gained that the peripheral arterial filling and venous phase contrast intensities were perhaps somewhat superior with Conray 60.

D. Experiences with Angio-Conray 80 (Sodium Iothalamate Injection 80%) in Aortography

Our tentative experiences with Angio-Conray 80 have not been encouraging. Ten abdominal aortograms were carried out using 40 ml. of Angio-Conray 80. Two patients reacted moderately severely, complaining of pain in the back and intense heat. Two patients experienced intense pain in the back and abdomen with resultant motion blur on the radiographs. Repeat injections with 40 ml. of Urografin 76% in the same patients produced satisfactory results. The contrast quality of the aortograms obtained with Angio-Conray 80 was excellent and laboratory tests did not demonstrate tissue damage in any patient. It must be remembered, however, that Urografin 76% has an iodine content about 25% less than that of Angio-Conray 80.

DISCUSSION

Our investigation confirmed the findings of previous investigations conducted with Conray 60. The extremely low toxicity of this medium was confirmed. In a large series of excretory urograms it gave rise, in our experience, to significantly less nausea than other contrast media of similar iodine content. The contrast density with Conray 60 was satisfactory. The low viscosity of Conray 60 allows it to be administered rapidly when necessary.

From our experiences with the intra-arterial injection of Conray 60 in cranio-angiography it may well be the contrast medium of choice at present for the visualization of medium-sized and smaller vascular channels where rapid injection with maximum diffusion of contrast is the requirement. This pertains to cerebral angiography, vertebral angiography, upper and lower limb angiography (particularly in young and small patients) and also in cardio-angiography and aortography in the young. When angiography is essential in debilitated and critically ill patients, contrast intensity should be sacrificed to some extent and the use of Conray 60 should be entertained.

As regards Angio-Conray 80 (sodium iothalamate injection, 80%) we are reserving our opinion. Our own experiences and consultation with colleagues in the United Kingdom has led to a hesitancy to deliver large quantities of Angio-Conray 80 in or on the left side of the heart. The manufacturers have introduced recently a 70% injection of sodium iothalamate under the name Conray 420 which, by virtue of its lower iodine content (420 mg./ml.) and lower viscosity, compared with Angio-Conray 80, may prove satisfactory not only for angiocardiography and aortography but also for intravenous urography.

Since the commencement of this investigation, the various iothalamate preparations have been re-designated by the manufacturers as follows:

Conray 280	Meglumine iothalamate injection 60% (containing 280 mg. iodine/ml.) 28% iodine	Formerly known as Conray 60
Conray 420	Sodium iothalamate injection 70% (containing 420 mg. iodine/ml.) 42% iodine	
Conray 480	Sodium iothalamate injection 80% (containing 480 mg. iodine/ml.) 48% iodine	Formerly known as Angio-Conray 80

SUMMARY

1. A new contrast medium, meglumine iothalamate injection 60% (Conray 280—formerly known as Conray 60) was extensively investigated in intravenous urography and cerebral angiography. The results are analysed.

2. The very low toxicity of Conray 280 and its possible advantages in intravenous urography and cerebral angiography are discussed.

3. Our experiences with Conray 480 (sodium iothalamate injection 80%) are briefly mentioned.

We wish to thank the staff of the X-ray Department, King Edward VIII Hospital, Durban, for their valuable assistance in carrying out these trials; Maybaker (S.A.) (Pty) Ltd. for adequate trial material; and Dr. R. Nupen, Medical Superintendent, for permission to publish.

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