Evaluation of Contrast Media used in Coronary Arteriography

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Coronary arteriography was first performed in dogs in 1933 by injection of a large quantity of contrast medium into the root of the aorta (Roushöi, 1933). The same "flush" technique was used in man in 1945 by Radner. The injection of contrast medium directly into each coronary artery consecutively, selective coronary arteriography, was developed in 1962, and has been shown to be a relatively safe and effective means of obtaining precise information on the distribution of lesions in the coronary arterial tree (Sones and Shirey, 1962). In addition to the hazard of mechanical damage to the arteries, the injection of contrast medium produces changes in the electrocardiogram (Benchimol and McNally, 1966) and may lead to asystole or ventricular fibrillation. The risk of these complications is not great even with selective injections provided effective treatment is readily available, but the mode of production of the electrocardiographic changes should be fully understood, and if differences exist between media the safest should be used.

We report the results of an experiment designed to test contrast media in current use for their toxic

effects when injected selectively into the coronary arteries of dogs.

MATERIALS AND METHODS

Eleven healthy mongrel dogs (weight 12 to 18 kg.) were lightly anaesthetized with intravenous pentobarbitone, 30 mg. per kg. body weight. A No. 7 Sones coronary catheter was passed from the right carotid artery to the root of the aorta. The left coronary artery was then engaged, the catheter being firmly placed in the ostium. This manoeuvre produced no electrocardiographic change in any of the dogs. Contrast media were then injected in random order using a Latin square table.

Five contrast media were used in 11 dogs: Hypaque 85 (Bayer); Triosil 75, old formula (Glaxo); Triosil 75, new formula; Conray 480 (May and Baker); and Urografin 76 (Schering). The volume of each injection was adjusted so that the iodine content, and hence the radiographic contrast, was the same, Hypaque 85 being taken as standard. Table I shows the volume of each injection. Throughout each injection electrocardiographic leads I and II were recorded until any change had reverted to the normal pattern. Five minutes were allowed between each injection and all media were heated to 33°C. before injection.

The electrocardiograms were then analysed by an observer who had no knowledge of the order of injection

TABLE I
IODINE CONTENT AND VOLUME OF EACH MEDIUM TOGETHER WITH THEIR CONSTITUENTS

Medium	Proportion of constituents	Constituents	Iodine content (mg./ml.)	Volume injected (ml.)
Conray 480	1	Sodium iothalamate	480	5.2
Old Triosil 75	1	Sodium metrizoate	439	5.4
New Triosil 75	69	Sodium metrizoate	439	5.4
	3.5	Calcium metrizoate		
	2.5	Magnesium metrizoate		
Hypaque 85	1	Sodium diazoate	440	5.4
	2	N methylglucamate diazoate		
Urografin 76	10	Sodium amidotrizoate	370	6.0
	66	Methylglucamine amidotrizoate

FIG. 1.—Measurements taken before and after injection are indicated by the arrows.

of media. An objective assessment was made by taking the following measurements (Fig. 1).

(1) The maximum displacement of the ST-T complex from the P-Q baseline was measured before and after each injection. The difference between these measurements was then calculated.

(2) The maximum R-R interval was measured before and after each injection. Using these figures, the heart rate after injection was expressed as a percentage of the heart rate before injection.

(3) All ectopic beats were counted, and other dysrhythmias noted.

RESULTS

In all, 133 injections were made in 11 dogs, and the results are shown in Tables II, III, and Fig. 2.

TABLE II
MEAN CHANGE IN MM. OF DISPLACEMENT OF THE ST-T COMPLEX PRODUCED BY INJECTION OF CONTRAST MEDIA

Dog	Conray 480	Urografin 76	Old Triosil 75	New Triosil 75	Hypaque 85
1	6.7	3.2	9.0	1.5	0.5
2	3.0	6.0	3.0	4.3	4.6
3	8.3	6.3	6.3	6.3	6.0
4	1.8	1.0	3.0	6.0	1.3
5	1.0	2.0	7.0	2.0	9.0
6	0.5	2.7	4.0	0.5	1.3
7	10.0	9.0	10.0	5.7	7.5
8	4.0	0.7	3.5	2.0	2.7
9	4.7	2.0	5.3	4.0	3.0
10	3.0	3.0	0	3.0	3.0
11	—	0	1.0	0	3.0
Over-all mean	4.3	3.2	4.5	3.6	3.6
Total No. injections	24	31	22	24	32

FIG. 2.—The heart rate after injection is expressed as a percentage of the rate before injection. Each injection is represented by a single dot. The mean values are shown by the horizontal lines and the standard error by the vertical lines. Hypaque and Urografin produced least slowing and had a smaller range of change than the other media.

TABLE III
NUMBER OF ECTOPIC BEATS AND OTHER RHYTHM CHANGES AFTER INJECTION OF CONTRAST MEDIA

Dog	Conray 480	Urografin 76	Old Triosil 75	New Triosil 75	Hypaque 85
1	5	0	5	0	0
2	4	4	4	0	2
3	0	0	1	1	0
4	1st degree heart block	0	0	4	0
5	1	0	1	1	0
6	Ventricular fibrillation	2	4	1	0
7	10	0	3	0	0
8	3	0	12	0	0
9	3	0	2	5	0
10	Ventricular tachycardia	0	Ventricular fibrillation	0	0
11	—	0	Ventricular tachycardia	Ventricular fibrillation	0
Mean No. of ectopics	1.2	0.3	1.5	0.5	0.06
Total No. of injections	24	31	22	24	32

Changes in ST-T Segment. The differences between the ST-T segment deflections before and after each injection are given in Table II; each figure is the mean value for each dog. There was a wide variation between dogs in the degree of change seen, but in any one dog the changes were of the same magnitude and were consistent for each medium. Analysis of these results showed that Urografin 76 produced least change, but that none of the differences was statistically significant.

Changes in Rate. The results are shown in Fig. 2. Urografin 76 and Hypaque 85 produced less slowing than the other media, and the slowing was more consistent, though Urografin did produce an isolated episode of severe slowing. Analysis showed that the slowing produced by Urografin and Hypaque was significantly less than with other media (Table IV).

TABLE IV

PROBABILITY VALUE (p) OBTAINED BY STUDENT'S "t" TEST FOR DIFFERENCE OF MEAN SLOWING OF HEART RATE PRODUCED BY HYPAAQUE AND UROGRAFIN, COMPARED WITH CONRAY AND OLD AND NEW TRIOSIL*

	Conray	Old Triosil	New Triosil
Hypaque	<0.001	<0.001	<0.01
Urografin	<0.005	<0.005	<0.05

* No other comparisons reached significance at the 1 per cent level.

Changes in Rhythm. These changes are shown in Table III. The numbers given are the total number of ectopic beats seen, whether ventricular or supraventricular, in each dog. No statistical analysis of these figures has been attempted, but it is clear that Urografin and Hypaque caused fewer ectopic beats per injection. They were the only two media which did not cause ventricular fibrillation at any time despite the fact that together they

constituted nearly half of the total number of injections. Typical changes induced are shown in Fig. 3.

DISCUSSION

The mechanism of the changes in the cardiogram after the injection of contrast medium into the coronary arteries is not known. The changes depend on the artery injected; in man, injection into the right coronary artery causes depression of the ST segment, with inversion of the T wave, whereas injection into the left coronary artery causes the T wave to become taller and peaked (Benchimol and McNally, 1966). In the dog, the changes resulting from injection into the left coronary artery resemble those seen after injection into the right coronary artery of man. Anatomical differences between the coronary arteries of man and dog probably explain the difference in the response to injected medium as reflected by the electrocardiogram. Since the right coronary artery in man supplies the diaphragmatic surface of the heart, the changes are caused by changes in the myocardium in that area. In the dog the circumflex artery, which supplies the diaphragmatic surface of the heart, arises very close to the origin of the left coronary artery, so that a high proportion of the medium injected into that artery may pass directly to the diaphragmatic surface.

The changes may be caused by hypoxia since each injection fills the coronary tree and has a very low oxygen content. However, there is some evidence that these changes cannot be caused by hypoxia alone. We injected blood taken from the coronary sinus and found that it did not cause any change. Neither did we find any changes resulting from injection of isotonic saline into the coronary arteries, though other workers have reported slight changes (Gensini and Di Giorgi, 1964). Even if the changes were due to hypoxia this would not

FIG. 3.—Electrocardiographic changes characteristic of various media. The time of injection is indicated by the square wave. The cardiogram returned to the configuration before injection in all cases.

explain the differences between the media, as the largest volume we gave, and hence the most prolonged hypoxia to the myocardium, was of Urografin, and this caused less change than three of the other media.

The physical nature of the media may cause changes in the myocardium which are reflected in the electrocardiogram. Gensini and Di Giorgi (1964) claimed that methylglucamine salts of these media, which are weakly ionized, produced less change than the more strongly ionized sodium salts. Our findings give support to this in that the two media which caused least change both contained a high proportion of methylglucamine salts (Table I). Triosil new formula was developed in an attempt to reduce the free ion content by increasing the proportion of calcium and magnesium salts, which are not so highly ionized as the sodium salts, but it does not appear to have significantly reduced the incidence of the changes.

The other major constituent of the media which could be responsible for these changes is the iodine. Since the iodine content of each dose was kept constant, though the concentration varied a little, it seems unlikely that the differences seen were due to this substance. Hypaque 85, which produced least changes, was injected in the same concentration as both Triosil media, which caused conspicuous changes; this difference was statistically significant (Table IV) as far as the changes in rate were concerned.

Gensini (1963) is of the opinion that only those media containing a high proportion of methylglucamine salts should be used for coronary arteriography, and our results confirm this. There appears to be a need to reiterate this point so that the safest medium may be chosen for clinical use: of 3312 coronary arteriograms reported from several centres in the U.S.A. (Ross and Gorlin, 1968), Hypaque and Urografin were used in 80 per cent and together caused 19 episodes of ventricular fibrillation, whereas other media produced 5 episodes.

We agree with Porstmann (1965) that it is important with any new medium produced for use in coronary arteriography to assess its effect on the experimental animal in the situation in which it is to be used clinically, in addition to the usual estimations of LD50 after intravenous injection or of detection of toxic effects resulting from injection into large vessels. In our experience the most informative measurements to assess toxicity in coronary arteriography are the changes in heart rate and alterations in rhythm.

SUMMARY

We present the results of experiments showing the changes produced in the heart rate, rhythm, and electrocardiogram when five different contrast media were injected into the coronary arteries of dogs. We found that Hypaque 85 or Urografin 76 are the media of choice. We reaffirm that methylglucamine salts are the least toxic, and suggest that more realistic tests of toxicity should be applied before new contrast media are used on patients.

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