

Joseph M. Edelstein,¹ M.D.

Sudden Death Following Administration of Radio Contrast Media

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ABSTRACT: Six patients died suddenly following the administration of radio contrast media. All had received the so-called older agents which are being replaced by newer contrast agents, which are characterized by reduced osmolality. Five of the six patients experienced almost immediate difficulty in breathing followed by death.

KEYWORDS: pathology and biology, death, radio contrast media, sudden death

Several instances of sudden death following the administration of radio contrast media have been documented. According to data from the manufacturers, about 5.2 million contrast studies per year are now being carried out [1]. Experts estimate that there are about 520 deaths and 1800 life-threatening reactions per year. The safer new agents which are low osmolality, nonionic, or monoacid dimer formulations, if given to everybody, could decrease the occurrence of adverse reactions [1]. The actual mechanism of adverse reactions to iodinated contrast media is disputed and probably multifactorial.

There are six patients who form the basis of this report, all of whom received a radio contrast medium and died suddenly, almost immediately after the injection.

Case Reports

Case 1

A 35-year-old woman, with a history of dysfunctional uterine bleeding, was injected with 10 cc of Sinografin® into the cervical canal and immediately developed bradycardia followed by cardiac arrest [2]. Autopsy showed pulmonary edema and narrowing of the anterior descending branch of the left coronary artery. Edema of the larynx was not seen.

Case 2

A 21-year-old student was injected with 40 cc of Renografin® in preparation for a pyelogram. He developed tightness in his chest, flushed face, frothing from the mouth, and died almost immediately afterwards. Autopsy (ACC085-4634) showed pulmonary edema. There was no laryngeal edema.

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¹Formerly, associate pathologist, Allegheny County Coroner's Office, Pittsburgh, PA.

Case 3

A 59-year-old man was injected with MD 60 (Mallinckrodt) in preparation for aortography and immediately experienced nausea, a feeling of increased heat, respiratory difficulty with wheezing, and respiratory arrest. Autopsy (ACC085-4453) showed cardiac hypertrophy, a heart weight of 600 g, myocardial fibrosis, and a narrowing of the coronary arteries. The aorta showed severe atheroma. Laryngeal edema was not seen.

Case 4

A 61-year-old woman was injected with Renografin 60 following which she complained of feeling ill and had difficulty in breathing followed by death. Autopsy (ACC084-723) showed coronary atherosclerosis. Laryngeal edema was not seen.

Case 5

A 71-year-old woman was injected with 5 cc (500 mg) of Funduscein® following which she was choking, had difficulty in breathing, and collapsed. Autopsy (ACC084-625) showed atherosclerosis of coronary arteries, fatty change in the liver, and leiomyoma of the uterus. Laryngeal edema was not seen.

Case 6

A 62-year-old man was injected with Hypaque® 60 in preparation for a pyelogram. He experienced immediate "dry heaves" with shallow respiration, sweating, followed by death. Autopsy (ACC085-1211) showed slight edema of the epiglottis and vocal cords. The heart was enlarged.

The pertinent data of the above six patients are shown in Table 1.

Each person died suddenly and difficulty in breathing was a prominent sign and/or symptom. Of the agents used, the basis is a small molecule, triiodobenzoic acid. Variations involve substitutions of two small side chains off the benzene ring with the choice of either the meglumine complex or sodium salt of the benzoic acid (see Fig. 1).

The reactions that are of concern are urticaria angioedema, bronchospasm, laryngospasm, and cardiovascular collapse [3]. These relatively unpredictable reactions remain poorly understood and dangerous [3].

In a report dealing with adverse reactions to contrast media, Shehadi reported 11 fatalities in 112 003 procedures [4]. He also reported 38 patients who required hospitalization, 1769 patients who required emergency treatment in the radiology department, and 3640 patients who had reactions that did not require treatment. The contrast agents that have been widely

TABLE 1—*Pertinent data of the six patients.*

Patient	Age	Sex	Agent Injected	Immediate Symptoms and Signs
1	35	F	Sinografin	bradycardia cardiac arrest
2	21	M	Renografin	difficulty in breathing
3	59	M	MD 60 (Mallinckrodt)	difficulty in breathing, wheezing
4	61	F	Renografin 60	difficulty in breathing
5	71	F	Funduscein	difficulty in breathing
6	62	M	Hypaque 60	difficulty in breathing

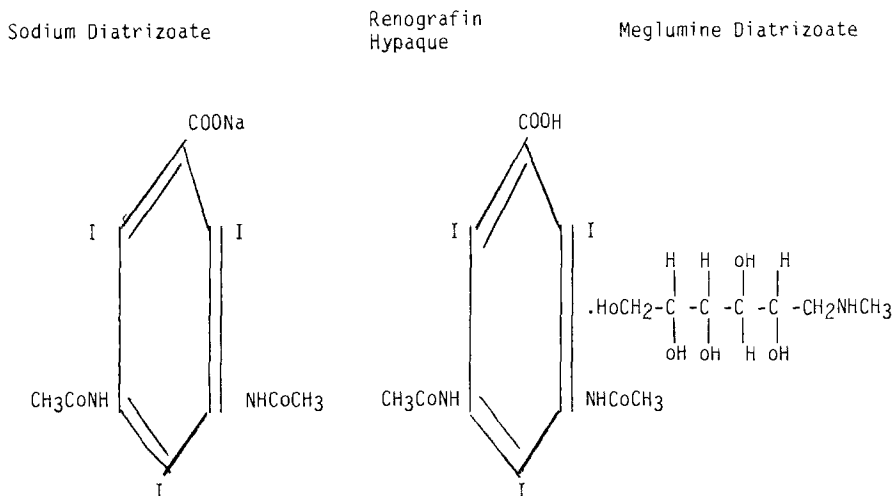


FIG. 1—Chemistry of common iodinated contrast agents.

used in this country present the same problem. To pack enough of them into volumes small enough to inject into patients and still provide high contrast density, very high concentration solutions have to be prepared [5]. The result is that they are hyperosmolar with respect to plasma. Osmolalities of conventional contrast agents range from 4.5 to 7.5 times that of plasma, and this is responsible for a variety of effects. At the objective level, there is an acute and rapid expansion of plasma volume with possibly important hemodynamic consequences for some patients; effects on red cell morphology, and more importantly, on red cell rigidity with implications for the microcirculation of various organ system; and perhaps most important of all, damage to the vascular endothelium at the injection site [5].

Other investigators have stressed the cardiovascular effects as very hazardous. Wolf [6] noted that pump failure, hypotension, and cardiac arrhythmias were the important adverse effects related to contrast agents.

Contrast media cause electrophysiologic and hemodynamic alterations. The most important effects, according to Higgins [7] are asystole, ventricular fibrillation, myocardial depression, and vasodilation. He stated that the predominant hemodynamic effect of intravenous, ventricular, or intraaortic injection of contrast media is *hypotension* as a consequence of vasodilation.

A new generation of intravenous contrast agents with an osmolality reduced to half and less than that of conventional agents has been introduced recently [8]. These low osmolality agents are widely used in Europe. Representative members of this new class include monoionic dimer ioxaglate (Hexabrix®) and a nonionic monomer, iopamidol (Solustrast®).

Before a contrast medium is injected, it is not known which pathophysiologic mechanism or which combination of mechanisms happen to be the greatest risk for that patient on that occasion [9]. The pathophysiologic mechanisms that may play a role in adverse reactions are:

- (1) vasodilation with possible arterial hypotension;
- (2) increased rigidity of red blood cells;
- (3) endothelial damage;
- (4) cardiac effects with arrhythmia or ventricular fibrillation;
- (5) pulmonary edema;
- (6) renal failure;

- (7) penetration of blood brain barrier by contrast medium molecules causing seizures;
- (8) interaction with various enzymes;
- (9) direct cellular effects with release of histamine, serotonin, or other substances causing symptoms of anaphylactoid reaction;
- (10) activation of complement with signs of anaphylactoid reaction; and
- (11) interaction with antibodies, with anaphylactic shock.

Five of the six patients in this report experienced almost immediate difficulty in breathing, suggesting that laryngospasm and or bronchospasm played a major role in their collapse.

Summary

Six patients who had been injected with a radio contrast medium experienced sudden death. Difficulty in breathing was a prominent symptom and suggests laryngospasm and or bronchospasm as playing a major role in these deaths. A new class of compounds has recently been introduced, especially in Europe. The newer agents have a relatively low osmolality because they are nonionic. The new agents are associated with a reduced incidence of bronchospasm. The newer agents have also achieved a lower chemotoxicity.

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Address requests for reprints or additional information to
 J. M. Edelstein, M.D.
 5558 Bellerock Place
 Pittsburgh, PA 15217