Appendix E: Mechanistic and Clinical Characteristics of Hypersensitivity Reactions

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Terminology

Hypersensitivity, in particular anaphylaxis and anaphylactoid reactions, as found with contrast agents, is due to two main mechanisms and with a range of clinical severity due to each of these. Definitionally, anaphylaxis and anaphylactoid reactions have been separated by these two mechanisms and clinical findings.[1,2]

> Mechanistically, *anaphylaxis* has been defined as "a systemic immediate hypersensitivity caused by the rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral blood basophils." In contrast, *anaphylactoid reactions* are "those clinical events caused by mediator release from mast cells and basophils by non-IgE-mediated triggering events."
>
> Clinically, some have reserved the term *anaphylaxis* for severe and immediate allergic reactions characterized by cardiovascular and respiratory compromise including angioedema and laryngeal edema, airway obstruct, hypotension and at times cardiopulmonary collapse. Anaphylactoid reactions are those with lesser degrees of hypotension and/or respiratory effects which may be immediate or delayed in onset.

Clinical and mechanistic aspects

As noted, Type I hypersensitivity is the immediate and the "classical" type of severe anaphylaxis usually mediated by IgE due to preexisting sensitization. However, Type I hypersensitivity can also occur with direct mast cell activation by an agent (since not IgE mediated, often called anaphylactoid).

The clinical manifestations [1,2] of Type I hypersensitivity are, by organ system:

- Skin-urticaria or rash and pruritis
- Airway- angioedema with dyspneas, wheezing or bronchospasm. Severe airway obstruction and respiratory collapse can occur.
- Cardiovascular-flush or erythema. When severe, peripheral vasodilation, hypotension, shock, cardiac arrest may follow.
- Gastrointestinal-nausea and vomiting, pain, diarrhea

When IgE mediated, there may be substantial and rapid release of mediators including histamine resulting in profound effects. The direct degranulation of mast cells by releasing mediators due to an agent without involvement of IgE mechanism is probably the most common for noniodinated contrast agents. It should be noted that both mechanisms can be also associated with anaphylactoid, milder, clinical effects.[2]

Examples and distinctions between IgE and direct mediator release based reactions.
Examples of hypersensitivity inducing agents include IgE sensitizers such as hymenoptera venom and penicillin. Upon exposure after sensitization, even of minute amounts, severe anaphylaxis may occur. Examples of direct releasers of mast cell mediators include ciprofloxacin, vancomycin and radiocontrast agents. A critical issue and distinction between these two mechanisms and groups of agents is that for the latter agents, total dose and rate of exposure are related to severity of the reaction. [2,3,4,5]

Fatal reactions are generally due to airway obstruction or vascular collapse. It is estimated that 70% of deaths are from respiratory causes and 24 % from cardiovascular collapse (see table in reference 2). Cardiovascular collapse alone as a sole manifestation is rare, occurring in just 1% of a series of patients with severe Type I hypersensitivity reactions.[3]

Parenteral penicillin has been on of the most frequent causes of all deaths from anaphylaxis with most of the rest due to insect venom in some of the literature. Contrast agents are also important causes of anaphylaxis. The rate of anaphylaxis from penicillin is estimated to be 0.01 to 0.05% per exposure [2,4].

High molecular weight protein compounds known to elicit immunologically mediated anaphylaxis include streptokinase, insulin, protamine, erythropoetin and vaccines. [6]

Contrast Agents

Iodinated agents
The older literature and labels[7] give rates of allergic type reactions for high osmolality/ionic radiocontrast agents of 5-8% with life threatening reaction rates of 0.1-0.5%. Both IgE and direct mediator release mechanisms have been identified for these agents. Newer low osmolality and nonionic agents have lower overall reaction rates presumably due to lower osmolarity resulting in less non IgE triggering of mediator release.[8,9,10,11,12] The major risk factor identified for allergic risk is a history of allergic reactions to medications.[7] The rate of serious adverse reactions recorded in approved labeling include 1.5% for Oxilan and 1.2% for Iohexal.[13]

MR agents
Generally MR agents are thought to be safer than nonionic iodinated contrast agents.[14,15] In the published literature for Optimark, a gadolinium MR agent there were rates of 5.2% for vasodilation and 0.9% for rash compared to rates for Magnevist of 2.1% and 2.1% respectively. Overall for Optimark the skin reaction rate was 2.1% and there was a trend toward an increase in this rate with increased dosing reaching 4.1% for 0.3 mmol/kg.[16]

Parenteral iron products

As noted, hypersensitivity reactions have occurred with all these products. However, it should be emphasized that the risk appears to vary greatly with such reactions occurring at a rate estimated to be as high as 2% for iron dextran and as low as 1 per 1,000 for iron gluconate.[17,18] Hypotension may be related to the rate of administration and the total dose administered. The hypotensive reactions are no associated with signs of hypersensitivity and have usually resolved within one or two hours.[19,20]

Management of hypersensitivity reactions

Treatment of hypersensitivity reactions depends upon their severity and clinical course. Anaphylaxis and severe anaphylactoid reactions often commence with cutaneous and/or airway symptoms. Initial management consists of placement in a recumbent position, maintenance of an airway, administration of oxygen, subcutaneous or intramuscular epinephrine, and antihistamines. Bronchospasm therapy may include beta 2 agonists and/or aminophylline. If hypotension occurs, initial treatment includes intravenous fluids. Vasopressors such as dopamine may be considered. (See American College of Radiology and table 2 in Shellock 1999 reference 15).

References

1. Dorland Medical Dictionary, 27th Edition

2. Supplement to Journal of Allergy and Clinical Immunology, June 1998

3. Treatment of Acute Anaphylaxis, Review and letters, Fisher, Malcolm, BMJ, 1995;311:731-733

4. R. de Shazo, S. Kemp, Allergic Reactions to Drugs and Biologic Agents, JAMA, 1997;258, No. 22,

5. Role of Mast Cells, Basophils and Their Mediators in Adverse Reactions to General Anesthertics and Radiocontrast Media, A. Genovese, Archives of Allergy and Immunology, 1996;110:13-22.

6. Data from product package inserts

7. FDA Class labeling for Diagnostic I.V. Radiopaque drugs, 1982

8. Systemic Anaphylactoid Reactions to Iodinated Contrast Media During Cardiac Catheterization Procedures: Guidelines for Prevention, Diagnosis and Treatment, J. Goss, C. Chambers, F. Heupler, Catheterization and Cardiovascular Diagnosis 1995, 34:99-104

9. Selective Use of Radiographic Low Osmolality Contrast Media in the 1990s, J. Ellis, R. Cohan, S. Sonnad, N. Cohan, Radiology 1996;200:297-311

10. Mechanisms of Severe, Immediate Reactions to Iodinated Contrast Material, D. Laroche, I. Aimone-Gastin, F. Dubois, H. Huet, P. Gerear, M. Vergnaud, C. Faivre, J. Gueant, M. Laxenaire, H. Bricard, Radiology 1998;209:183-190

11. Acute Reactions to Intravaxcular Contrast Media: Types, Risk Factors, Recognition, and Specific Treatment, W. Bush, D. Swanson, AJR, 1991, 157:1153-1161

12. Adverse Events with Radiographic Contrast Agents: Results of the SCVIR Contrast Agent Registry, M. Bettmann, T. Heeren, A. Greenfield, C. Goudey, Radiology 1997;203:611-620

13. Oxilan and Iohexal package inserts

14. Safety of Approved MR Contrast Media for Intravenous Injection, V. Runge, JMRI, 2000 12:205-213

15. Safety of Magnetic Resonance Imaging Contrast Agents, F. Shellock, E. Kanal, JMRI 1999, 10:477-484

16. J. Brown, R. Kristy, G. Stevens, J. Pierro, The OptiMARK Clinical Development Program: Summary of Safety Data, JMRI, 2002, 15:466-455

17. Sodium Ferric Gluconate Complex in Sucrose: Safer Intravenous Iron Therapy, than Iron Dextrans, G. Faich, J. Strobos, AJKD, 1999; Vol.33, No.3, pp 464-470

18. Intravenous Iron Dextran in Clinical Medicine, R. Hamstra, M. Block, A. Schocket, JAMA, 1980, Vol. 243, No.17, pp 1726-1731

19. Ferrlecit package insert

20. Venofer package insert

Other References

Epidemiology

1.Anaphylaxis in the US-Epidemiology. Neugut AI, Ghatak AT, Miller RL Arch Intern Med. 161;15-21, 2001

2. Anaphylaxis. Rusznak C, Stokes Peebles R. Postgrad Med 111,101114, 2002

PCN

1. Bochner BS. Anaphylaxis NEJM 1991;324:1785-99.
2. Anaphylaxis. J Allergy Clin Immunol 1998;101 (suppl):S465-S528.
3. Weiss ME Immediate hypersensitivity rxts ot Pcn and related antibiotics. Clin Allergy 1988:18:515-524

Occurrence and Death rates

1. Boston Collaborative. Drug induced anaphylaxis. JAMA 1973;224:613-15.
2. Stark BJ. Anaphylaxis. J Allergy Clin Immunol 1986:78:76-83
3. Valentine M. Allergic emergencies. In: Krause RM Asthma and other allergic diseases. Bethesda Md. NIH 1979:467-507. NIAID Task Force Report.

Contrast agents

1. Ansell G. Reactions to iv contrast . Invest rasdiol 1980:18;S32-S39.
2. Anaphylaxis. J Allergy Clin Immunol 1998;101 (suppl):S465-S528
3. Sue MA. Pcn anaphylaxis fatality. Am J Emerg Med 1988:6;456-458.
4. Katayama H. Adverse rxt to nonionic contrast. Radiology 1990;175:621-628
5. Lieberman Anapylactoid rxt to contrast. Immunol Allergy Clin North Am 1992:12;649-670
6. Shehadi W Adverse rxt to contrast. Am J roentgenol Radium Ther nucl med 1975
7. Greenberger Pa Prevention of immediate rxts to radiocontrast J Allergy Clin Immunol 1991;87:867-72.

Parenteral iron

1.Coyne DW, Michael B, Warnock, DG, Strobos J, Adkinson NF. Serum Tryptase (Tryp) Changes in HD Patients after Sodium Ferric Gluconate Complex (SFGC): SFGC Is Not an Allergen.JASN 12:A1819, 2001.

2. Warnock DG, Coyne DW, Michael B, Strobos J, Ferrlecit Publication Committee. Administration of Sodium Ferric Gluconate Complex (SFGC) to Iron-Dextran (ID)-Sensitive Hemodialysis (HD) Patients. JASN 12:A1880, 2001.

3. Seligman P, Schleicher R, Meyer G, Strobos J, Nissenson A. Fast IV Iron: Sodium Ferric Gluconate Complex (SFGC) Is Safe with No "Free" Iron Toxicity. JASN 11:297A, 2000.

4. Eschbach JW, Strobos J, Ferrlecit® Safety Group, Sodium Ferric Gluconate Complex (Ferrlecit®):Prospective Experience in 1122 Hemodialysis Patients. JASN 11:249A, 2000.

5. Warnock DG, Adkinson NF, Coyne DW. Strobos J, Ferrlecit Sodium Ferric Gluconate Complex in Hemodialysis Patients: II. Adverse Reactions in Iron Dextran-Sensitive and Iron Dextran-Tolerant Patients. Kidney Int'l. *Accepted for Publication PendingRevisions.* Michael B, Coyne DW, Fishbane S, Folkert V, Lynn R, Nissenson AR, Agrawal R, Eschbach

6. Fadem SZ, Trout JR, Strobos J, Warnock DG. Sodium Ferric Gluconate Complex in Hemodialysis Patients: Adverse Reactions Compared to Placebo and Iron Dextran. Kidney Int'l 61:1830-1839, 2002.

7. Faich GA, Strobos J, Ferrlecit: Safer Intravenous Iron Therapy Than Iron Dextran. Am J of Kid Dis 33:3:464-470. 1999

Overviews -summaries

1. Anaphylaxis in the US Neugut AI, Ghatak AT, Miller RL Arch Intern Med. 161;15-21, 2001

2. Radiopaque Contrast Media anaphylaxis rate 0.22 to 1%, may be lower for LOCAs.

3. Anaphylaxis Rusznak C, Stokes Peebles R. Postgrad Med 111,101114, 2002