FDA SAFETY ALERT:

Anaphylactoid Reactions Associated with ACE Inhibitors and Dialyzer Membranes

March 6, 1992

To hemodialysis personnel:

This is to alert you to a potentially life-threatening situation that can occur in a dialysis facility when patients maintained on angiotension converting enzyme (ACE) inhibitors are dialyzed with polyacrylonitrile (PAN) dialyzer membranes; it is also possible that other membranes, new or reprocessed, may be involved. If this situation occurs, quick recognition and appropriate treatment are critical. ***Please share this alert with those in your organization who are responsible for patient care.***

Current medical literature (1-3) and FDA investigations are raising concerns about an increasing number of anaphylactoid reactions in dialysis patients. FDA has received reports that some dialysis patients being maintained on ACE inhibitors are experiencing a sudden onset of symptoms which can and have progressed rapidly to death. (This reaction is ***not*** the same as the hypersensitivity reaction of first-use syndrome). Most of these current, published reports have involved PAN membranes. Symptoms include nausea, abdominal cramps, burning, angioedema, and shortness of breath with rapid progression to severe hypotension. One death has been attributed to this interaction.

NOTE: Symptoms are not relieved by antihistamines in these newly described, anaphylactoid reactions. When the reaction occurs, you **MUST STOP** dialysis immediately and start more aggressive, first line therapy for an anaphylactoid reaction. This alert is not to be constructed as a recommendation to remove patients from ACE inhibitors or to stop using PAN membranes. Rather, FDA's intent is to warn you of the potential for this severe and rapid reaction, so that you can be ready to initiate aggressive treatment should such a reaction occur.

An earlier FDA safety alert (4) and reports in the medical literature described hypersensitivity reactions to Cuprophan hollow fiber dialyzer membranes. The hypersensitivity reactions (first-use syndrome) described in that safety alert appear to be of a different etiology. Following the manufacturer's directions to adequately prime and rinse the dialyzers before initiating dialysis appears to effectively limit this earlier problem.

Because the mechanism of the newly reported interaction between ACE inhibitors and dialyzer membranes, new and reprocessed, has not been established, and the incidence and scope of this problem are unknown, FDA asks that you report any suspected reaction to FDA's device Problem Reporting System by calling toll-free 1-800-638-6725. In your description of the event, please provide the information outlined in the attached guidance.

Also, under FDA's new user facility reporting regulations (5), you are obligated to report device-related deaths directly to FDA and to the manufacturer, and to report device-related serious injuries or illnesses to the manufacturer (or to FDA if the manufacturer is unknown) within 10 working days. All user facility reports should be sent to FDA at the following address:

Food and Drug Administration
Center for Devices and Radiological Health
MDR User Report
P.O. Box 3002
Rockville, MD 20847-3002

Thank you for your help in this important matter.

Sincerely yours,

James S. Benson
Director
Center for Devices and
Radiological Health

References:

1. Tielemans, C. et al. Anaphylactoid reactions during hemodialysis on membranes in patients receiving ACE inhibitors. Kidney Int. 1990; 38:984.

2. Verresen, L. et al. Angiotensin-converting-enzyme inhibitors anaphylactoid reactions to high-flux membrane dialysis. Lan 1990; 336:1360-1362.

3. Parnes, E.L. and Shapiro, W.B. Anaphylactoid reactions (AR) hemodialysis patients treated with the AN69 dialyzer. Kidney Int. 1991; 40:1148-1152.

4. Center for Devices and Radiological Health, FDA, HHS. Rockville, MD., Doctor re:dialyzers; first-use syndrome. November 30, 1983.

5. Medical devices; medical device, user facility, distributor, manufacturer reporting, certification, and registration. Fed Register. November 26, 1991; 56:60024-39.

FDA Problem Reporting Program 1-800-638-6725
GUIDANCE FOR REPORTING DIALYSIS REACTIONS

Please include the following additional information, as available, about anaphylactoid reactions in your center during the past 12 months. Your assistance is appreciated. We will inform you of the results of our investigation.

Patient age and sex.

Date and symptoms of anaphylactoid reaction. WE ARE INTERESTED IN INCIDENTS INVOLVING TWO OR MORE OF THE FOLLOWING SYMPTOMS OCCURING WITHIN 10 MINUTES OF STARTING DIALYSIS:

(1) ABDOMINAL CRAMPS, NAUSEA, VOMITING, OR DIARRHEA
(2) SHORTNESS OF BREATH, TIGHTNESS OF CHEST, WHEEZING, OR BRONCHOSPASM
(3) FACIAL SWELLING, ANGIOEDEMA, OR LARYNGEDEMA
(4) HYPOTENSION ($\geq$30 MM HG DROP IN SYSTOLIC BP)
(5) FLUSHING OR WARMTH
(6) NUMBNESS OR TINGLING OF FINGERS, TOES, LIPS, OR TONGUE

Dialyzer brand, model, and lot number.

Membrane type (ACRYLONITRILE SODIUM METHALLYL SULFONATE (AN), CELLULOSE ACETATE, CUPRAMMONIUM RAYON, CUPRAPHANE^{R}, HEMOPHANE^{R}, POLYACRYLONITRILE (PAN), POLY-METHYLMETHACRYLATE (PMMA), POLYSULFONE, OR SAPONIFIED CELLULOSE ESTER (SCE)).

How long had the patient been using this type of membrane?
With what solution and volume was membrane primed?
Was dialyzer CONVENTIONAL OR HIGH-EFFICIENCY; NEW OR REPROCESSED?
If membrane was reprocessed, what procedures were employed:

Method type- MANUAL OR AUTOMATED?
Cleaning agents-type (H_2O_2, BLEACH, PERACETIC ACID, WATER, OTHER) and brand?
Disinfectants- type (FORMALDEHYDE, PERACETIC ACID, GLUTARALDEHYDE, OTHER) and brand?

If membrane was reprocessed, how many times had it had been used?

What treatments for anaphylaxis were administered?

(E.G., OXYGEN, CORTICOSTEROIDS, EPINEPHRINE, ANTIHISTAMINES, OTHER)?

Was dialysis session interrupted or stopped for that day?

What changes, if any, were made to dialyzer, membrane, or other equipment?

Was hospitalization for the event required? Did death result?

Was patient taking an angiotensin converting enzyme inhibitor

(E.G., BENAZEPRIL [LOTENSIN^{R}], CAPTOPRIL [CAPOTEN^{R} OR CAPOZIDE^{R}], ENALAPRIL [VASOTEC^{R} OR VASERETIC^{R}], LISINOPRIL [PRINIVIL^{R}, PRINZIDE^{R}, ZESTRIL^{R}, OR ZESTORETIC^{R}], FOSINOPRIL [MONOPRIL^{R}] QUINAPRIL [ACCUPRIL^{R}], OR RAMIPRIL [ALTACE^{R}])? If yes, give type, dose, and duration.

Does patient have a history of other sensitivities?
(E.G., ASTHMA, HAY-FEVER, DRUG-RELATED, FOOD-RELATED, OR OTHER DIALYSIS MEMBRANE-RELATED)?

In your opinion, what was the cause of the anaphylactoid reaction?
Has patient had subsequent episodes of anaphylaxis? Please explain the circumstances, including frequency of reactions and interim changes in dialysis procedure or medications.

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