Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. We report five life-threatening anaphylactoid reactions occurring within the very first minutes of hemodialysis on polyacrylonitrile (AN69) capillary dialyzers in three patients receiving ACE inhibitors. Such reactions were not observed either in patients treated with ACE inhibitors but dialyzed on other membranes (N = 9), nor in patients on AN69 who did not receive ACE inhibitors (N = 19). These anaphylactoid reactions could be due to bradykinin accumulation, as a result of both increased synthesis—by interaction of blood with the AN69 polymer—and catabolism blockade by ACE inhibitors.

A spectrum of anaphylactoid reactions has been reported in patients undergoing hemodialysis (HD) with Cuprophan dialyzers [1]. We have recently observed five severe anaphylactoid-like reactions in three chronic HD patients dialyzed on single-used polyacrylonitrile (AN69) capillary dialyzers and treated concomitantly with angiotensin converting enzyme (ACE) inhibitors. As such reactions were not observed in patients receiving ACE inhibitors but dialyzed on other membranes, we suggest that both the interaction of blood with the AN69 polymer and ACE inhibition are involved in the pathogenesis of these anaphylactoid reactions. The life-threatening character of these reactions has urged us to draw the attention of nephrologists on this phenomenon.

Methods
Case reports

Case 1. Case 1 is a 67-year-old man who had been dialyzed for seven months using a AN69 capillary dialyzer (Filtral 16, Hospal, France). On 13 August 1989, enalapril maleate (Renitec®, Merck, Sharp & Dohme) was started for moderate hypertension (2.5 mg daily). On August 21st, at the start of HD, he experienced a mild edema of the mucosae of eyes and mouth, and hypotension. At the next HD session, he developed a severe swelling of the face, and of the buccal and laryngeal mucosae, hypotension, vomiting, and abdominal cramps. These symptoms occurred immediately after the first passage of blood through the extra-corporeal circuit. The patient was shifted on a hemophan capillary dialyzer (Alwall GFS Plus 12, Gambro, Sweden) and enalapril was stopped. No further episodes were observed, even after the reintroduction of enalapril (2.5 mg/day) one month later.

Case 2. Case 2 is a 49-year-old male on HD since February 1987. He had been doing well on a Filtral 16 dialyzer since June 1987. On 22 January 1990, enalapril (2.5 mg/day) was started for hypertension. On 16 February, immediately after the initiation of the dialytic procedure, he suffered from chest discomfort, bronchospasm, abdominal cramps, hypotension, and edema of the face, tongue, and lips. At the start of the next HD, the same symptoms recurred with greatly increased severity. Since then, he has been dialyzed using a hemophan dialyzer (Hemoflow E4S, Fresenius, FRG), without any further problem. ACE inhibitors have been maintained unchanged.

Case 3. Case 3 is a 50-year-old woman who has been dialyzed since December 1981. She had a history of allergy to ampicillin and of idiosynchronia to radioccontrast media. On January 1st, 1990, captopril (Capoten®, Squibb) was started for cardiac insufficiency (6.25 mg, twice daily). This medication was stopped 48 hours later because of an allergic rash, and lisinopril (Zestril®, ICI Pharma) was introduced on 9 February (2.5 mg daily) and was well tolerated. On 14 February, she was shifted from a Cuprophan (Alwall GFE 18, Gambro, Sweden) to a AN69 dialyzer (Filtral 20, Hospal, France). On 3 March, immediately after the initiation of the dialytic session, she developed a severe anaphylactoid reaction, including angioedema, bronchospasm, abdominal crampoid pain, and shock. Lisinopril therapy was continued, but from that time she has been dialyzed on a hemophan dialyzer (Hemoflow E4S, Fresenius, FRG), and no additional adverse reaction has been noted.

The control of these five anaphylactoid reactions required the HD to be stopped in three cases, i.e. fluid replacement in five cases, hydrocortisone and epinephrine administration in five and three cases, respectively. Symptoms resolved slowly within 2 to 12 hours. All three patients had normal peripheral eosinophil counts (324, 370, and 130 per mm³, respectively), normal IgE levels (40, <5, and <5 U/ml, respectively), and a negative RAST for ethylene oxide. A testing of basophil histamine release was performed in the presence of enalaprilat (N = 2), ethylene oxide (N = 3), and of the effluent obtained by
Table 1. Anaphylaxis, AN69 dialyzers and ACE inhibition in dialysis patients

<table>
<thead>
<tr>
<th>Anaphylactoid reaction</th>
<th>ACE inhibitors (N = 13)</th>
<th>No ACE inhibitors (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AN 69</td>
<td>Other membranes</td>
</tr>
<tr>
<td>Present(^c)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Absent(^b)</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Statistical significance(^d)</td>
<td>(P &lt; 0.05)</td>
<td>(P &lt; 0.005)</td>
</tr>
</tbody>
</table>

\(^a\) Cellulose acetate (Duoflax, CD Medical); \(N = 6\); cuprophan (Alwall GFE 18 E, Gambro); \(N = 3\)

\(^b\) Cellulose acetate; \(N = 20\), cuprophan; \(N = 18\), hemophan (Alwall GFS Plus 12, Gambro, and Hemoflow E4S, Fresenius); \(N = 5\)

\(^c\) Number of patients who developed at least one episode of anaphylactoid reaction

\(^d\) As compared with the patients dialyzed on AN69 and receiving ACE inhibitors (\(\chi^2\) test, with Yate’s correction for small samples).

Rinsing a new Filtral 16 dialyzer \((N = 3)\), and was negative in each case.

Results

Complementary epidemiological data

We reviewed the charts of the 75 patients dialyzed throughout the last year in our in-hospital HD center. All were hemodialyzed on single-used dialyzers. Results are summarized in Table 1 and show that anaphylactoid reactions were exclusively associated with the combined use of the AN69 capillary dialyzer and of an ACE inhibitor. Only one patient had no adverse effect after three months of exposure to both AN69 and ACE inhibitors (enalapril 10 mg/day).

Discussion

ACE inhibitors are now widely used to treat hypertension and have been recently recommended as the first step treatment in mild to moderate hypertension [2]. Angioedema is a rarely reported side effect of this therapy, occurring in 0.1 to 0.2% of patients, usually during the first month of therapy [3]. By contrast, angioedema arose in 3 out of 13 of our HD patients receiving ACE inhibitors (that is, 23%). The chronological link between this acute phenomenon we observed at the start of the dialysis session strikingly suggests a close interaction between ACE inhibitors and the dialytic process itself.

To our knowledge, there has been no previous report of such anaphylactoid-like reactions occurring as a result of ACE inhibition in patients hemodialyzed using AN69 membranes. However, we know about a similar case observed in another Belgian hemodialysis unit (Cuvelier, personal communication).

ACE inhibitors have been developed to block the renin-angiotensin-aldosterone system. However, their mechanisms of action are not restricted to the inhibition of the conversion of circulating angiotensin I to angiotensin II, but also concern other hormonal systems, such as kinins and prostaglandins [4-6]. Indeed, it has been hypothesized that angioedema developing in patients treated with ACE inhibitors might be secondary to modification in bradykinin metabolism [3].

In our HD patients, anaphylactoid reactions occurred exclusively in those patients exposed to both ACE inhibitors and to the AN69 membrane. This complication was observed in three of the four patients of this group after 5, 8, and 25 days of exposure, respectively. Since certain dialysis membranes could activate bradykinin formation [7, 8] and since kinins catabolism is blocked by ACE inhibitors [9], we assume that kinins accumulation might be involved in the pathogenesis of the anaphylactoid reactions reported in our patients. Indeed, it is known that bradykinin formation in human plasma may be initiated by activation of the Hageman Factor (HF) by contact with certain negatively charged surfaces [9, 10]. Interestingly, the negatively-charged AN69 membrane has been shown to be a most potent activator of HF in vitro [7]. Whether HF is actually activated during HD in vivo remains, however, a matter of controversy [8, 11]. Activated HF converts prekallikrein to kallikrein, which in turn cleaves HMW kininogen to release bradykinin [9]. The latter is an important mediator of inflammation, which could induce the symptoms observed in our patients, including angioedema, abdominal cramps, vomiting, chest pain, bronchospasm, hypotension, and shock [9].

Alternatively, substance P could be involved in the physiopathology of the anaphylactoid reactions that we observed. Indeed, this tachykinin, which is known to induce vasodilatation, hypotension, and intestinal smooth muscle contraction [12, 13], has also been shown to be catabolized by the ACE [14].

In conclusion, nephrologists must be warned that life-threatening reactions may occur as a consequence of ACE inhibition in patients dialyzed on AN69 membranes. This is of great practical importance since a large number of uremic patients may be potential candidates for ACE inhibition therapy, either for hypertension or heart insufficiency, while there has been a recent trend to the more generalized use of synthetic high flux dialyzers, including AN69 [15]. Our observations also constitute a unique example of complex interaction between blood, artificial surfaces, and drugs. Further studies are required to investigate the pathogenesis of anaphylactoid reactions due to the combined use of ACE inhibitors and the AN69 membrane.

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References