Angioedema Associated With Angiotensin-Converting Enzyme Inhibitor Use

Outcome After Switching to a Different Treatment

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Background: Angiotensin-converting enzyme (ACE) inhibitors are associated with angioedema episodes that are potentially life-threatening. Few data are available on the outcome of patients reporting this adverse effect when they are switched to another drug. Scattered reports of angioedema associated with angiotensin II receptor blocker (ARB) use question the safety of using these drugs in patients with ACE inhibitor–related angioedema. We describe 64 consecutive patients with ACE inhibitor–related angioedema, the outcome after discontinuing this treatment, and the safety of using ARBs.

Methods: Retrospective analysis of 64 consecutive patients (January 1993 to June 2002) presenting with angioedema onset while receiving treatment with an ACE inhibitor.

Results: Patients were recommended to stop ACE inhibitor use, substituting it upon advice of the physician. Fifty-four patients were available for follow-up (median follow-up, 11 months; range, 1-80 months): 26 had switched to an ARB, 14 to a calcium antagonist, and 14 to other antihypertensive drugs. Angioedema disappeared or drastically reduced upon withdrawal of the ACE inhibitor in 46 patients (85%). For the remaining 8 patients, angioedema was due to a cause other than ACE inhibitor use in 2; angioedema persisted independent of the treatment and without apparent cause (idiopathic angioedema) in 4; angioedema persisted after switching to an ARB and disappeared upon its withdrawal in 2.

Conclusions: Stopping ACE inhibitor use without further assessments is a successful measure in the large majority of patients developing angioedema while taking this drug. Only a small percentage of patients with ACE inhibitor–related angioedema continue with this symptom when switched to an ARB.
fecting bradykinin metabolism should not present a risk of angioedema for patients who had this complication while taking ACE inhibitors.

Angiotensin II receptor blockers (ARBs), introduced in 1995 for treatment of hypertension, have a pharmacological profile similar to ACE inhibitors in blocking the renin-angiotensin system. Because they do not theoretically affect bradykinin, they are good candidates to substitute for ACE inhibitors in patients with bradykinin-related adverse reactions to these drugs. Nevertheless, occurrence of angioedema with different ARBs has been reported and the safety of these drugs for this indication is now debated.

The reports that describe large series of patients with angioedema during treatment with ACE inhibitors or ARBs are reviews of data from institutes for pharmacovigilance or from hospital files, and do not contain information on the recurrence of angioedema after treatment was changed. Thus, they lack a main clue to substantiate the diagnosis of drug-related angioedema. Actually, it is possible that angioedema will continue independent of the treatment, either because of the presence of a preexisting condition causing the angioedema or because the association with the drug was fortuitous.

We report on the outcome of 64 consecutive patients with ACE inhibitor–related angioedema after discontinuing ACE inhibitor treatment and on the safety of using ARBs.

**METHODS**

**STUDY POPULATION**

From January 1993 through June 2002 we saw at our outpatient clinic 1168 patients for symptoms of angioedema with or without urticaria. Sixty-four of these patients were receiving treatment with an ACE inhibitor and had no other obvious causes for angioedema; 38 were men and 26 were women. Median age was 63 years (range, 46-84 years). Known causes of angioedema were excluded by clinical history that included detailed information about personal and familial allergies; relationship of angioedema to potential causative agents (eg, food, drugs, and chemicals); and complete physical examination. If known causes were excluded, patients were simply recommended to discontinue the ACE inhibitor and, after obtaining informed consent to participate in this study, to return for follow-up.

**PLASMA MEASUREMENT**

To rule out the possibility of a deficiency of C1 inhibitor (C1-INH) as the cause of angioedema, all patients were tested for C1-INH function, as measured by chromogenic assay (Baxter), and for C1-INH, C4, C3, and Clq antigens, as measured by radial immunodiffusion (NOR-Partigen, LOW-Partigen for C1q; Behringwerke AG, Marburg, Germany).

**RESULTS**

The ACE inhibitors used by the 64 patients at the time of onset of angioedema are shown below.

<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril maleate</td>
<td>35 (54)</td>
</tr>
<tr>
<td>Fosinopril sodium</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Quinapril hydrochloride</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Captopril</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Benazepril hydrochloride</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Delapril</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Scattered but unequivocal symptoms of angioedema before starting the ACE inhibitor therapy were recorded in 6 patients, and in 4 patients it could not be clarified whether angioedema or urticaria had previously been present. These patients were included in the study because the frequency of angioedema clearly worsened after starting ACE inhibitor therapy. Fifty-four patients denied any previous symptoms of urticaria or angioedema. The median length of ACE inhibitor treatment before the appearance of angioedema was 12 months (range, 0-156 months) and the median duration of ACE inhibitor use after the appearance of the first angioedema episode was also 12 months (range, 0-120 months). Grouping of the patients according to the duration of ACE inhibitor use after the first episode of angioedema is as follows: less than 1 month, 14 patients; 1 to 6 months, 12 patients; 6 to 12 months, 11 patients; and longer than 12 months, 27 patients. For patients continuing to take ACE inhibitors for 1 year or more after the first episode of angioedema, 7 (22%) had recurrences after 12 years; 9 (28%) had recurrences for 6 to 11 years; and 16 (50%) had recurrences between 1 and 5 years.

The face was the site most commonly involved (55 patients), followed by the tongue (25 patients). Other cutaneous locations were rare (9 patients) as well as abdominal symptoms referable to edema of the bowel mucosa (3 patients). Six patients had episodes of dyspnea due to laryngeal involvement. One of them underwent endotracheal intubation.

Withdrawal of the ACE inhibitor was recommended to all patients. Ten patients did not return for the follow-up visit and therefore are not further considered. Of the remaining 54 patients, 26 switched to an ARB, 14 to a calcium antagonist, and 14 to other treatments (β-blocker [5], α-lytic [1], diuretic [3], no treatment [5]). In these 3 groups, patients were not significantly different in terms of age, sex, duration of ACE inhibitor treatment before and after appearance of angioedema symptoms, presence of angioedema and/or urticaria before starting the ACE inhibitor use, or frequency of angioedema recurrence. The median length of the follow-up was 11 months (range, 1-80 months). Withdrawing the ACE inhibitor resulted in complete disappearance of angioedema in 37 patients (69%) and in drastic reduction in frequency and severity, so that the patients considered them negligible, in additional 9 patients (17%). Eight patients (15%) did not experience any improvement. Evolution of angioedema by means of the new therapeutic regimen is reported in the Table.

The 8 patients who did not benefit from stopping ACE inhibitor use (5 who switched to ARBs and 3 to cal-
Occurrence of angioedema has been reported with the use of all ACE inhibitors and it is considered a class-related side effect.\(^3\) Our data confirm this finding, listing 10 different ACE inhibitors used at the time of onset of angioedema. The strikingly higher rate of recurrence with enalapril (55%) is remarkable. However, this is by far the most commonly used ACE inhibitor in Italy. Although we cannot exclude that enalapril carries a higher risk for angioedema compared with other preparations, it is still likely that our finding is just the consequence of its prominent position on the market. Angioedema related to ACE inhibitor use belongs to the group of an-gioedema that occurs in absence of significant rush of urticaria.\(^24\) The best recognized example in this group is hereditary angioedema, which is due to C1-INH deficiency, and likely is mediated by bradykinin.\(^25\) Along with these clinical and pathogenetic analogies, ACE inhibitor–related and hereditary angioedema share the emblematic, unexplained feature of recurrence of symptoms at randomly variable frequency, despite the constant persistence of the etiologic factor (C1-INH deficiency on one hand, ACE inhibitor treatment on the other).\(^26,27\) Efforts to identify the additional condition(s) that could link up with the initial cause in order to have angioedema to emerge remain unconvincing. A partial C1-INH deficiency has been hypothesized to be the predisposing factor for ACE inhibitor–related angioedema,\(^3\) but this supposition has never been confirmed; moreover, our patients’ complement parameters were normal.

The severity of a condition characterized by angioedema depends on the rate of recurrences rather than on the risk of fatalities. Analysis of patients who remained on the ACE inhibitor for 1 year or longer after the first angioedema episode shows that in half of them symptoms recurred from a minimum of one every other month up to a weekly frequency. Considering that each attack lasts 48 to 96 hours, it results in disability of 10 to 120 days per year. This fact, along with the mentioned risk of fatality (in our series 1 patient underwent tracheos- tomy), emphasizes the importance of recognizing ACE inhibitors as a cause of angioedema. Unfortunately, the knowledge of this important adverse effect of ACE inhibitor use among practitioners is still lacking. The median of 10 months between appearance of angioedema and withdrawal of the drug should be regarded as an unacceptably low. error that needs to be corrected because it exposes patients to severe risks.

We examined the outcome of patients upon withdrawal of the ACE inhibitor. In most, angioedema recurrence stopped or was drastically reduced, thereby reinforcing the evidence of a cause-effect relationship between the side effect and the treatment. The beneficial effect of stopping the drug was also verified in patients with a previous history of angioedema, which is an acknowledged risk factor for developing ACE inhibitor–related angioedema. A favorable outcome upon stopping the treatment was recorded in all 6 patients with such a history. Thus, since 85% of the patients solved the problem just upon stopping the drug, we recommend that this simple measure, without further assessments, should be immediately taken in patients who experience angioedema while taking ACE inhibitors.\(^28,29\)

The final relevant point from this study concerns the safety of ARBs. As highlighted, these drugs appear the more obvious substitutes for ACE inhibitors, but reports of angioedema with their use suggest to reserve their use for patients with ACE inhibitor–related angioedema. Based on animal studies showing that the hypotensive effect of ARBs could be realized in part through release of vasodilators such as bradykinin,\(^30\) it also has been postulated that with these drugs angioedema could be bradykinin dependent.\(^31\) However, we found that these drugs do not worsen the frequency and the severity of symptoms in patients with hereditary angioedema, as one would expect with a drug

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**Abbreviations**: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

*The differences among the 3 groups were statistically nonsignificant (P > .05) by t test and Mann-Whitney test.*
that increases bradykinin levels or activity, and as it oc-
curs with ACE inhibitors.30,31 Six of our patients with her-
editary angioedema are taking an ARB for hypertension
or renal disease since 6 months or more without effect on
angioedema recurrences.

In the case of patients with ACE inhibitor–related
angioedema, our overall experience on using ARBs as sub-
titutive therapy is largely favorable, and this confirms
another recent report32 on this issue. Twenty percent of
patients in both the group taking calcium antagonists and
ARBs did not benefit from just stopping the ACE inhibitor.
However, this percentage also comprises patients in
whom the association between antihypertensive drug and
angioedema was shown to be just fortuitous. That an ARB
could have sustained angioedema was a possibility for 2
(8%) of the 26 patients who switched to this class of drugs.
This limited percentage does not seem a strong argu-
ment to consider ARBs as a contraindication in patients
with ACE inhibitor–related angioedema.

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REFERENCES

2001;24:599-606.
2. Israfil ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-
converting enzyme inhibitor therapy: a review of the literature and pathophy-
3. Vleeming W, van Amsterdam JG, Stricker BH, de Wildt DJ. ACE inhibitor-
18:171-188.
4. Brown NJ, Snowden M, Griffin MR. Recurrent angiotensin-converting enzyme
5. Dean DE, Schultz DL, Powers RH. Asphyxia due to angiotensin converting en-
zyme (ACE) inhibitor mediated angioedema of the tongue during the treatment
2002;346:175-179.
7. Kaplan AP, Joseph K, Silverberg M. Pathways for bradykinin formation and in-
associated angioedema is characterized by a slower degradation of des-arginine
P in individuals with a history of angio-oedema on ACE inhibitors. Lancet. 2002;
359:2088-2089.
1911.
12. Lo KS. Angioedema associated with candesartan. Pharmacotherapy. 2002;22:
1176-1179.
13. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in pa-
ients with previous ace inhibitor-induced angioedema? Drug Saf. 2002;25:73-
76.
angioedema: on the heels of ACE inhibitor angioedema. Pharmacotherapy. 2002;
22:1173-1175.
15. Chiu AG, Krownik EJ, Deeb ZE. Angioedema associated with angiotensin II re-
ceptor antagonists: challenging our knowledge of angioedema and its etiology.
Laryngoscope. 2001;111:1729-1731.
16. Warner KK, Visconti JA, Tschampel MM. Angiotensin II receptor blockers in pa-
nents with ACE inhibitor-induced angioedema. Ann Pharmacother. 2000;34:
526-528.
2000;356:608-609.
935.
19. van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. Angioneurotic edema at-
20. Sharma PK, Yium JJ. Angioedema associated with angiotensin II receptor an-
21. Frye CB, Pettigrew TJ. Angioedema and photosensitive rash induced by valsar-
22. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker lo-
23. Kleiner GI, Gliclas P, Stadtmueller G, Cunningham-Rundles C. Unmasking of ac-
quired autoimmune C1-inhibitor deficiency by an angiotensin-converting en-
26. Schiller PI, Messmer SL, Haefeli WE, Schlienger RG, Bircher AJ. Angiotensin-
converting enzyme inhibitor–associated angioedema: late onset, irregular course,
27. Carugati A, Pappalardo E, Zingale LC, Cicardi M. C1-inhibitor deficiency and angio-
28. Orlan N, Patterson R, Dykewicz MS. Severe angioedema related to ACE inhibi-
tors in patients with a history of idiopathic angioedema. JAMA. 1996;276:1287-
1289.
29. Agostoni A, Cicardi M. Contraindications to the use of ACE inhibitors in patients
30. Sosa-Canache B, Cierco M, Gutierrez CI, Israel A. Role of bradykinins and nitric
oxide in the AT2 receptor-mediated hypotension. J Hum Hypertens. 2000;14
(suppl 1):S40-S46.
31. Ebo DG, Stevens WJ, Bosmans JL. An adverse reaction to angiotensin-
converting enzyme inhibitors in a patient with neglected C1 esterase inhibitor
32. Gavaz L, Gavras A. Are patients who develop angioedema with ACE inhibitor at
risk of the same problem with AT1 receptor blockers? Arch Intern Med. 2003;
163:246-241.