

Cough and Angioedema in Patients Receiving Angiotensin-Converting Enzyme Inhibitors. Are They Always Attributable to Medication?

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SUMMARY

Cough is very frequent in patients receiving angiotensin-converting enzyme inhibitors (ACEIs); patients develop dry cough, frequently associated with sore and itchy throat. A causal relationship between ACEI and cough is not always present. Causality is established if cough disappears after the drug is withdrawn and reappears when it is re-administered (dechallenge - rechallenge). This method does not carry any risk and reduces the overdiagnosis of this association; however, it is not widely accepted and few experts do not recommend it. On the other hand, some studies have reported that cough might disappear despite continuing treatment. ACEI-induced angioedema is the most severe adverse effect. Typically, it involves the face, lips and tongue. Most cases are not severe and do not require treatment. However, recurrences may occur if angioedema is not detected, increasing the severity of the reaction. The goal of this review is to analyze the most relevant adverse effects of this important family of drugs.

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Key words

> Hypertension - Cough - Angioedema - Treatment

Abbreviations

>	ACCP	American College of Chest Physicians	ACE	Angiotensin-converting enzyme
	ARB	Angiotensin-II receptor blocker	ACEI	Angiotensin-converting enzyme inhibitor

There are two ways to slide easily through life; to believe everything or to doubt everything. Both ways save us from thinking.

ATTRIBUTED TO **ALFRED KORZYBSKI**
Polish-American scientist (1879-1950)

Cough is a frequent cause of consultation that is sometimes a challenge for the attending physician. (1) In addition, it is the most common adverse effect in patients treated with angiotensin-converting enzyme inhibitors (ACEIs). Although other agents can also produce cough, ACEIs are the group of drugs mostly associated with this effect. The different guidelines and reviews about chronic cough (1-4) recommend making a thorough interrogation about the drugs used by the patient, especially ACEIs.

Angioedema is an uncommon yet dramatic episode that jeopardizes the patient's life. It is the most severe adverse effect of ACEIs; fortunately, its frequency is extremely low.

The goal of the present review is to analyze the relation between this family of drugs and cough

and angioedema, two adverse effects that should be recognized due to their frequency or severity.

ADVERSE EFFECTS OF ACEIs

The experts agree (5-12) that ACEIs are safe and well tolerated first-line drugs for the treatment of several conditions. Captopril was the first ACEI approved in the USA in 1981 for the treatment of refractory hypertension and was used in doses that doubled (8) the maximal dose currently used. (7) In consequence, the incidence of dose-related effects was high. Initially, adverse effects as dysgeusia and skin rash were more commonly observed with captopril compared to enalapril, (8) probably due to the presence of a sulfhydryl group in the first drug. Subsequently, these differences were attributed to the use of nonequivalent doses. (8, 9)

ACEIs are classified in three categories according to the presence of a sulfhydryl, a carboxyl or a phosphoryl group which may generate differences in each drug; however, the clinical relevance of such

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differences has never been demonstrated (5) and may do not even exist.

MAGNITUDE OF COUGH

Curiously, cough was not initially identified as an ACEI-related adverse effect. (8, 9, 13) Postmarketing studies estimated that the incidence of cough ranged between 1% and 3%. One explanation proposed is that cough is a common symptom that is not traditionally associated with drug use. (4, 13)

Thus, the information reported differed from that observed in clinical practice. Sebastian et al. (13) conducted one of the first studies to determine the incidence of ACEI-related cough. They compared the frequency of cough in patients receiving captopril versus enalapril with that of patients in a "control" group treated with hydrochlorothiazide. The incidence of cough was 19% in patients treated with ACEIs - no significant differences were observed between both treatment groups - and 9% in patients treated with hydrochlorothiazid e. The authors attributed that the high incidence of cough might be due to the fact that the study design asked patients to respond to specific questions about cough, instead of reporting the prevalence of spontaneous, patient-initiated complaints.

Although cough is an ACEI-related adverse effect well documented, the published risk varies from 5% to 30%. (2, 4-7, 10) Most large studies did not consider cough as an endpoint.

The mechanism of cough remains uncertain. Several theories have been proposed, yet none of them have given conclusive explanations. (6, 14, 15) The accumulation of bradykinin, substance P and other products usually degraded by the angiotensin-converting enzyme (ACE) might trigger or facilitate coughing. Other authors consider that these drugs do not have a direct effect but sensitize the cough reflex, putting into evidence other causes of cough without previous clinical expression. (4)

WHEN SHOULD ACEI-INDUCED COUGH BE SUSPECTED?

The diagnosis of ACEI-induced cough is a complex process due to the lack of physical findings and complementary tests. For this reason, this condition should be suspected to avoid making the patient undergo useless examinations and therapeutic tests. However, this entity is not the most common cause of chronic cough (1-6, 16) as asthma, gastroesophageal reflux disease and upper airway cough syndrome, previously known as "postnasal drip". Therefore, although ACEIs should be withdrawn in the presence of cough, it is important to consider other highly prevalent conditions. (16)

ACEI-induced cough is dry, non-productive, usually persistent and frequently associated with sore and itchy throat. ACEI cough may be associated with upper respiratory symptoms of rhinitis, and it is probably underappreciated that these drugs may lead to rhinitis. (15) Patients with heart failure, (6) women, non-smokers, individuals with ACE genotype II, and those of black or Asian ethnicity have been

reported to be at increased risk of ACEI-induced cough. (6, 14, 15) The intensity of cough is generally mild to moderate, but is sometimes severe enough to require discontinuation of the drug. It is difficult to determine the percentage of patients requiring drug discontinuation as the information available is contradictory.

In 1992, Reisin and Schneeweiss described six patterns of cough (17) associated with ACEIs. An important number of patients presented spontaneous attenuation or disappearance of symptoms despite unaltered administration of these drugs and without any treatment aimed against this symptom; other subgroup developed intermittent cough with cough free periods of 2 weeks to 3 months. In another series published in the same year, the same authors reported that more than 50% of patients developed complete disappearance of symptoms despite continuing with treatment. (18) However, no other studies focused on this finding of continuation of ACEIs, monitoring the development of cough. We believe that more evidence is necessary for decision-making on special situations.

It has been classically postulated that ACEI-induced cough is a "class effect" of these drugs. Yet, it is not possible to establish if all ACEIs have the same ability to induce coughing. While some studies and consensus statements (5, 13) have established that there are no differences among them, a recent study (19) has found differences among cilazapril, enalapril, perindopril and imidapril. The incidence of cough was greater in patients receiving cilazapril and enalapril, compared with those treated with perindopril and imidapril. The authors could not explain the difference. Interestingly, both drugs with greater incidence of cough were more efficient to control blood pressure levels. We estimate that more studies are necessary to draw definite conclusions.

The time interval from initiating treatment to the development of cough is very variable; therefore this information is insufficient to draw diagnostic conclusions. Cough may appear a few hours or months after initiating treatment. (6, 10) In general, cough develops within the first year in most patients, (10), particularly within the first 6 weeks. (19) The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines recommend that in patients presenting with chronic cough, in order to determine that the ACE inhibitor is the cause of the cough, therapy with ACE inhibitors should be discontinued regardless of the temporal relation between the onset of cough and the initiation of ACE inhibitor therapy (grade of recommendation, B). The diagnosis is confirmed by the resolution of cough, usually within 1 to 4 weeks of the cessation of the offending agent; however, the resolution of cough may be delayed in a subgroup of patients for up to 3 months. Despite this experts' recommendation, we think it appropriate to make some observations. Naranjo et al. (20) developed the most frequently used algorithm for adverse drug reactions. This 10- item questionnaire allows the estimation of the likelihood of causal association.

The development of the adverse effect after initiating treatment and symptom recurrence when the drug is readministered (rechallenge) is the strongest criteria of this scale. In the study by Tumanan-Mendoza (19) cough was labeled as secondary to the specific ACEI if such medication fulfilled the criteria involved in the dechallenge and rechallenge phases. The dechallenge/rechallenge criteria resulted to lower incidences of true ACEI related cough as compared to that observed only after discontinuing the drug. In other words, in a significant number of patients with ACEI-induced cough, the symptom disappeared after drug discontinuation but did not reappear when the drug was readministered. The same ACCP guideline recommends that in patients whose cough resolves after the cessation of therapy with ACE inhibitors, and for whom there is a compelling reason to treat with these agents, a repeat trial of ACEI therapy may be attempted (grade of evidence A).

Other two strategies have not been considered by the ACCP guidelines: dose reduction or switching to other agent of the same family. The information available is scarce and controversial. There is general agreement that cough does not have a direct relation with the dose; (6-9) however, some authors have reported improvement with dose reduction. (9, 14) More studies are necessary before recommending switching to other agent of the same family.

THE PROBLEM OF ANGIOEDEMA

Angioedema is a self-limiting, nonpitting edema that occurs in the skin and mucous membranes, typically of sudden onset and short duration, associated with an extensive erythematous area. (8) It can involve nearly any part of the body. When the airways are affected it can be life-threatening. However, many mild cases remain unnoticed even for the own patients.

The underlying mechanism of ACE inhibitor angioedema is thought to be the same as that of ACE inhibitor-induced cough. (15, 23) Interestingly, most patients who develop ACEI-induced cough have a low trend to present angioedema, and vice versa; this finding has no explanation yet. (15)

The incidence of angioedema associated with ACEIs use is low, on the order of 0.1 or 0.2%. (7-10, 21) In the OCTAVE study, Kostis et al. reported a greater incidence of enalapril-induced edema: 0.68%. (24, 25) They studied the occurrence of angioedema, comparing also the efficacy and safety of enalapril with omapatrilat, a dual inhibitor of angiotensin converting enzyme and neutral endopeptidase which degrade the natriuretic peptide. Omapatrilat produced greater reduction of blood pressure levels; yet the rate of angioedema was approximately 3 times higher and the drug was not put on the market. (25)

Miller et al. conducted the largest study to estimate incidence of ACE-related angioedema. (22) The estimated incidence of angioedema in ACEIs was 0.197% per year with an adequately narrow confidence interval (0.171% to 0.218%). The authors informed that 1 out of 2600 patients using an ACEI would develop angioedema within the first month

of treatment and 1 out of 1000 would present the symptom during the first year. The risk of angioedema was 3.56 times higher with ACEIs compared to other antihypertensive agents; however, this adverse effect occurred, though exceptionally, with all the agents, including ARBs.

The study by Miller et al. included a larger number of patients, had a longer follow-up period and investigated the presence of angioedema with other antihypertensive drugs, compared to the OCTAVE study. In addition, as it was an observational and retrospective study, it included older patients with multiple comorbidities that would have been rejected in a randomized trial. In this way, the results can be applied to daily practice. On the other hand, and due to its design, undercounting of some mild or atypical cases of angioedema might have occurred and thus explain the differences found in the incidences.

Both the OCTAVE study and the study by Miller et al. (22, 24) found that the risk of developing angioedema was not the same for all patients, as it had already been published. (9) The angioedema rates are nearly 3-4-fold higher in blacks. (22, 24) The risk is higher in women compared to men; surprisingly, diabetics have less risk than non-diabetics. The OCTAVE study reported that smoking, advanced renal disease, age > 65 years, history of rash induced by other agents different from ACEIs and seasonal allergy were associated with greater risk of angioedema. (24, 25) This information was not available in the study by Miller et al. and therefore both studies cannot be compared. The incidence of heart failure and coronary artery disease was higher in the latter study. (22) Other authors have reported that individuals with ACE genotype II and those of Asian ethnicity have greater risk of developing angioedema. (15) Hereditary angioedema is a rare and severe disease due to C1 esterase inhibitor deficiency. (26) The use of ACEIs should be avoided in patients with this condition. (15)

Angioedema due to ACEIs does not present significant rash or urticaria, as hereditary angioedema. ACE inhibitor-related and hereditary angioedema share the feature of recurrence of symptoms at randomly variable frequency and a differential diagnosis should be made. (21) Bradykinin is the main mediator of both types of angioedema; (26) partial deficit of C1 esterase inhibitor has also been associated with ACEI-related angioedema but has not been demonstrated. Some studies found normal C1 esterase inhibitor levels. (21)

ACEI-related angioedema typically involves the face, lips and tongue. (10, 15, 21, 23, 25) Other cutaneous locations are rare (21) and abdominal symptoms may referable to edema of the bowel mucosa. (21, 23) The development of angioedema is not related with the dose administered. (9) It is considered a class effect and is not more frequent with a determined drug of the family. The time course of onset of angioedema after the initiation of therapy may make the diagnosis difficult. Angioedema may occur few minutes after taking the medication, (25)

though most cases occur within four to six weeks of treatment. (9, 10, 21-25) After this period, the risk of angioedema declines significantly, (25) but remains for an indefinite time. (6) Cicardi et al. reported that angioedema may occur after 13 years of initiating treatment. (21) The median length of ACE inhibitor treatment before the appearance of angioedema was 12 months and the median duration of ACE inhibitor use after the appearance of the first angioedema episode was also 12 months. It has been shown that continuing use of ACE inhibitors after the first episode of angioedema results in a markedly increased rate of angioedema recurrence with serious morbidity. (21)

Angioedema disappears upon withdrawal of the ACE inhibitor within a few days; yet, some studies have reported that it may persist for months. (10) In these cases, it would be advisable to rule out other causes or angioedema. In the study by Ciccardi et al., angioedema persisted despite stopping the medication in 8 patients; in 6 patients it was concluded that angioedema was not due to the antihypertensive treatment. (21)

PREVENTION AND MANAGEMENT OF ADVERSE EFFECTS

Several treatments have been used to reduce or stop ACEI-induced cough. (6, 27) In general, the studies showing positive results included a few patients during short periods of time. Larger studies have

demonstrated nonuniform favorable responses. Currently, cessation of therapy is the only effective treatment for ACE inhibitor-induced cough. (1, 6) In patients for whom the cessation of ACE inhibitor therapy is not an option, pharmacologic therapy, including that with sodium cromoglycate, theophylline, sulindac, indomethacin, amlodipine, nifedipine, ferrous sulfate, and picotamide that is aimed at suppressing cough should be attempted. Although these treatments have been recommended by international guidelines, (1, 6) the long-term effectiveness is uncertain, particularly in terms of safety. (22) In this sense, it may be reasonable to switch to an angiotensin-II receptor blocker (ARB).

ACEI-related angioedema does not have a specific treatment and the response to classical therapy is poor. (13) Fortunately, most cases are not severe and do not require treatment at all. In the OCTAVE trial, 86 out of 12,557 patients receiving enalapril developed angioedema. 44 patients did not require treatment and 22 received antihistamines. One patient required epinephrine and no deaths were reported.

Table 1 summarizes the different adverse effects.

ARBs AS ALTERNATIVE TO ACEIs: ARE THEY USEFUL AND SAFE?

Theoretically, angiotensin-II receptor blockers should not produce cough as they do not inhibit angiotensin-

Table 1. Summary and comparison of adverse effects.

	Cough	Angioedema
Dose-related	No	No
Frequency	5% to 40%	0.1% to 0.68%
Class effect	Yes; possible differences between them ¹	Yes
Characteristics	Dry, non-productive Associated with sore and itchy throat	Sudden onset and short duration. Nonpitting. Associated with an erythematous area. Absence of significant skin rash or urticaria.
Localization	---	Face, lips, tongue; possibly in any part of the body.
Type	Classically persistent; may be self-limited or intermittent ²	Atypical presentation (abdominal symptoms)
Associated presentations	Rhinitis and/or URI	No
Intensity	Mild to moderate; may be severe	Usually mild; worsens with recurrence
Onset	First year of treatment, particularly within the first 6 weeks Maximal range: hours-years	First year of treatment, particularly within the first 4 to 6 weeks. Maximal range: minutes-years
Recurrence	Possible Low risk; recommended for diagnosis	Frequent; worse reaction with time
Disappearance	1-4 weeks; sometimes > 3 months	Usually in days; exceptionally lasting months
Diagnosis	Clinical; readministration (rechallenge) may be recommended	Clinical
Higher risk	Black (greater risk) or Asian ethnicity; individuals with ACE genotype II, women	
Treatment	Drug discontinuation. Nonuniform response to treatment (see text)	Self-limited; drug discontinuation; occasionally antihistamines; eventually epinephrine
Observations	The intensity may decrease if drug is continued	Mild cases remain unnoticed even for the own patients.

¹See text for more explanation and reference 19.

²See text for more explanation and references 17 and 18.

URI: Upper respiratory infection.

converting enzyme and therefore do not increase bradykinin and other mediators as substance P. (6, 15) However, several studies and clinical experience have demonstrated the opposite. (6, 15, 29) In addition, some studies have estimated that cough is the main cause of discontinuing therapy with ARBs. (29) For this reason, the validity of switching from an ACEI to an ARB has been discussed. Some studies demonstrated that the incidence of cough induced by ARBs is similar to that produced by thiazides or placebo and significantly lower than ACEI-induced cough. (15)

The development of angioedema has also been reported in patients treated with ARBs; many of them have a history of ACEI-related angioedema. Therefore, the ARBs may not be safe for patients who developed ACEI-related angioedema. In fact, many authors have proposed that these agents should be avoided in patients with previous ACEI-induced angioedema. (30) However, this evidence comes from case reports and not from specially designed clinical trials. In the study by Cicardi et al., (21) only 2 (8%) out of 26 patients who developed angioedema with ACEIs, also presented this adverse effect with ARBs. These findings show that although cross-reactions may occur, the incidence of adverse effects is not significant enough to discourage the indication of these agents considering their important beneficial effects.

Finally, and beyond some experts' suggestions, different studies comparing ARBs to ACEIs in hypertension and heart failure failed to demonstrate the superiority of the former over the latter in the occurrence of hard endpoints. However, these studies concluded that the incidence of adverse effects was lower with ARBs. (31-36) Therefore, and considering that both families present similar additional benefits (37) beyond lowering blood pressure levels that are partially independent of this action, ARBs should be considered a first-line alternative therapy when ACEIs cannot be used.

CONCLUSIONS

ACEIs are generally well tolerated; yet, as they are widely used, the development of uncommon adverse effects has a significant clinical relevance. For the same reason, we should be cautious when evaluating a patient who may present an adverse effect in order not to deprive him/her from an efficient, safe and inexpensive drug. Thus, we must avoid the temptation of simplifying our analysis of attributing a symptom or condition to the medication or, on the contrary, denying that the medication can be the cause.

In patients with suspicion of ACEI-induced cough, the readministration of the agent is a safe method (1, 5, 6) which does not increase the incidence of any of the other adverse effects, not even angioedema, and may reduce the overdiagnosis of this association. However, the rechallenge strategy is not used in daily practice nor recommended by experts once the drug has been discontinued and identified as the probable cause of coughing; in fact, it is replaced by other medication. A sudden and unjustified decision of

discontinuing a safe, inexpensive and highly effective drug counteracts with the possibility of turning a generally asymptomatic condition as hypertension in symptomatic due to the presence of an adverse effect. The period of time between drug discontinuation, the disappearance of cough and rechallenge with the real chance of recurrence of the symptom impairs patient's adherence to treatment and, consequently, with the possibility of achieving blood pressure targets.

We must pay attention to the fact that some studies have reported spontaneous disappearance of cough without discontinuing the drug. This must be considered in mild cases that do not affect the patient's quality of life. In these cases, it is advisable to explain the patient about the benign nature of the symptom and the real possibility of spontaneous resolution.

The recent study by Tumanan-Mendoza (16) leaves the following question: do all ACEIs induce cough with the same frequency and does this have any relation with blood pressure targets?

Another possibility is that the fact that the patient knows about the possibility of cough induced by these drugs may exert some positive or negative influence in the development of the adverse effect. Although we have not found any reference about this matter, there is increasing evidence that it may play some kind of role, especially in specific subgroups of patients. "Symptomatic conditioning" - the development of adverse effects with placebo when the patient believes that he/she is taking the active drug that produced such effects - is well documented. (38)

The occurrence of angioedema, an uncommon adverse effect, should be elicited by specific inquiry. In the SOLVD study, the reported rate of angioedema was about 10 times higher when a specific question on its occurrence was asked. (25) This remarks the importance of adopting this approach in daily practice. Abdominal symptoms due to edema of the bowel mucosa are very rare and there is no conclusive information about its incidence without angioedema in other sites of the body or how it should be managed. Finally, we must remember that this dangerous adverse effect may present at any moment regardless of the time of treatment initiation.

The comprehensive understanding of the drugs used in daily practice is not an easy task; however, it is the only chance to avoid the professional inertia that threatens to replace reasoning and clinical judgment by the automatism of "habit".

RESUMEN

Tos y angioedema en pacientes tratados con inhibidores de la enzima convertidora de la angiotensina: ¿siempre es culpable la medicación?

El uso de inhibidores de la enzima convertidora de la angiotensina II (IECA) en el primer trimestre del embarazo se asocia con un incremento de 2,71 veces del riesgo de malformaciones congénitas mayores (MCM). La tos es un conocido efecto adverso de los inhibidores de la enzima convertidora de la angiotensina (IECA); suele ser seca, no productiva y, muchas veces, asociada con picazón o

sensación desagradable en la garganta. La asociación entre el consumo de un IECA y este fenómeno no siempre es causal. Actualmente, el modo más adecuado de establecer causalidad es observar la desaparición de la tos al suspender el tratamiento y su reaparición al reintroducir la droga (dechallenge-rechallenge). Esto no ha demostrado riesgo alguno y reduce el sobrediagnóstico de esta asociación; sin embargo, esta práctica no es aceptada por todos los expertos y muchos la desaconsejan. Por otro lado, algunos trabajos han encontrado que la tos podría desaparecer pese a que se continúe con el tratamiento, sin necesidad de medidas adicionales.

El angioedema es el efecto adverso más grave de los IECA. Afecta principalmente la cara, los labios y la lengua. La mayoría de los casos son leves, sin requerimiento de tratamiento alguno. Sin embargo, no detectarlo predispone a la recurrencia del cuadro, con incremento en su gravedad. El propósito de esta revisión es analizar dos de los efectos adversos más relevantes de esta importante familia de drogas.

Palabras clave > Hipertensión - Tos - Angioedema - Terapéutica

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Competing interests

None declared.

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