Drug-induced angioedema: an update on new cases and new drugs

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Abstract

Introduction: drug-induced angioedema is a transient swelling of the subcutaneous layer of the skin or submucosal layer of the respiratory or gastrointestinal tracts. These drugs decrease the activity of the enzyme responsible for the degradation of bradykinin, which is then overproduced causing vasodilation and increased permeability. The aim of this piece of research is to identify descriptions of new drugs that can induce angioedema, in light of the latest scientific discoveries.

Materials and methods: a bibliographic research was conducted using keyword “angioedema drug-induced” limited to human race, identifying 267 articles in the last 5 years (2012-2016). Exclusion criteria were applied and the data obtained was organized in a database. The overall sample is composed of 5,387 patients who have had angioedema and are reported in 12 articles; in 4,732 cases angioedema is due to one (or more) drugs.

Results: the average age of patients with angioedema is 65 +/- 11 years, with a slight predominance of the female gender. Some of these patients were already hospitalized, generally in Critical Care Units such as the Stroke Unit; some others were directly hospitalized from the Emergency Room.

Discussion: evidence has shown bradykinin playing a crucial role in the pathogenesis of most forms of non-allergic angioedema, while histamine acts as the major biological mediator in allergic angioedema, with urticaria, rash and flushing, and bronchostriction. This review highlights the need of training for both emergency physicians in Emergency Departments, and nurses in Triage stations on the diagnosis of this disease that, whilst rare, may be induced by several drugs, whose number is growing.

KEY WORDS: angioedema, drug, emergency.
Knowledge on the topic is constantly evolving. The awareness of this has prompted us to conduct a review of the recent literature, performing a meta-analysis of studies [starting from the last meta-analysis of trials on angioedema induced by ACEI /ARB published in 2012 by Makani (9) on angioedema bradikinin-mediated]. The aim of this piece of research is to identify descriptions of new drugs that can induce angioedema, in light of the latest scientific discoveries. Up to 2012, the scene has been dominated by descriptions of cases of angioedema induced by molecules of ACEI, renin inhibitors, NSAIDs, antibiotics, thrombolytics, ARB, and antidepressants. This study assesses the number of reported cases, and identifies in the studies of the last five years any new responsible molecule.

Materials and methods

We have conducted a bibliographic research, updated 8th March 2016, using keyword “angioedema drug - induced” limited to human race, identifying 267 articles in the last 5 years (2012-2016). We had to exclude several of those because of their focus either on istaminergic induced - angioedema (approximately 100 articles), or hereditary angioedema (approximately 20). Some other articles didn’t have up to date database, or included specific problems, such as the pathogenesis elements and therapy (overall 40 articles); other studies were lacking of data. At first we selected the articles by reviewing their abstracts. Then, from those articles, we collected details on: place and type of study, period of data collection, total number of patients, number of case studies on induced- angioedema and non induced angioedema, average age, gender, outcome of patients, kind of drugs involved and molecules of drugs. At this stage we had to exclude other studies that did not provide useful information on the targets (Figure 1).

The data obtained was organized in a database to analyze the incidence of drug-induced angioedema in literature, and to highlight all drugs involved and the new drugs discovered. At the end we recruited 25 case reports and 12 studies; these studies involved 5387 patients with angioedema, 4372 of which were angioedema drug-induced.

Results

Table 1 shows the meta-analysis on studies conducted from 2012 to 2016, to search for forms of angioedema drug-induced and bradikinin mediated.

The overall sample is composed of 5.387 patients who have had angioedema and are reported in 12 articles; in 4.732 cases angioedema is due to one (or more) drugs. The average age of patients with angioedema is 65 +/- 11 years with a slight predominance of the female gender. Some of these patients were already hospitalized, generally in Critical Care Units such as the Stroke Unit; some others were directly hospitalized from the Emergency Room. Three cases series have retrospectively reported cases evaluated over the years in specific clinical setting (surgery and referral centers). The most numerous number of molecules involved is reported in Table 2; the Table does not include the ACEI, as much more numerous than all the others, and already largely reported in the literature.
Table 1 - Studies conducted from 2012 to 2016.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Time (m = month)</th>
<th>Total patient</th>
<th>Ate total case</th>
<th>Drug-induced Ate</th>
<th>Average age</th>
<th>Sex</th>
<th>In-Hospital patient</th>
<th>Drug/ n° of Patient</th>
<th>Authors and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.R.</td>
<td>6m</td>
<td>120.000</td>
<td>447</td>
<td>62</td>
<td>51 ± 20</td>
<td>M 43%</td>
<td>89%</td>
<td>NSAIDS:22</td>
<td>Bertazzoni G. (17) 2014</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>ANTIHIST:15 β BLOCKERS:3</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>ACE INHIBITORS:3</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>β2 AGONISTS:3 CORTICOSTEROIDS:2</td>
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<td></td>
<td></td>
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<td></td>
<td>ANTIHISTAMINERGICS:2</td>
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<td>PPI:6 ANALGESICS:5</td>
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<td>ANTIEPILEPTICS:3 ANTIARRHEAL:2</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OTHER:19</td>
<td></td>
</tr>
<tr>
<td>E.R.</td>
<td>30m</td>
<td>-</td>
<td>127</td>
<td>62</td>
<td>63</td>
<td>M 56%</td>
<td>44%</td>
<td>ACE INHIBITORS</td>
<td>Javahd N. (18) 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ACE-I</td>
<td>Bas M. (19) 2015</td>
</tr>
<tr>
<td>E.R.</td>
<td>18m</td>
<td>-</td>
<td>30</td>
<td>30</td>
<td>M 63 ±10 F: 70 ± 16</td>
<td>M 56%</td>
<td>NR</td>
<td>NR</td>
<td>Amey G. (20) 2013</td>
</tr>
<tr>
<td>E.R.</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>77</td>
<td>M 100%</td>
<td>100%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Stroke unit</td>
<td>-</td>
<td>236 rtPA</td>
<td>8</td>
<td>8</td>
<td>NR</td>
<td>--</td>
<td>100%</td>
<td>rtPA 8</td>
<td></td>
</tr>
<tr>
<td>Stroke unit</td>
<td>11 y</td>
<td>559 rtPA</td>
<td>5</td>
<td>5</td>
<td>NR</td>
<td>M 40%</td>
<td>100%</td>
<td>rtPA 5</td>
<td></td>
</tr>
<tr>
<td>Stroke unit</td>
<td>-</td>
<td>580 rtPA</td>
<td>42</td>
<td>42</td>
<td>70</td>
<td>NR</td>
<td>100%</td>
<td>rtPA-42</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>42 m</td>
<td>-</td>
<td>72</td>
<td>5</td>
<td>55 ± 21</td>
<td>M 25%</td>
<td>NR</td>
<td>ACE-I</td>
<td></td>
</tr>
<tr>
<td>SURGERY</td>
<td>-</td>
<td>165</td>
<td>52</td>
<td>52</td>
<td>49</td>
<td>M 21%</td>
<td>NR</td>
<td>ACE-I</td>
<td></td>
</tr>
<tr>
<td>DATABASE</td>
<td>10 y</td>
<td>45.11</td>
<td>45.11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NR</td>
<td>ACE-I</td>
<td></td>
</tr>
<tr>
<td>AE bradykinin-mediated reference center</td>
<td>10 y</td>
<td>-</td>
<td>89</td>
<td>55</td>
<td>47</td>
<td>M 34%</td>
<td>NR</td>
<td></td>
<td>ACE-I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ARBs:3</td>
<td>Javahd N. (28) 2013</td>
</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>
| NR = not reported.
records molecules such as acetylsalicylic acid, ketoprofen, vildagliptin (+ ACE), alteplase, paracetamol and lansoprazole. Table 3 shows all case reports over the same period of time, relating to drug-induced angioedema bradikinin mediated. It is composed of 23 studies on as many cases. The only drug that not mentioned in previous studies is the urapidil, an antihypertensive medication. There are cases in which the drugs are numerous and it is difficult to give a secure role to only one of these.

Discussion

Angioedema refers to a group of disorders with multiple etiology, similar clinical manifestations and different mechanisms such as genetic mutations, allergic reaction and non-allergic reactions (29,30). Hereditary angioedema, due to a genetic deficiency of C1 inhibitor is the best known, but there is a rare form of angioedema, caused by increased levels of circulating bradykinin (31, 32). Evidence has shown bradykinin playing a crucial role in the pathogenesis of most forms of non-allergic angioedema, while histamine acts as the major biological mediator in allergic angioedema, with urticaria, rash and flushing, and bronchoconstriction (33). Allergic and non-allergic angioedema need to be considered in patients presenting with symptoms of swollen pharynx and larynx, and a correct diagnosis is mandatory to determine the appropriate treatment. In fact, allergic histaminergic angioedema is responsive to antihistamines, cortisone and epinephrine, while non-allergic, non-histaminergic angioedema is not. These are two similar diseases from a clinical point of view, but two different diseases from a treatment perspective.

Analyzing the data of Truven Health Analytics Micromedex bank (34) reporting information on drug-interactions, adverse reactions, and intoxications, angioedema was reported as an adverse event for about 300 drugs. Interestingly enough, considering non-histaminergic angioedema, i.e. angioedema not related to urticaria, pruritus, erythema, rash and flushing, and bronchoconstriction, we found about 50 drugs clinically related to non-histaminergic angioedema. The suspicion of bradysin-mediated drug-induced angioedema has been on history and medical visit. No specific laboratory analysis that could have helped to better define the mechanisms behind the drug-induced angioedema (i.e. bradykinin, complement fraction, triptase, etc.) was performed on these patients, as this is not the aim of the present study.

Therapies that have been used in case of angioedema do not respond to traditional medications (antihistamine, cortisone, and epinephrine), are alternatives, off label and expensive: icatibant (Firazyr® 30 mg in 3 mL, via subcutaneous injection) especially when angioedema is present in a patient taking an ACE-inhibitors; Plasma C1-inhibitor concentrate (Berinert® 20 U/kg body weight, intravenous infusion), Ecallantide Kalbitor® (30 mg, via subcutaneous injection), recombinant human C1 inhibitor (Ruconest® 50 U/kg body
Table 3 - Case Report from 2012 to 2016.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Hospedalized</th>
<th>Drugs</th>
<th>Active principle/ N° of patient</th>
<th>Authors and year</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>1</td>
<td>62 aa</td>
<td>M</td>
<td>ACE-I</td>
<td>Ramipril</td>
<td>Illing E.J. (35) 2012</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>71 aa</td>
<td>M</td>
<td>ACE-I PPI THIAZIDIC</td>
<td>Lisinopril pantoprazole hidrochlorothiazide</td>
<td>Miller D.G. (36) 2012</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>74 aa</td>
<td>F</td>
<td>ACE-I β BLOCKERS THIAZIDIC rtPA</td>
<td>Lisinopril atenololo hidrochlorothiazide rtPA</td>
<td>Fugate J.E. (37) 2012</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>76 aa</td>
<td>M</td>
<td>ACE-I THIAZIDIC</td>
<td>Lisinopril hidrochlorothiazide</td>
<td>Gallitelli M. (38) 2012</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>38 aa</td>
<td>F</td>
<td>ACE-I β BLOCKERS THIAZIDIC rtPA</td>
<td>Lisinopril spironolactone carvedilol rtPA</td>
<td>Cuypers S. (39) 2011</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>66 aa</td>
<td>M Yes</td>
<td>ACE-I NSAIDS β BLOCKERS DIHYDROPYRIDINES rtPA</td>
<td>Enalapril Asa Metoprolol nicardipine rtPA</td>
<td>Maertens M. (40) 2011</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>65 aa</td>
<td>F Yes</td>
<td>Many drugs + ARBs</td>
<td>Valsartan colchicine methotrexate hidrochlorothiazide Sulfolazina enoxaparin, UFH rtPA</td>
<td>Ekmekçi P. (41) 2011</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>50 aa</td>
<td>M Yes</td>
<td>ACE-I; + rtPA</td>
<td>NR; + rtPA</td>
<td>Madden B (42) 2015</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>72 aa</td>
<td>F Yes</td>
<td>Many drugs + ARBs</td>
<td>Irbesarten furosemide ASA Acyclovir venlafaxine gabapentin paracetamol oxocodon</td>
<td>Bertazzoni G. (43) 2015</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>80 aa</td>
<td>F Yes</td>
<td>ACE-I</td>
<td>Lisinopril</td>
<td>de Ruiter M.H. (44) 2014</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>47 aa</td>
<td>F Yes</td>
<td>ACE-I</td>
<td>Lisinopril</td>
<td>Goncalves B.M. (45) 2013</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>60 aa</td>
<td>M</td>
<td>DPP-IV INHIBITOR</td>
<td>Angliptin</td>
<td>Hamasaki H. (46) 2013</td>
</tr>
</tbody>
</table>

To be continued
weight, intravenous infusion). However, when angioedema causes an airway obstruction, they can save the patient’s life; when angioedema causes abdominal attacks with severe pain, they may avoid an unnecessary surgery; this is the reason why it is appropriate to be able to recognize and differentiate angioedema Bradykinin - induced, from histaminergic induced.

This study is useful for updating knowledge about drugs that can induce angioedema. The number of descriptions in the literature is growing over time, and new drugs are constantly being added.

Limits:

1. Up until now, any specific biomarkers that can be easily obtained in emergency routine settings have been identified to help in differential diagnosis. This makes the diagnosis of certainty of these patients difficult, especially in emergency. Gathering information on drug-induced angioedema could help to diagnose and manage drug-induced angioedema appropriately.

2. In some cases more drugs were taken concomitantly, those cases leave doubts on the role of every single one of these in the genesis of angioedema.

Drug-induced angioedema is an evolving topic; this review highlights the need of training for both emergency physicians in Emergency Departments, and nurses in Triage stations on the diagnosis of this disease that, whilst rare, may be induced by several drugs, whose number is growing. This can justify the use of life - saving drugs, even though off label: future advancements and new knowledge will bring additictional experience.

References

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