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Drug-induced non-immune-mediated angioedema

● **Combinations of drugs that increase vascular permeability increase the risk of angioedema.**

Angioedema is a localised oedema of the skin or mucous membranes caused by extravasation of fluid into the interstitial tissue due to loss of vascular integrity. It typically affects the face, lips, tongue, throat, ears, hands, feet and external genital organs (1).

Bradykinin accumulation or histamine release. Drug-induced angioedema is often an immune-mediated allergic reaction. But some drugs cause angioedema through non-immune-mediated mechanisms involving an influx of inflammatory mediators that increase capillary permeability: bradykinin or histamine (1).

Angioedema due to drug-induced bradykinin accumulation is not associated with pruritus or urticaria. It often includes bowel wall oedema with abdominal pain. The drugs implicated are mainly angiotensin-converting enzyme (ACE) inhibitors and *aliskiren*, and more rarely angiotensin II receptor blockers (ARBs or sartans) and *racecadotril* (see also below) (1,2). Antihistamines and corticosteroids are ineffective in treating this type of angioedema.

Some drugs cause histamine release through a direct pharmacological effect on mast cells rather than through an allergic reaction. The main drugs implicated are opioids and radiographic contrast media, the antifungal *caspofungin*, nonsteroidal anti-inflammatory drugs (NSAIDs) and *aspirin* (1,3).

The immunosuppressive agents *sirolimus* and *everolimus* provoke angioedema through an unknown non-immune-mediated mechanism (1,3).

In practice. Angioedema is not always immune-mediated. Concomitant use of several drugs known to increase vascular permeability increases the risk of angioedema.

ACE inhibitors are the most commonly implicated drugs in non-allergic angioedema. They also worsen angioedema induced by other drugs.

Selected references from Prescrire's literature search.

1- Zuraw B et al. "An overview of angioedema: pathogenesis and causes" UpToDate. www.uptodate.com accessed 29 September 2015: 8 pages.

2- Prescrire Editorial Staff "Angioedema due to ACE inhibitors" Prescrire Int 1998; **7** (35): 92-93.

3- "Noscapine" + "Dextromethorphan" + "Pethidine" + "Morphine" + "Sirolimus". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 26 September 2015: 77 pages.

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Noscapine: angioedema

● **Opioids can trigger angioedema.**

Noscapine is an opioid used to treat cough (1).

In July 2015, the Netherlands Pharmacovigilance Centre Lareb announced that it had received 10 reports of angioedema associated with the use of *noscapine* between 1987 and 2013 (2).

The underlying mechanism could be an immune-mediated allergic reaction or *noscapine*-induced histamine release. Histamine increases vascular permeability. *Morphine* and other opioids cause dose-dependent histamine release provoking disorders such as pruritus, urticaria, hypotension, flushing and angioedema.

Opioids, including antitussives, are a possible cause of angioedema.

Selected references from Prescrire's literature search.

1- "Noscapine" + "Opioid analgesics". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 26 September 2015: 77 pages.

2- Lareb "Noscapine and angioedema" 3 July 2015: 5 pages.

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Racecadotril + ACE inhibitors: angioedema

● **A combination that is best avoided.**

In April 2015, the French Health Products Agency (ANSM) reported evidence of an increased risk of angioedema associated with concomitant use of the antidiarrhoeal *racecadotril* and an angiotensin-converting enzyme (ACE) inhibitor (1).

An 80-year-old woman treated with an ACE inhibitor had three episodes of angioedema, two of which occurred when she was also taking *racecadotril* (1).

A search of the French national pharmacovigilance database identified 11 reports of angioedema in patients taking both an ACE inhibitor and *racecadotril*; in 9 of these cases, the temporal relationship between the use of this drug combination and the onset of angioedema was highly suggestive of a causal link (1).

Racecadotril inhibits the neutral endopeptidase involved in the metabolism of bradykinins, which are inflammatory mediators that increase capillary permeability (1). Angioedema is a known adverse effect of ACE inhibitors through a mechanism that involves reduced bradykinin degradation rather than an allergic reaction (see also above) (2).

About 10 years ago, the US Food and Drug Administration (FDA) denied a request for approval of *omapatrilat*, a drug that inhibits both neutral endopeptidase and angiotensin-converting enzyme. The reason for this rejection was the higher risk of severe angioedema demonstrated in a head-to-head trial versus an ACE inhibitor (1).

In practice, it is best that patients with hypertension or heart failure who are taking an ACE inhibitor avoid using *racecadotril* if they develop diarrhoea. Patients should be warned about this risk in advance, because some of them might self-medicate with *racecadotril* without seeking advice from a health professional.

Selected references from Prescrire's literature search.

1- ANSM "GT interactions médicamenteuses - Séance du 13 avril 2015. Racécadotril et inhibiteurs de l'enzyme de conversion" 8 June 2015: 4-5.

2- "ACE inhibitors". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 23 September 2015: 36 pages.