Review Article

Drug-induced chronic cough and the possible mechanism of action

Hongmei Ding[1,2#], Cuiqin Shi[1#], Xianghuai Xu[1], Li Yu[1]

[1]Department of Pulmonary and Critical Care Medicine, Tongji Hospital, Tongji University School of Medicine, Shanghai, China; [2]Department of Pulmonary and Critical Care Medicine, Shanghai Putuo District People's Hospital, Shanghai, China

Contributions: (I) Conception and design: L Yu, X Xu; (II) Administrative support: L Yu; (III) Provision of study materials or patients: H Ding, C Shi; (IV) Collection and assembly of data: H Ding, C Shi; (V) Data analysis and interpretation: H Ding, C Shi; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Dr. Li Yu, MD; Dr. Xianghuai Xu, MD. Department of Pulmonary and Critical Care Medicine, Tongji Hospital, Tongji University School of Medicine, No. 389 Xincun Road, Shanghai 200065, China. Email: yuli0219@sina.com; 05849@tongji.edu.cn.

Abstract: Chronic cough is defined as a cough lasting for ≥8 weeks with a normal chest radiograph. The common causes of chronic cough are cough variant asthma (CVA), upper airway cough syndrome/postnasal drip syndrome (UACS/PNDs), eosinophilic bronchitis (EB), gastroesophageal reflux-related chronic cough (GERC) and atopic cough (AC). Drug-induced chronic cough, a rare cause of chronic cough, refers to a chronic cough caused by certain drugs. In addition to angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), there are cases reporting that some drugs such as omeprazole and leflumide that can cause cough. An important step in the diagnosis and treatment of chronic cough is to determine the history of the patient with regard to any drugs that can induce chronic cough. If the cough occurs after taking the medicine, a suspected diagnosis of drug-induced cough should be established. If the cough resolution occurs within 1 to 4 weeks after drug withdrawal, it would be considered as a side effect of the medication. we should be alert to the possibility of drug-induced chronic cough after excluding CVA, UACS, EB and other common causes of chronic cough. This article reviews the relevant drugs that may cause cough and their possible mechanisms of action.

Keywords: Chronic cough; angiotensin-converting enzyme inhibitor (ACEIs); angiotensin receptor blocker (ARBs)

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Chronic cough is defined as a cough lasting for ≥8 weeks with a normal chest radiograph. The common causes of chronic cough are cough variant asthma (CVA), upper airway cough syndrome/postnasal drip syndrome (UACS/PNDs), eosinophilic bronchitis (EB), gastroesophageal reflux-related chronic cough (GERC) and atopic cough (AC). Drug-induced chronic cough is a relatively rare cause of chronic cough caused by certain drugs and resolves on its own within 1 to 4 weeks after the withdrawal of the relevant drugs, although it may linger for up to 3 months (1,2). According to the Guidelines for Diagnosis of Chronic Cough in China, patients with chronic cough should first exclude drugs as a cause. If the cough can be completely or partially relieved after drug withdrawal, the economic burden and drug adverse reactions can be reduced, and complicated examinations and the use of additional drugs can be avoided (1). It is important for diagnosis and treatment to determine the history of the patient with regard to any medications that can induce chronic cough. In addition to angiotensin-converting enzyme inhibitors (ACEIs), a relatively common drug that induces chronic cough, there are other drugs that can cause chronic cough (3-12). This article reviews the relevant drugs that may cause chronic cough and their possible mechanisms of action.

ACEIs

Cough caused by ACEIs is common in the clinical diagnosis and treatment of chronic cough (13). The biggest challenge to continuing the use of ACE inhibitors is the adverse reaction of cough. In regard to the incidence of cough after taking ACEIs, it is more common in Japan, where it reaches 20–30%, compared with Western countries, where it reaches 5–10% (13-16). Our previous study found that ACEI-associated cough accounted for approximately 3–9% of the 940 patients with chronic cough for 5 consecutive years (17). A more frequent incidence of ACEI-associated cough was noticed among elderly patients than among nonelderly patients (18). As one of the first-line treatments for hypertension (19,20), ACEIs are reportedly effective and positively indicated in patients with chronic heart failure with decreased contractility, myocardial infarction, cerebrovascular disorders, and chronic kidney disease (21-24). The above diseases are more common in elderly patients, leading to a high incidence of ACEI-associated cough among the elderly population.

Omboni *et al.* retrospectively analyzed twenty-three studies, with 5,794 hypertensive patients in three studies, including 1,455 post-myocardial infarction patients exposed to zofenopril at dosages of 7.5–60 mg once daily, and they found that there was a dose-effect relationship between the incidence of cough and the dosage of ACEIs. In addition, some patients experienced the relief of symptoms over time (25). In a prospective study of the frequency and characteristics of cough during ACEI treatment, Sato found that an adverse reaction of cough was observed in 20% of 176 patients with hypertension. Cough as an adverse reaction occurred at a low frequency when the medication was taken at bedtime or combined with concomitant calcium antagonists or diuretics (26). In 27,492 patients with cardiovascular disease, 1,076 patients discontinued the ACEI perindopril due to cough (3.9%) and the clinical determinants of cough were older age, female sex and the concomitant use of lipid-lowering agents (3). A study on the clinical prediction rule for ACEI-associated cough indicated that the independent multivariate predictors of cough were older age, female sex, non-African American race (with East Asians having the highest risk), no history of previous ACEI use, and a history of cough due to another ACEI (27).

The mechanism of ACEI-inducing cough mainly includes the following aspects.

(I) Accumulation of bradykinin and substance P.

Ramipril has been found to increase citric acid-inducing cough in guinea pigs with elevated BK and PGE2 levels in the bronchoalveolar lavage fluid (BALF). The enhancement of citric acid-induced cough caused by ramipril was reduced by the kinin B2 receptor antagonist MEN16132 (28). After taking enalapril, the concentration of substance P in the sputum of the group with a cough was significantly higher than that in the subjects without a cough (29). The cough induced by lisinopril was reversed by bradykinin B2 and NK1 receptor antagonists (30). Treatment of guinea pigs for two weeks with captopril led to an increasing cough response to inhaled citric acid, which was prevented by concomitant treatment with the bradykinin receptor antagonist icatibant. In electrophysiological studies performed *in vitro*, the responses of single vagal C fibers to capsaicin applied to receptive single-fiber units in the trachea were also markedly elevated after perfusion with bradykinin (31). These results indicated that bradykinin/substance P might be involved in ACEI-associated cough through the upregulation of vagal nerve excitability. The effects of ACEIs on blood pressure and cough are shown in *Figure 1*.

(II) Enhanced acetylcholine (Ach)-induced contraction of bronchial smooth muscle.

Bronchial smooth muscle is dominated by the vagus nerve (parasympathetic), which mediates the contraction (cholinergic) and relaxation (noncholinergic) responses of smooth muscle (32,33). A study indicated that M2 and M3 muscarinic acetylcholine receptors were expressed in airway smooth muscle (34). Ach produces a concentration-dependent increase in bronchial smooth muscle contractions. Pretreatment with captopril significantly augments the Ach-induced contractions at each concentration. This sensitization might be responsible for the dry cough associated with ACEI captopril therapy (35). Pretreatment with aprotinin (kinin synthesis inhibitor) or heparin (inositol triphosphate, IP3 inhibitor) blocks the captopril-induced augmentation of bronchial smooth muscle contractions evoked by Ach, suggesting that the IP3 pathway in addition to bradykinin might also be involved in the process of Ach-induced bronchial smooth muscle contractions. Intracellular calcium ions play an important role in smooth

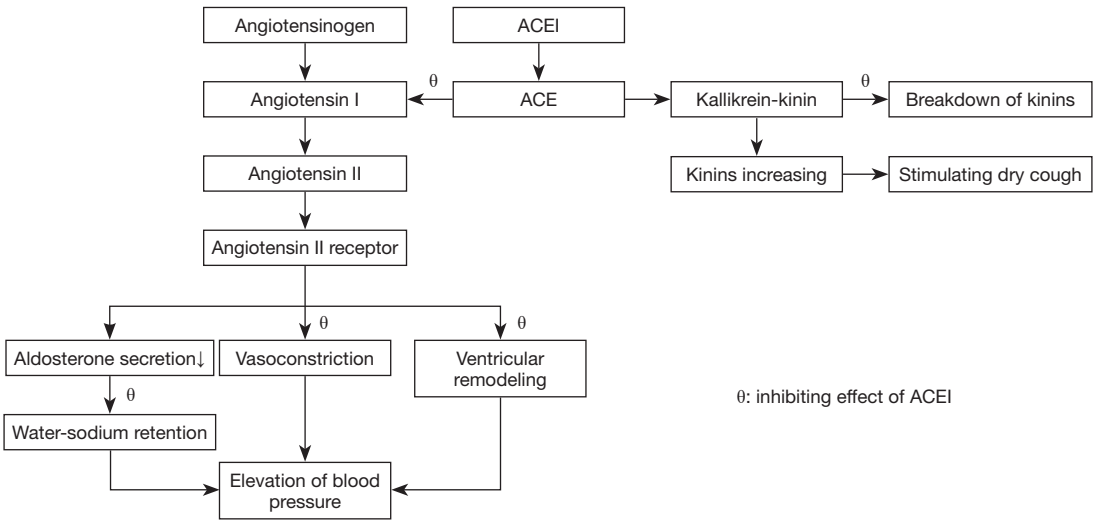

Figure 1 The effects of ACEIs on blood pressure and cough. θ, inhibiting. ACEIs, angiotensin-converting enzyme inhibitors.

muscle contraction. The influx of extracellular calcium ions into the cell causes a massive release of calcium ions in the endoplasmic reticulum, which triggers a series of changes that promote smooth muscle contraction. IP3 allows the inflow of calcium ions by releasing the calcium ions from the smooth endoplasmic reticulum, which opens store-operated Ca^{2+} channels (SOCCs) controlled by the calcium reservoir (36). Furthermore, captopril-induced augmentation of bronchial smooth muscle contractions is absent in calcium-free medium (35), indicating that the enhancement of bronchial smooth muscle contraction induced by acetylcholine by captopril is involved in the extracellular calcium internal flow. Another study advised caution when administering of ACEIs in asthmatic patients and those with known bronchial hyperreactivity (37). This study confirmed that ACEI-associated cough in asthmatic patients might be correlated with bronchial hyperreactivity.

(III) Gene polymorphisms.

A genome-wide association study (GWAS) of ACEI-associated cough found that differences in the introns of the Kv channel interacting protein 4 (KCNIP4) on chromosome 4 may modulate the risk of ACEI-induced cough (38). GWASs in mice have shown a link between KCNIP4 and airway hyperresponsiveness (AHR), which has been confirmed in studies of human asthma and AHR (39). In addition, ABO genetic polymorphisms have recently been associated with angiotensin-converting enzyme (ACE) activity and inflammation, which play a critical role in the pathogenic mechanism of ACE inhibitor-induced cough. A study of ABO genetic polymorphisms in 450 essential hypertensive Chinese patients treated with enalapril indicated that the rs495828 polymorphism was associated with enalapril-induced cough. The results for the rs8176740 polymorphism were significant in the female subgroup (40). At the same time, there was a strong interaction between rs495828 and rs8176746. Bradykinin II (B2) receptor polymorphism was also associated with ACEI-associated cough, while the B2-9 allele reduced ACE activity and caused a cough (41). In addition, the bradykinin II receptor gene rs8016905 was also associated with ACEI-induced cough (42), suggesting the importance of bradykinin in the pathogenesis of ACEI-associated cough. Furthermore, studies on NK-2 receptor gene polymorphisms found that Gly231Glu was negatively correlated with cough (43).

Angiotensin receptor blockers (ARBs)

ARBs can be used as an alternative treatment for patients with ACEI drug intolerance because they cause a lower incidence of cough, are better tolerated and obtain similar

or better antihypertensive effects (4). Cough was the most frequent reason to stop ACEI treatment according to a study of 27,492 patients taking ACEIs, and the rate of switching to ARBs as a second-line alternative due to cough was approximately 4% (3). ARBs carry a risk of cough similar to that of a placebo/diuretics, and it is significantly lower than that related to ACEIs. It is necessary to be alert to the occurrence of cough during treatment with ARBs because the incidence of ARB-associated cough was found to be as high as 20% in early studies (44). As mentioned above, elevated bradykinin levels were thought to be connected to ACEI-associated cough and ARBs could obtain similar bradykinin levels as ACEI due to the reduced metabolism by ACE and neutral endopeptidase, which might be one of the causes of ARB-associated cough (45,46). ACEI-associated cough might be influenced by multiple factors. In addition to substance P, ACEIs might also affect ACE function in susceptible patients, and an increase in the level of kinin might be caused by a gene polymorphism of the bradykinin receptor (42,47). Therefore, the incidence of ARB-associated cough is significantly lower than that of ACEI-associated cough in this specific population.

Opioids

Cough is one of the most common complications of opioids. According to previous studies, the incidence of opioid-induced cough was approximately 28–66%, although lidocaine, propofol and other drugs could partially inhibit this side effect (48,49). The following aspects may be involved in the mechanism underlying opioid-induced cough. First, opioids may inhibit central sympathetic outflow and, in turn, activate the vagus nerve. The enhancement of the parasympathetic nervous system is suggested to cause cough and bronchoconstriction (5,50). Second, the pulmonary chemoreflex may be another likely mechanism. Studies have shown that fentanyl and morphine may cause coughing by promoting the release of histamine, which could enhance the excitability of rapidly adapting receptors (RARs) (51,52). Third, opioid receptors exist in the upper pulmonary mucosa and opioid-induced tracheal and bronchial smooth muscle constriction may trigger the cough reflex (53). Moreover, opioid-induced muscle rigidity, which can cause sudden adduction of the vocal cords or supra-glottic obstruction by soft tissue, may be a possible mechanism (53,54). Former smokers are more likely than current smokers to experience cough, according to a study about the association of fentanyl-induced cough and smoking (55). Desensitization of the cough receptors within the airway epithelium and increased airway mucus secretion covering cough receptors after long-term tobacco smoking may be a possible mechanism for the suppression of cough sensitivity in smoking patients (56,57).

Statins

The statins 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors can effectively reduce plasma low-density lipoprotein (LDL) levels and cholesterol levels, improving the incidence of cardiovascular events and mortality (58,59). Patients diagnosed with hypercholesterolemia and undergoing treatment with statins can experience a series of side effects including coughing, and all the symptoms achieve remission after discontinuation of the treatment for 7–15 days, although the improvement rate of cough only reaches 91.7% (60). According to an analysis from 2004 to 2012 using the Australian database of Adverse Event Notifications (DAEN), the Canada Vigilance Adverse Reaction Online Database and the United States Food and Drug Administration Adverse Event Reporting System (AERS), cough as an adverse reaction is not uncommon in the clinical application of statins. There might be two possible explanations for statin-induced cough. First, the administration of statins could induce PG synthase and increase prostacyclin production, which might cause coughing. Second, statins could stabilize the mRNA of endothelial nitric oxide (NO) synthase, leading to enhanced enzyme expression and NO generation that could increase cough reflex sensitivity (61). According to the case report, statins have interstitial lung disease as a side effect, which could manifest as coughing, but the specific mechanism leading to lung injury is unknown (62). According to three major international adverse event databases, 88% of patients with statin-induced cough lacked lung injury, suggesting that the mechanism underlying statin-induced cough is inconsistent with lung injury (61). The hypothesis is that the mechanism underlying statin-induced bronchial hypersensitivity might be related to the inhibition of HMG-CoA reductase, although further studies are needed to confirm the connection (6). In addition, Liesmaa *et al.* found that lovastatin up-regulates bradykinin type II receptor expression on human coronary artery endothelial cells *in vitro* (63), which is related to the mechanism underlying ACEI-associated cough (41). This finding might also explain why cough is more likely to occur when ACEIs are combined with lipid-lowering drugs,

although the exact mechanism requires further research.

Rare case reports of other drugs

Omeprazole

GERC is one of the common causes of chronic cough. Empirical treatment of suspected GERC is recommended in guidelines from several countries, and the most common treatment is a proton pump inhibitor (PPI) combined with a gastroprokinetic agent (1,2,64,65). Prescription information for omeprazole and pantoprazole indicates that cough symptoms were observed in the trial population (66,67). In addition, case reports suggested that cough induced by omeprazole depended on the drug concentration and is mainly related to the plasma concentration of omeprazole. Therefore, many scholars maintain that cough may be a side effect of PPIs (8). The mechanism underlying omeprazole-induced cough is still unclear, and whether it has a direct pharmacological effect on the receptors involved in the cough reflex remains to be determined.

Leflunomide (LFM)

LFM is a disease-modifying antirheumatic drug. The long-term use of LFM affects multiple systems. The respiratory side effects included bronchitis (7%), bronchospasm and increased cough (3%), respiratory tract infection (15%), pharyngitis (3%), pneumonia (2%), rhinitis (2%) and sinusitis (2%) (68). The cough caused by LFM should be considered for two reasons. First, infection including tuberculosis after immunosuppression might account for the occurrence of cough (69). Second, a cough may be directly caused by LFM, although the mechanism needs to be further explored.

Interferon (IFN) and ribavirin

Dry cough in chronic hepatitis C patients treated with interferon-α monotherapy might result from the indirect effects of IFN immunological pathways (9). After IFN treatment, soluble interleukin-2 (IL-2) receptor levels are significantly increased in patients with chronic hepatitis C (70). It is interesting that plasma soluble IL-2 receptor levels are significantly elevated in patients with acute asthma attacks (71). The association supports the possibility of an immune mechanism in the pathogenesis of interferon-related cough. The combination of pegylated interferon and ribavirin has become standard therapy for chronic hepatitis C infection (72). Dicpinigaitis found that 4 patients without a history of respiratory symptoms developed chronic cough temporally related to the initiation of therapy with pegylated interferon and ribavirin for chronic hepatitis C infection. The cough resolved after the completion of therapy. Capsaicin cough challenge testing was performed to measure the patients' cough reflex sensitivity. In all patients, cough reflex sensitivity was significantly enhanced during treatment compared to 1 month after the completion of therapy (73). Previous studies have observed that cough occurs more commonly in patients receiving the combination of interferon and ribavirin compared to those receiving interferon alone (74,75). The mechanism by which ribavirin might induce cough remains a matter of speculation, although it might enhance UACS/PNDs or gastroesophageal reflux (2), which are known causes of chronic cough. Alternatively, ribavirin might directly stimulate coughing through the activation of the transient receptor potential (TRP) V1 or A1 ion channels, the importance of which in the induction of cough has recently been elucidated (76,77).

Sitagliptin

Sitagliptin is a highly selective oral dipeptidyl peptidase-4 (DPP IV) inhibitor that inhibits the breakdown of incretins such as glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (78), which is used as a monotherapy or as a component of combination therapy for the treatment of patients with type 2 diabetes (79). In a placebo-controlled trial assessing the efficacy and tolerability of sitagliptin in patients with type 2 diabetes mellitus who were inadequately controlled on metformin alone, the incidence of cough as a side effect was reported to be higher in the sitagliptin group compared with the placebo group (80). A case series described 15 patients intolerant to sitagliptin, where 13 of them reported cough with other respiratory symptoms such as rhinorrhea or dyspnea/wheeze. All of them had underlying allergic rhinitis, and the frequency was significantly higher than that in sitagliptin-tolerant patients. Nasal and inhaled glucocorticoids may control the underlying allergic inflammation and abrogate this new sitagliptin-induced pharmacological syndrome. Potential mucosal and central nervous system mechanisms include disruption of neuropeptides and/or cytokines that rely on DPP IV for activation or inactivation, and T cell dysfunction (81). However, the risk of cough was not evident

in any other RCTs or pooled analyses comparing sitagliptin and placebo (82-85). Placebo controlled trials with other DPP IV inhibitors, including linagliptin, saxagliptin and vildagliptin, also did not report any increased risk of cough (86-88). Based on these studies, many scholars maintained that there was a slight increased risk of nasopharyngitis with the use of sitagliptin compared with placebo. However, sufficient evidence is not available to associate an increased risk of acute cough, chronic cough or lower respiratory tract infection with sitagliptin or any other DPP-4 inhibitor (89). These findings collectively suggested the risk of sitagliptin-induced cough is not clear, which need more researches to be determined.

Summary

Although drug-induced chronic cough is not one of the common causes of chronic cough, it accounts for a proportion of the incidence. More attention should be focused on the patient's medication history and identifying the drugs that can induce cough in a timely manner. If the cough occurs after taking the medicine, a suspected diagnosis of drug-induced cough should be established. If the cough resolution occurs within 1 to 4 weeks after drug withdrawal, it would be considered as a side effect of the medication. To support the clinical diagnosis and treatment of chronic cough, we should investigate the newest research on drug-induced cough and identify relevant drugs that may cause chronic cough. For unexplained chronic cough, after excluding CVA, UACS, EB and other common causes of chronic cough, the possibility of drug-induced chronic cough should be considered.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-819). The authors have no conflicts of interest to declare.

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