Dear Editor

**Maculopapular-Type Drug Eruption Caused by Coughcode®-N Combination Tablets**

Coughcode®-N combination tablets (Mylan Pharmaceutical, Tokyo, Japan) are oral antitussive tablets consisting of acetaminophen, bromovalerylurea, dihydrocodeine phosphate, diphenhydramine salicylate, diprophylline, and dl-methylephedrine hydrochloride. Here, we describe a case of maculopapular-type drug eruption caused by Coughcode®-N that was reproduced by oral challenge test.

An 18-year-old Japanese woman visited our department for diagnosis of a faint erythematous rash over the whole body. She stated that she had taken Coughcode®-N and Toclase® (penoxyverine citrate; Dainippon Sumitomo Pharma, Osaka, Japan) for 4 days and over-the-counter medication Kaigen® (Kaigen, Osaka, Japan) for 6 days for a cough and common cold, respectively. Three days before her first visit to our department, she noticed the eruption. Therefore, she had stopped all drugs 2 days before her first visit based on her own judgement.

In an initial physical examination in our department, she had recovered from the common cold. Faint erythematous and maculopapular lesions were present over the whole body (Fig. 1a-c), but there were no mucosal lesions associated with Stevens-Johnson syndrome. Laboratory tests were within normal limits, including complete blood cell count, liver and kidney functions, and serum levels of C-reactive protein (CRP). However, the eosinophil percentage (10.9%; normal 0-8%) was elevated. On the basis of her history and blood test results, drug eruption caused by Coughcode®-N, Toclase® or Kaigen® was suspected.

Lymphocyte transformation tests (LTTs) to Coughcode®-N (stimulation index 0.9; normal <1.8) and Toclase® (stimulation index 0.8; normal <1.8) were negative. The eruption disappeared in 12 days with oral administration of fexofenadine hydrochloride 120 mg/day and topical application of clobetasone butyrate 0.05% on her neck and difluprednate 0.05% on her trunk and extremities. Patch tests were performed using Coughcode®-N (50%, 30%, 10% in petrole-
latum), Toclase® (20% in petrolatum), and Kaigen® (50%, 30%, 10% in petrolatum) according to the guidelines of the International Contact Dermatitis Research Group. Petrolatum was used as a vehicle. All patch tests were negative. Therefore, oral challenge tests were performed in an inpatient setting using Coughcode®-N (1/10, 1/5, 1/2, 1 therapeutic dose), Toclase® (1/10, 1/5, 1/2, 1 therapeutic dose), and Kaigen® (1/10, 1/5, 1/2, 1 therapeutic dose). The test reactions to Toclase® and Kaigen® were all negative. However, the skin eruption was reproduced over the whole body within 2 hours after taking a Coughcode®-N combination tablet at 1 therapeutic dose. The eruption reached its peak intensity after 48 hours (Fig. 1d). At this time, laboratory tests were within normal limits, including eosinophil percentage, but mild fever (37.1°C) and general malaise were present.

Based on these results, we diagnosed this case as a maculopapular-type drug eruption caused by Coughcode®-N combination tablets. The eruptions, as well as mild fever and general malaise, disappeared without treatment within 4 days. Patch tests were performed individually for three of the components of Coughcode®-N (20% acetaminophen, 20% bromovalerylurea, 20% diprophylline) in an outpatient setting, and all were negative. Patch tests to the other three components (dihydrocodeine phosphate, diphenhydramine salicylate, dl-methylephedrine hydrochloride) were not performed because we were unable to obtain these drugs individually. Among the 6 components, acetaminophen is often used for relief of fever and aches and pains associated with many conditions. Thus, the patient requested an oral challenge test to acetaminophen to check for the allergy. Tests using acetaminophen (1/10, 1/5, 1/2, 1 therapeutic dose) were performed in an inpatient setting, and all were negative.

The Coughcode®-N combination tablet was developed in 2002 and is only available in Japan. It is approved for cough suppression, relief of pain, and antipyrexia in common cold syndrome and for cough suppression in bronchitis. Coughcode®-N is a modified tablet in which phenacetin and barbiturates in the Coughcode® tablet were replaced by acetaminophen. Coughcode® tablets were often used for cough and common cold before bronchitis until 2001, but the distribution was stopped because of the occurrence of chronic renal failure due to long-term use of drugs including phenacetin. There have been cases of fixed drug eruptions caused by Coughcode® tablets, but to our knowledge this report and that of Sato et al.8 are the only two descriptions of drug allergy induced by Coughcode®-N combination tablets in the English- and Japanese-language literature. Sato et al.8 reported a case of Stevens-Johnson syndrome caused by acetaminophen in Coughcode®-N given for treatment of cough and common cold for 4 days before the appearance of the eruption. LTTs to Coughcode®-N and acetaminophen were positive in Sato et al.8 while the patient in our case had a negative LTT and patch test reaction to Coughcode®-N, but a positive oral challenge test. However, acetaminophen was not the causative drug based on a negative oral challenge test. Thus, we were able to identify the causative drug of the eruption, but not the causative component. This component may have been one of the 3 untested components. Alternatively, the drug eruption might have been due to a cooperative mechanism involving plural components in Coughcode®-N, similar to the multiple fixed drug eruptions due to drug combination.9,10 Cross-sensitivity reactions may occur with chemically related drugs. However, all the components of Coughcode®-N were not chemically similar or related. Therefore, in our case the underlying mechanism of drug eruption due to a drug combination was unclear, but the possibility of some unknown chemical interaction occurring in the manufacture of the combined preparation might also be considered as described by Verbov.10

Oral administration of Coughcode®-N combination tablets is a useful and convenient treatment for cough and common cold because of the combined effects on symptoms. However, medical practitioners should be aware of potentially allergic reactions to Coughcode®-N, with recognition that identification of the causative component might be difficult compared to a product containing a single agent.

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Japanese).


