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S-Carboxymethyl-L-cysteine-induced Fixed Drug Eruption

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S-carboxymethyl-L-cysteine (carbocisteine, SCMC) is a mucoregulating drug with a normalizing effect on airway mucus and a repairing effect on mucosa. The drug is used in a wide range of age groups, from infants to elderly patients. SCMC has chronopharmacological characteristics, i.e. its metabolic pathway and metabolites vary according to the time of day when the drug is orally ingested (1, 2). Thiodiglycolic acid (TDA), a metabolite produced during the night, has been assumed to be a component responsible for fixed drug eruption (FDE) associated with SCMC (3). This report presents a case of SCMC-induced FDE in which an oral challenge test induced a skin eruption following oral administration of SCMC in the evening only for 2 days.

CASE REPORT

A 4-year-old boy presented with an erythema, which had developed on the left forearm after treatment with oral SCMC (500 mg every 12 h), tipepidine hibenzate (30 mg every 12 h) and other drugs was initiated 7 months previously. The patient had cold symptoms 1 month before he visited another hospital. SCMC and tipepidine hibenzate were administered orally for several days before the erythema was noted. Subsequently, a brown pigmented macule remained, and the patient visited our department for examination. On initial assessment, a relatively well-defined brown spot, 21×15 mm in size, was noted on the flexor side of the left forearm (**Fig. 1**a). The patient did not report any symptoms such as itching. His family history and past medical history were non-contributory. SCMC- or tipepidine hibenzate-induced FDE was suspected based on the above clinical findings. To identify the responsible agent, a patch test (PT) and oral challenge testing were performed.

Four weeks after the first visit to our department, PT was performed. In the PT, SCMC 20% petrolatum (pet), TDA 10% pet, and TDA 20% pet were applied on the affected area on the left forearm. The SCMC 20% pet was negative, whereas TDA 10% pet and TDA 20% pet were (?+) at 72 h and (+) on day 5 according to the International Contact Dermatitis Research Group (ICDRG) criteria (Fig. 1b, 1c). ((ICDRG criteria) −: no reaction <negative reaction>, ?+: faint erythema only <doubtful reaction>, +: erythema, infiltration, possibly papules <weak positive reaction>, ++: erythema, infiltration, papules, vesicles <strong positive

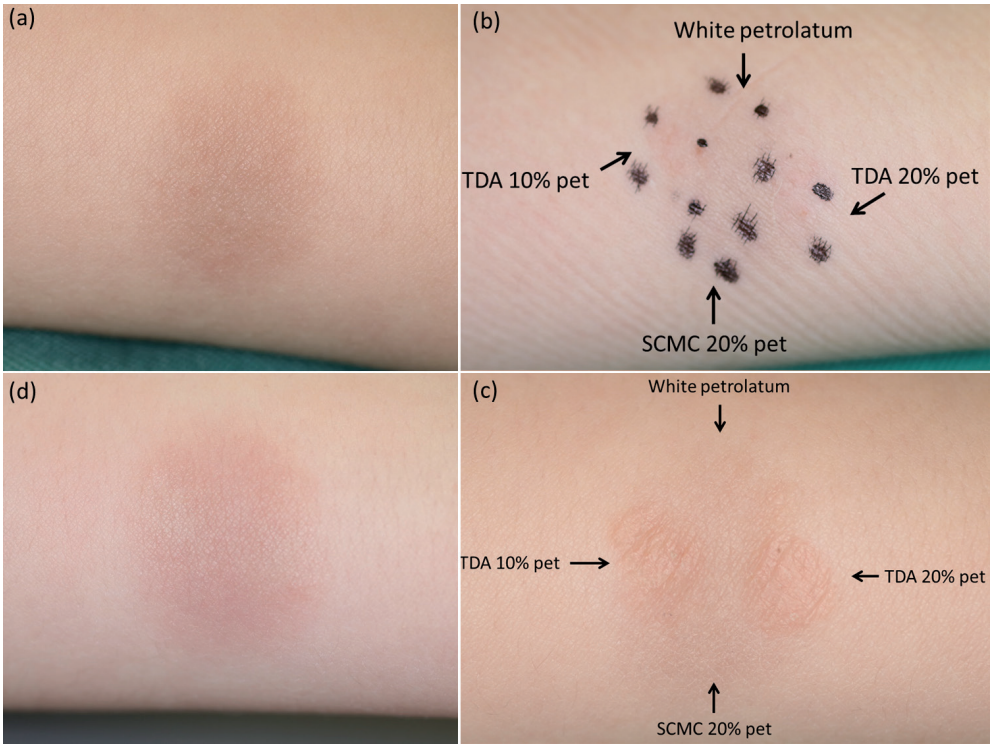

Fig. 1. (a) A relatively well-defined brown spot was noted on the flexor side of the left forearm during the patient's first visit to our hospital. (b) The thiodiglycolic acid (TDA)10% pet and TDA 20% pet were (?+) according to the International Contact Dermatitis Research Group (ICDRG) criteria after 72 h from the patch application. (c) The TDA 10% pet and TDA 20% pet were (+) according to the ICDRG criteria from 5 days after the patch application. (d) An erythema developed on the brown spot during the night when a single dose of S-carboxymethyl-L-cysteine (carbocisteine, SCMC) was orally ingested in the evening for 2 days.

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reaction>, +++: intense erythema, infiltrate, coalescing vesicles <extreme positive reaction>, IR: various morphologies, e.g. soap effect, bulla, necrosis <irritant reaction>) (4) For tipepidine hibenzate, the affected area was too small for a PT. Nine days after the PT, oral challenge testing was performed. In the oral challenge test, oral ingestion of a single dose of tipepidine hibenzate for 1 day, half of a single dose of SCMC in the morning for 2 days, and a single dose of SCMC in the morning for 2 days did not result in an induction of skin eruption. However, erythema developed on the brown spot during the night after a single dose of SCMC was orally ingested in the evening for 2 days (Fig. 1d). Based on the above, the condition of this patient was diagnosed as FDE induced by TDA, a metabolite of SCMC.

As for the subsequent treatment and clinical course, oral SCMC was discontinued, and the patient was followed up without any treatment. His skin eruption gradually resolved.

DISCUSSION

SCMC is a mucoregulating drug, which, in the daytime, is metabolized to S-carboxymethyl-L-cysteine S-oxide and S-methyl-L-cysteine (SMC) through the oxidation of sulfhydryl groups because of its high activity of S-oxidase. During the night, on the other hand, an increased level of TDA is produced through tricarboxylic acid cycle because of lower activity of S-oxidase due to its chronopharmacological characteristics (1, 2).

Although SCMC is used in a wide range of age groups, from infants to elderly patients, few instances of cutaneous adverse drug reactions (cADRs) have been reported (2, 3, 5, 6). Takahashi & Fukuda (7) aggregated 65 cases of SCMC-induced cADRs that have been reported in Japan. FDE was reported in 43 of these cases (66.2%), which accounted for over half of all SCMC-induced cADRs. Other cases of SCMC-induced cADRs included severe forms, i.e. 4 cases of acute generalized exanthematous pustulosis (6.1%), 3 cases of Stevens-Johnson syndrome (4.6%) and 3 cases of toxic epidermal necrolysis (4.6%). The eruption reported in our case was FDE, the most common SCMC-induced cADRs.

Tests performed to identify the component responsible for SCMC-induced FDE were a PT, a drug-induced lymphocyte stimulation test (DLST), and an oral challenge test. In the PT, 3 of 29 patients tested positive for SCMC (10.3%), 10 of 12 tested positive for TDA (83.3%), and 0 of 3 tested positive for SMC (0%). In the DLST, one of 10 patients tested positive for SCMC (10.0%), 0 of 5 tested positive for TDA (0%) and 0 of 3 tested positive for SMC (0%) (7). Thus, the PT for TDA is considered useful for identifying the component responsible for SCMC-induced FDE, while DLST may be less useful. In the current case, the PT for TDA was positive; oral administration of SCMC in the morning did not induce a skin eruption, whereas oral administration in the evening induced a skin eruption in the oral challenge test. As a result, TDA was considered responsible for the skin eruption.

As for most FDEs, induction of a skin eruption in an oral challenge test rarely takes more than one day. The current case was distinct, in that the skin eruption was induced following 2 days of oral administration in the evening only. In the case of SCMC-induced FDE, skin eruptions have been reported to develop in less than one day in 3 of 29 patients (10.3%), more than one day but less than 3 days in 14 patients (48.3%), and more than 3 days in 12 patients (41.4%) in oral challenge tests (7). Thus, SCMC-induced FDE is characterized by the delayed induction of skin eruption that takes several days in oral challenge tests.

The reason why it takes several days for a skin eruption to be induced in oral challenge testing would be that a level of TDA exceeding the response threshold is required for the manifestation of symptoms (3). In the current case, the skin eruption was not induced by a single dose of SCMC administered orally in the morning for 2 days but was induced during the night when a single dose of the drug was administered orally in the evening for 2 days. Therefore, the level of TDA, a major metabolite produced during the night, is considered necessary to exceed the response threshold for the manifestation of symptoms, as described previously.

As above, a case of SCMC-induced FDE was reported. This is the first case report on the manifestation following the oral administration of SCMC in the evening only for 2 days in oral challenge testing. For common FDEs, an oral challenge test typically induces skin eruptions within several hours to one day. For SCMC-induced FDE, however, it should be kept in mind that, to induce skin eruptions in the oral challenge test, the drug must be administered for several days, in the morning and the evening, in many cases.

The authors have no conflicts of interest to declare.

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