

Non-pigmenting fixed drug eruption caused by allylisopropylacetylurea

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An unusual case of a non-pigmenting fixed drug eruption caused by allylisopropylacetylurea is reported. Several hours after taking an analgesic (New Kaiteki A[®]), a 30-year-old Japanese woman, who had experienced similar eruptions several times after taking other analgesics, developed numerous variously sized, itchy, round-to-oval erythematous eruptions on the trunk and extremities. After she discontinued taking this drug, all such eruptions resolved within 2 weeks, without leaving postinflammatory pigmentation. Patch testing with New Kaiteki A[®] itself and one of its active ingredients, allylisopropylacetylurea, on lesional skin, but not on uninvolved skin, showed positive erythematous reactions after 2 days.

Key words: allylisopropylacetylurea; analgesics; cutaneous adverse drug reactions; non-pigmenting fixed drug eruption; positive lesional patch test. © Blackwell Munksgaard, 2003.

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Allylisopropylacetylurea [(2-isopropyl-4-pentenoyl) urea] is a monoureoid compound made by binding the carbonyl group of a fatty acid with the amino group of uric acid (Fig. 1a). It is a sedative with antipyretic and analgesic actions and is usually used for the relief of anxiety and strain from pain and for the enhancement of the effects of analgesics (1). In Japan, 57 over-the-counter drugs containing allylisopropylacetylurea are currently available (2). Recently, there have been increasing numbers of reports of fixed drug eruptions (FDEs) caused by such drugs (3–5).

We here report a case of non-pigmenting fixed drug eruption (NPFDE), with a symmetrical distribution of erythematous macules, caused by allylisopropylacetylurea, which was proved to be the causative agent by lesional patch testing.

Case Report

A 30-year-old Japanese woman consulted us with 5-year history of repeated episodes of itchy red oval eruptions on the trunk and extremities. In the most recent episode, her eruptions appeared a few hours after oral intake of New Kaiteki A[®] (Fuji Yakuhin Co., Ltd, Saitama, Japan) to relieve menstrual pain. She had experienced

similar episodes of rashes at the same sites after taking oral analgesics, even though she had used several different ones. These were EveA[®] (SSP Co., Ltd, Tokyo, Japan), New Sedes[®] (Shionogi & Co., Ltd, Osaka, Japan), Norshin[®] (ARAX Co., Ltd, Nagoya, Japan) and Bufferin[®] (Lion Corporation, Tokyo, Japan), as well as New Kaiteki A[®] (Table 1). The erythematous eruptions usually cleared without pigmentation within 2 weeks after she stopped taking the drug. The eruptions seemed to increase in number with each episode.

At her first visit, more than 100 purplish red round macules were symmetrically distributed on her trunk and extremities (Fig. 2a, b). The mucous membranes were not affected. Based on these observations, we made a clinical diagnosis of NPFDE caused by the analgesics, because there was no residual pigmentation. She was successfully treated for 3 days with oral prednisolone (30 mg/day), which was tapered off over 2 weeks, and with the topical application of a potent corticosteroid. There was no remaining visible postinflammatory pigmentation.

There were no abnormal laboratory findings other than an increased level of plasma C-reactive protein [2.8 mg/dl (normal range: <0.5 mg/dl)], an

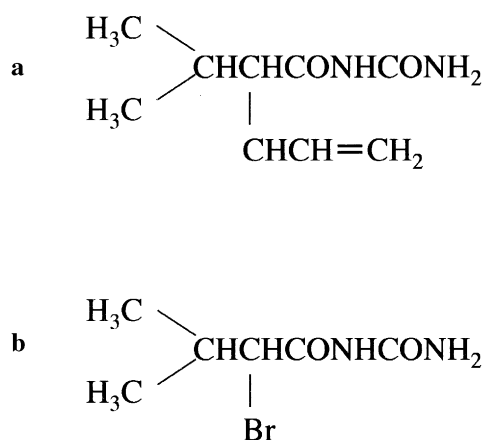


Fig. 1. Chemical structures of allylisopropylacetylurea and bromvalerylurea.

increased titre of antistreptolysin O [301 Todd units (normal range: ? 166 Todd)] and abnormal γ -glutamyl transpeptidase (GTP) [70 IU/l (normal range: 8–57 IU/l)] and glutamic-pyruvic transaminase (GPT) [37 IU/l (normal range: 8–35 IU/l)].

Methods and Results

First, in order to find the causative drug(s), we carried out 2-day patch testing with the drugs that she had taken previously. These are listed in Table 1. Using Finn Chambers[®], the test materials were patch tested on uninvolved skin such as the upper back and on previously involved skin such as the right wrist, flanks and legs. Readings were taken according to the International Contact Dermatitis Research Group (ICDRG) scale at 30 min (D2) and 1 day (D3) after removal of the chambers. Among the drugs we tested, New Kaiteki A[®] 20% in petrolatum (pet.), Eve A[®] 20% pet. and New Sedes[®] 20% pet. showed weak positive (+) reactions on the ICDRG scale on previously involved skin, although they were negative on uninvolved skin. The other drugs, Norshin[®] and Bufferin[®]

that did not contain allylisopropylacetylurea, did not show positive reactions on either involved or uninvolved skin.

Next, we examined the declared ingredients of all the analgesics that she had used. The common ingredients contained in the 3 drugs that had showed positive reactions were allylisopropylacetylurea and caffeine anhydride. Table 2 summarizes the results of patch testing with all the ingredients. Only allylisopropylacetylurea showed a positive reaction on previously involved skin (Fig. 3) but not on uninvolved skin. Moreover, patch testing with allylisopropylacetylurea in 3 healthy controls was negative. A drug lymphocyte stimulation test to all these drugs was negative.

Skin biopsy from an erythematous lesion showed epidermal acanthosis and a perivascular lymphocytic infiltrate containing some eosinophils in the upper dermis. There was no liquefaction degeneration or dermal melanophages, which are histological characteristics of pigmenting FDE. Only some necrotic keratinocytes with eosinophilic cytoplasm and slight vacuolar degeneration of the basal layer were recognized in step sections (Fig. 4a, b).

Provocation tests for alternative non-steroidal anti-inflammatory drugs such as Solantal[®] (Fujisawa Pharmaceutical Co., Ltd, Osaka, Japan), Mobic[®] (Daiichi Pharmaceutical Co., Ltd, Tokyo, Japan), Pyrinazin[®] (Yamanouchi Pharmaceutical Co., Ltd, Tokyo, Japan), Loxonin[®] (Sankyo Co., Ltd, Tokyo, Japan) and Imigran[®] (GlaxoSmithKline K. K, Tokyo, Japan), which did not contain allylisopropylacetylurea, were all negative.

Discussion

In the present case, we succeeded in demonstrating that only 3 among 5 drugs that the patient admitted to having taken in her history, comprising New Kaiteki A[®], EveA[®] and New Sedes[®] along with allylisopropylacetylurea, which was a component of these all 3 drugs, showed positive

Table 1. Ingredients of the drugs that the patient had taken

Ingredients	Drugs				
	New Kaiteki A [®]	EveA [®]	New Sedes [®]	Norshin [®]	Bufferin [®]
Acetylsalicylic acid					○
Acetaminophen	○		○	○	
Allylisopropylacetylurea	○	○	○		
Aluminium glycinate					○
Benfotiamine	○				
Caffeine				○	
Caffeine anhydride	○	○	○		
Ethenzamide	○		○	○	
Ibuprofen		○			
Magnesium carbonate					○

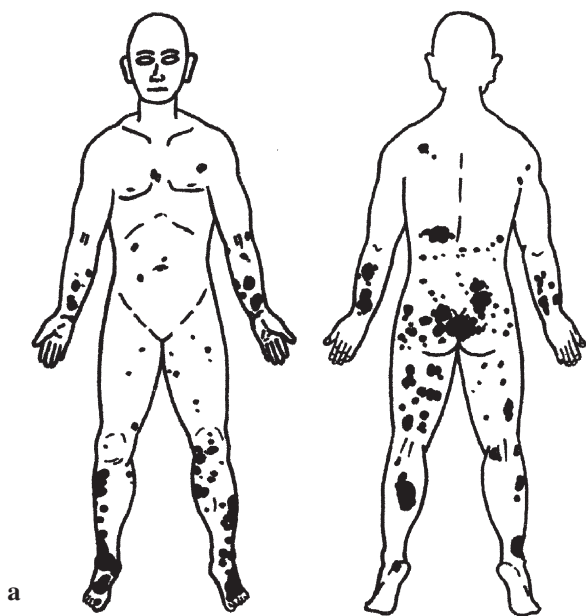


Fig. 2. (a) Diagram showing the distribution of eruptions. (b) Numerous purplish-red patches were observed on the patient's buttocks.

lesional patch test reactions. Therefore, we concluded that allylisopropylacetylurea was the causative agent. Recently, there have been accumulating reports of drug eruptions caused by allylisopropylacetylurea in Japan (1, 3–5), and among them, the multiple type of FDE is the most common (77%) (5).

It has been reported that systemic exposure to the drug can cause more extensive lesions after repeated occurrences of FDE (6, 7). There was even a case of multiple FDE in which the pro-

Table 2. Patch test results with the drugs that the patient had taken and the ingredients of these drugs

	Involved skin		Uninvolved skin	
	D2	D3	D2	D3
Drugs				
New Kaiteki A [®]	+	+	–	–
EveA [®]	+	+	–	–
New Sedes [®]	+	+	–	–
Norshin [®]	–	–	–	–
Bufferin [®]	–	–	–	–
Ingredients				
Acetylsalicylic acid	–	–	–	–
Acetaminophen	–	–	–	–
Allylisopropylacetylurea	+	+	–	–
Aluminium glycinate	–	–	–	–
Benfotiamine	–	–	–	–
Caffeine	–	–	–	–
Caffeine anhydride	–	–	–	–
Ethenzamide	–	–	–	–
Ibuprofen	–	–	–	–
Magnesium carbonate	–	–	–	–

Petrolatum 20% was used as the vehicle.

vocation test unfortunately resulted in the development of Stevens–Johnson syndrome (8). In Japan, there were 2 reported cases of a mucocutaneous-ocular syndrome-type of drug eruption due to allylisopropylacetylurea. These were not associated with FDE (9, 10).

In the present case, the patient tried but failed to find a safe analgesic, no doubt, because there are 57 over-the-counter analgesics (24%) containing allylisopropylacetylurea in Japan (2). Additionally, bromvalerylurea, which has a chemical structure similar to that of allylisopropylacetylurea (Fig. 1b) and is contained in 17% of Japanese over-the-counter analgesics, has been reported to show cross-sensitivity to allylisopropylacetylurea (4). It is important for doctors not only to recommend that patients refrain from taking the causative drugs but also to suggest safe alternative drugs.

Fixed drug eruption usually presents as hyperpigmented lesions that flare up at exactly the same sites after re-challenging with the causative drug. In 1987, Shelley and Shelley (11) described NPFDE as a type of FDE distinct from the classic pigmented type, which consisted of large, symmetrical, well-demarcated, tender erythematous plaques that suddenly occurred and recurred in the same location but resolved without residual pigmentation. Microscopic findings of pigmented FDE include manifest liquefaction of the epidermal basal cell layer and the presence of dermal melanophages. In contrast, in NPFDE, the histopathological features include a normal epidermis and a perivascular infiltrate with lymphocytes, neutrophils



Fig. 3. A positive patch test reaction on previously involved skin with allylisopropylacetylurea 20% petrolatum.

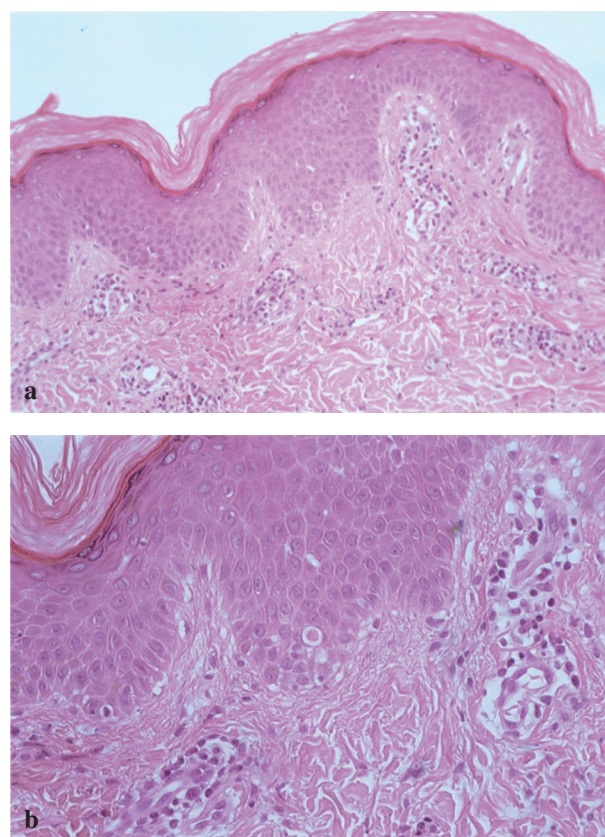


Fig. 4. (a) Low-power view shows acanthosis and mixed perivascular infiltrate (hematoxylin-eosin stain, $\times 100$). (b) Higher-power view shows necrotic keratinocyte and vacuolation changes of the basal layer (hematoxylin-eosin stain, $\times 400$).

and eosinophils in the upper dermis. It has been proposed that NPFDE may result in lesional pigmentation in the course of recurrences (12). The possibility cannot be excluded that lesional pigmentation may develop after resolution of the erythematous eruption in our patient, as a result of hydropic degeneration and pigmentary incontinence from repeated episodes of recurrence, although such epidermal changes were minimal in our case. At present, we conclude that our patient had the clinical and histological features consistent with NPFDE.

We report an unusual case of NPFDE caused by allylisopropylacetylurea, which is the 3rd such case reported in Japan (13, 14). Our patient finally came to develop numerous lesions after several episodes of NPFDE, which supports the previous observation that NPFDE is more serious than pigmenting FDE (15).

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