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Pseudoporphyria is a blistering disorder with increased skin fragility. It resembles porphyria cutanea tarda (PCT) in its reaction to the intake of certain drugs and sunlight exposure, but without disorders in the porphyrin metabolism. Only sunlight exposed areas of the skin are involved; face, dorsal surfaces of hands and feet and less often the neck except the area underneath the chin and behind the ears. Usually blisters heal with scarring and milia. Blisters are subepidermal and histology is identical to abnormalities found in PCT. PCT patients lack uroporphyrinogen decarboxylase, an enzyme of the heme biosynthesis, by contrast in pseudoporphyria porphyrin screen in erythrocytes, urine and feces is normal. Pseudoporphyria due to naproxen was believed to be a rare adverse reaction to the drug, although by now a hundred cases have been reported.

We report here three cases of pseudoporphyria due to naproxen and review briefly the literature, the establishment of diagnosis and hypothetical mechanisms.

Cases

Case 1

During holidays at the Canary Islands a 42-year-old white woman experienced blistering and skin fragility of the dorsa of both hands, fingers and feet for 8 weeks. Her medical history included a moderately active ankylosing spondylitis and in the past a pityriasis rosea. She had been taking an oral contraceptive for several years and naproxen 500 mg b.i.d. for 8 months. Earlier she had used other NSAIDs. There was no history of hepatitis, porphyria or other photosensitivity disorders. Examination of the skin revealed small blisters with slight scarring from old lesions. No hyperpigmentation, hirsutism, milia or atrophic scarring were present. Laboratory examination, repeated twice, revealed normal liverfunction tests and a normal porphyrin screen in erythrocytes, urine and feces was demonstrated twice. Perilesional skin biopsies showed subepidermal bullae formation. Direct immunofluorescence of the perilesional skin showed aspecific condensation of IgM and C3 at the edge of the bulla. IgG, fibrinogen, IgA and C4q were diffusely deposited in the dermal layer. No signs of bullous pemphigoid were present. Naproxen was discontinued, but new lesions occurred for another 8 weeks, thereafter blistering ceased with minimal scarring.

Case 2

A 58-year-old white man, who had used sunbeds regularly for several years, had a 6-week history of blistering and skin fragility of the dorsa of both hands. His medical history comprised a longstanding, moderately active, ankylosing spondylitis, for which he took NSAIDs for many years, and prostatism, without hepatitis, porphyria or photosensitivity disorders. The patient reported that he had experienced the same lesions about 5 to 6 years earlier, but to a lesser extent and degree. On both occasions he was using naproxen 500 mg b.i.d. Examination of the skin showed small blisters and some old lesions with slight scarring. No other abnormalities of the skin were seen. Liverfunction tests, porphyrin screen in erythrocytes and urine revealed normal. Skin biopsies were not conclusive be-
which skin lesions healed. In 14 cases the time needed for healing was described and was on average 5 weeks (range 1 week to 2 months).

All three cases described here manifested itself in the summer of 1992, which was an ordinary Dutch summer, though one case manifested itself at the Canary Islands. Pseudoporphyria due to naproxen was not seen earlier at our clinics. Our two adults took part in a 48-week double-blind study comparing β-cyclo-dextrin-piroxicam (n = 30) with naproxen (n = 29) in ankylosing spondylitis. One of our cases (case 2) differs from other cases in the literature as skin lesions healed while naproxen was still being administered, but patient had started to use a sunfilter. One case of pseudoporphyria due to nalidixic acid behaved similarly (10). No porphyrin screen was done in case 3, but the causal relation with discontinuation of naproxen and subsiding of characteristic skin lesions confirm the diagnosis.

Although phototoxicity is widely accepted, several hypotheses have been developed. Naproxen is known to stabilize the liposomal membrane in vitro and to be a potent inhibitor of cyclo-oxygenase. In most hypotheses sunlight plays a central role. The inflammation of the sun exposed skin may be due to: a. the chemical structure of NSAIDs itself which may induce photosensitization of the skin (4, 11); b. the release of free oxygen radicals by naproxen which may contribute to the phototoxic reaction (4, 8), probably as well aggravated by complement compounds (7). Other hypotheses suggest that pseudoporphyria patients have minor disturbances of heme-biosynthesis leading to symptoms in case of excessive sunlight exposure (5, 12), perhaps sometimes associated with intake of alcohol (5), estrogens (5) or eventually minor skin trauma (6).

The relation with sunlight exposure is confirmed especially in three patients with vitiligo in whom bullae were only present on areas of vitiligo (12–14). Not only exposure to a high intensity of sunlight may induce pseudoporphyria, but also multiple prolonged low-grade exposure may cause skin lesion resulting mostly in decreased adhesion of dermis and epidermis (9, 15).

It is not easy to explain the larger frequency of pseudoporphyria due to naproxen in children (Allen et al. (6) even reported that 6% of all children using naproxen experienced pseudoporphyria), especially as far less children than adults use naproxen. Possibly children experience more frequently trauma of the skin during sunlight exposure and are more exposed.

Pseudoporphyria might be seen as a ‘diagnosis per exclusionen’. PCT, epidermolysis bullosa acquisita and hydroa vacciniforme must first be ruled out as a diagnosis. The only difference between PCT and pseudoporphyria is the negative porphyrin screen in the latter.

It may be concluded that the pathogenesis of pseudoporphyria due to naproxen is still not clear, but there seems to be a relation to sunlight exposure and perhaps...
Pseudoporphyria due to naproxen

minor skin trauma. Discontinuation of naproxen is the best treatment. One should be aware of this adverse drug reaction, especially in fair skinned patients and even more in children.

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References