CASE REPORT

Pseudoporphyria due to Naproxen

A cluster of 3 cases

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Pseudoporphyria is a photo-induced blistering disorder with increased skin fragility, caused among others by nonsteroidal antiinflammatory drugs. Lesions heal with scarring and milia. Porphyrin screen studies are normal in this disease. Histology and immunofluorescence resembles porphyria cutanea tarda. In this report we describe a cluster of three cases of naproxen-induced pseudoporphyria, and review briefly previously reported cases induced by naproxen. The majority of reported cases involve children. Physicians should be aware of this reversible skin disorder.

Key words: side effects, nonsteroidal antiinflammatory drugs, naproxen, pseudoporphyria

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 C4 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
normalities. Naproxen was stopped in all patients after
ranged from a few weeks to several years before onset
in 11 of these 19 biopsies, immunofluorescence was
screening was done in the majority of cases and re­
had no history of hepatitis, porphyría or photosensitivity disorders. She
was taking methotrexate 10 mg weekly and naproxen
250 mg b.i.d. (20 mg/kg/day). She had not been treated
before with other NSAIDs. Skin examination showed
blistering with crustae and scarring of old lesions. Liverfunction tests were normal. A skin biopsy was not
felt to be justifiable in view of the age of the patient
and the site of the blistersing. After naproxen was
changed into diclofenac, no new blistersing occurred
and lesions healed within several weeks.

Case 3
A 9-year-old white girl with polyarticular systemic-onset juvenile chronic arthritis revealed blistersing and
skin fragility of the face and dorsa of both hands,
aggrevated by sunlight exposure. She had no history
of hepatitis, porphyría or photosensitivity disorders. She
was taking methotrexate 10 mg weekly and naproxen
250 mg b.i.d. (20 mg/kg/day). She had not been treated
before with other NSAIDs. Skin examination showed
blistering with crustae and scarring of old lesions. Liverfunction tests were normal. A skin biopsy was not
felt to be justifiable in view of the age of the patient
and the site of the blistering. After naproxen was
changed into diclofenac, no new blistersing occurred
and lesions healed within several weeks.

Discussion
Though other nonsteroild antiinflammatory drugs (NSAIDs) are known to cause pseudoporphyria as well, the majority of cases published were caused by
naproxen (1–9).
A total of 100 cases of pseudoporphyria due to
naproxen are known, remarkably 74 of these were children. The mean age of children was 7 years (range
1–18 years) and in adults age ranged from 21 to 84
years. In adults it appeared that mostly women were
involved (14 women versus 7 men, 5 not reported), in
most cases involving children sex was not reported.
Most cases manifested itself during summer, not
always clearly related to sunlight exposure, 3 cases oc­
curred after visiting a solariun. Dose of naproxen in
adults was 250 to 1500 mg/day, in children the mean
dose was 13 mg/kg/day, and the use of naproxen
ranged from a few weeks to several years before onset
of pseudoporphyria. Most frequently lesions occurred
on the dorsal surfaces of hands and feet, in some cases
in the face, in a few cases on the neck and in one case
also on both knees. Scarring usually remained after
healing but showed a tendency to fade. Porphyrín
screening was done in the majority of cases and re­
vealed normal. Histology was reported in 16 cases and
in 11 of these 19 biopsies, immunofluorescence was
done, all biopsies were conclusive for PCT-like ab­
normalities. Naproxen was stopped in all patients after
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) dif­
ers 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 nalidix 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 hypothe­
ses 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 photo­
sensisation 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 aggra­
vated by complement compounds (7). Other hypothe­
ses suggest that pseudoporphyria patients have minor
disturbances of heme-biosynthesis leading to symp­
toms 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 espe­
cially 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
exclusionem’. PCT, epidermolysis bullosa acquisita and
hydroa vacciniforme must first be ruled out as a diag­
nosis. The only difference between PCT and pseudo­
porphyria is the negative porphyrin screen in the latter.
It may be concluded that the pathogenesis of pseu­
doporphyria due to naproxen is still not clear, but there
seems to be a relation to sunlight exposure and perhaps
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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