The aim of the present prospective study was to substantiate possible side effects of short-term oral acitretin therapy (1 mg/kg/day) on peripheral nerve function of 13 patients with severe keratinization disorders. Clinical neurological examination before and 1 and 3 months after onset of treatment was unremarkable in all patients; however, a significant alteration of one or more neurophysiological, predominantly sensory, parameters was demonstrated in 3 out of 13 patients (23%) after 1 month and in 9 out of 13 (69%) after 3 months of oral acitretin therapy. These findings indicate that oral acitretin might be capable of causing a dysfunction of predominantly sensory nerve fibres in some individuals. Although in the investigated patients this dysfunction remained subclinical, it seems reasonable to suggest that neurological and neurophysiological evaluation of peripheral nerves should be added to the list of investigations that are routinely performed in patients receiving oral acitretin. Key words: vitamin A; retinoids; nerves; neuropathy.

(accepted October 8, 2001.)


E. Chroni, Department of Neurology, School of Medicine, University of Patras, P.O. Box 1045, Rio-Patras 26500 Greece. E-mail: echroni@yahoo.com

Acitretin, the main active metabolite of etretinate, is a synthetic oral retinoid of the second generation which has replaced the parent compound in the systemic management of severe and recalcitrant disorders of keratinization (1, 2). A broad spectrum of neurological adverse reactions, almost exclusively concerning the central nervous system, has been observed under oral treatment with synthetic retinoids (1–4). Two cases of peripheral neuropathy associated with long-term etretinate therapy have been reported previously (5, 6). Moreover, we have recently observed two patients with severe chronic plaque psoriasis and oral lichen planus who developed a peripheral sensory neuropathy after a 3- and 4-month treatment, respectively with oral acitretin (unpublished data). This observation prompted us to perform a prospective neurological and neurophysiological study on the effects of short-term oral acitretin therapy on peripheral nerve function.

PATIENTS AND METHODS

Thirteen patients (4 men and 9 women, aged 52±17 years) with severe lichen planus (n = 7), chronic plaque psoriasis (n = 4), pustular psoriasis (n = 1) and palmoplantar keratoderma (n = 1) orally treated with acitretin (1 mg/kg/day) were included in the study. Patients with diabetes mellitus, alcohol abuse and evidence or family history of hereditary neurological diseases or other conditions related to peripheral neuropathy were excluded. All participants gave an informed consent and underwent neurological and neurophysiological evaluation, before, 1 and 3 months after initiation of acitretin treatment. The clinical evaluation of neuropathy was based on Neuropathy Symptom Score (NSS) and Neurologic Disability Score (NDS) (7). NSS selected symptoms such as weakness, numbness or pain, which occur in neuropathy were scored as present (1) or absent (0). NDS functions of cranial nerves, tendon reflexes, muscle strength and sensation were scored as no deficit (0), mild deficit (1), moderate deficit (2), severe deficit (3) or absence of function/severest deficit (4). All neurophysiological studies were unilaterally (right side) performed by the same investigator (E.C.) employing standard methods and by means of surface stimulation and recording (8). In order to avoid the effects of high input resistance, only subjects with healthy skin over the stimulation and recording areas were included in the study. The distal skin temperature was maintained between 32°C and 34°C; if necessary, the limb under investigation was warmed up by immersion in a hot bath. The neurophysiological profile consisted of the following parameters: 1. Motor conduction of ulnar and peroneal nerves with measurements of peak to baseline amplitude of compound muscle action potential (a-CMAP), distal motor latency (DML), motor conduction velocity (MCV) and F-wave minimum latency estimated from measurements of 20 F-waves. 2. Sensory conduction of ulnar (orthodromic technique), sural and superficial peroneal nerves (antidromic technique and proximal segment) with measurements of peak-to-peak amplitude of sensory action potentials (a-SAP) and sensory conduction velocity (SCV). For longitudinal comparison of neurophysiological parameters of individual patients the following widely accepted criteria for identification of abnormalities were employed, which were based on serial measurements on healthy human subjects (8–10): (a) prolongation of distal motor latency by more than 1 ms; (b) slowing of motor or sensory conduction by more than 10 m/s; (c) reduction of potential amplitude by at least 50%; (d) prolongation of F wave minimum latency by at least 5 ms in the ulnar and by 7 ms in the peroneal nerve.

RESULTS

No patient complained of myalgia, muscle stiffness or weakness, numbness or any other neuropathic symptoms over the 3-month treatment period. Likewise, the clinical neurological examination before and 1 and 3 months after onset of treatment was unremarkable in all patients (NSS and NDS values were consistently within normal limits).

The results of the electrophysiological measurements performed before and 1 and 3 months after onset of treatment are summarized in Table I. Paired statistical analysis showed that the only significant change from baseline values observed in the treated patients was the decrease in the mean amplitude of sensory action potential of the superficial peroneal nerve after 1 and 3 months of therapy. However, the comparative evaluation of serial electrophysiological measurements in each patient separately showed that under oral acitretin therapy a substantial number of individual nerves of certain patients clearly fulfilled the criteria of abnormality. After 1 month of therapy, 3 patients showed sensory nerve abnormalities, i.e. reduced a-SAP of the superficial peroneal and/or sural nerves
Table I. Electrophysiological findings (expressed as x±SD) before and after 1 and 3 months of acitretin treatment (n=13)

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Motor conduction</th>
<th>Sensory conduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DML (ms)</td>
<td>a-CMAP (mV)</td>
</tr>
<tr>
<td>Ulnar</td>
<td>Before</td>
<td>2.6±0.3</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
<td>2.6±0.4</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>2.5±0.4</td>
</tr>
<tr>
<td>Peroneal</td>
<td>Before</td>
<td>3.9±0.7</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
<td>3.8±0.6</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>3.8±0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial Peroneal</td>
<td>Before</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Sural</td>
<td>Before</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td></td>
</tr>
</tbody>
</table>

DML = distal motor latency; a-CMAP = amplitude of compound muscle action potential; MCV = motor conduction velocity; F-wave = minimum F-wave latency; a-SAP = amplitude of sensory action potential; SCV = sensory conduction velocity. ND = not determined.

Motor conduction parameters cannot be estimated in superficial peroneal and sural nerves since they are sensory nerves.

The sensory function of peroneal nerve is served by the superficial peroneal nerve.

*p<0.02 for difference versus before.

and/or slowing of SCV of the superficial peroneal nerves. For example, in one patient the a-SAP amplitude of the sural nerve was reduced to 10µV after 1 month of acitretin therapy (baseline: 22µV). After 3 months of therapy, 9 patients showed 1 or more abnormal values of the tested parameters, i.e. reduced a-SAP of the ulnar nerve in 2 cases, of the sural nerve in one case, of the superficial peroneal nerve in 6 cases, and SCV slowing of the superficial peroneal nerve in 2 cases. For example, in one patient, the a-SAP of the superficial peroneal nerve was reduced to 3µV after 3 months of acitretin therapy (baseline: 12µV). Moreover, a prolongation of the ulnar F-wave minimum latency was seen in 3 patients.

In all patients who demonstrated electrophysiological abnormalities acitretin administration was discontinued and other therapeutic regimens were employed. Three out of the 9 patients who revealed electrophysiological abnormalities have presently completed a 6 month follow-up and show a gradual improvement of their neurophysiological profile.

DISCUSSION

Over the last decade, accumulating evidence indicates that synthetic retinoids may affect both the growth and differentiation of nervous tissue in vitro and in vivo (11–13). By analogy to hypervitaminosis A syndrome, benign intracranial hypertension (manifested by headache, papilloedema and cranial nerve palsies), myalgia, muscle stiffness, increased level of muscle enzyme and even true myopathy are among the most commonly reported neurological side effects of oral retinoids, especially isotretinoin and etretinate (1–4, 14–16). Acitretin, the main active metabolite of etretinate, has been less frequently implicated in neuromuscular adverse reactions but has also been shorter on the market, compared to the parent compound.

Neurophysiological abnormalities indicative of central nervous system dysfunction have been reported in patients orally treated with etretinate, the parent compound of acitretin. In a recent study, abnormalities of the auditory evoked potentials were detected in 8.7% of the tested patients after 3 weeks of oral etretinate therapy, which completely reversed within 6–9 months after cessation of treatment (17). In another study, alterations of somatosensory evoked potentials were observed in 7 of the 8 patients after long-term oral etretinate administration (18).

Peripheral neuropathy has been reported in two cases in association with long-term etretinate therapy. The first patient developed sensory neuropathy in both hands and feet after 4 years of etretinate therapy; this was confirmed by neurophysiology and sural nerve biopsy and resolved 2 years after discontinuation of treatment (5). In the second patient, the symptoms and signs of sensory neuropathy became overt after 18 months of etretinate therapy and resolved within 2 months after treatment cessation (6).

It has been recently reported that a patient who developed myopathy after 15 days of oral acitretin therapy revealed at the same time a neurophysiologically confirmed mild axonal neuropathy; interestingly enough the latter was considered by the authors as irrelevant to the medication (19). Another patient, who presented with visual disturbances due to keratocanus after acitretin treatment, reportedly developed a brachial neuritis after 4 months of therapy, but an association of the medication with the occurrence of neuritis was not postulated (20). Nevertheless, two patients with severe chronic plaque psoriasis and oral lichen planus who were treated by our group with oral acitretin developed peripheral sensory neuropathy after 3 and 4 months of therapy, respectively. Subsequent to discontinuation of acitretin administration, a gradual clinical and neurophysiological improvement was observed; however, complete remission of neuropathy occurred 2 and 2.5 years after cessation of therapy, respectively (unpublished data).

In the present study, a significant change of one or more neurophysiological parameters was demonstrated in 3 out of 13 patients (23%) after 1 month and in 9 out of 13 patients (69%) after 3 months of oral acitretin therapy. These subclinical
abnormalities predominantly concern the sensory conduction parameters and in particular the amplitude of sensory evoked potentials; the reduction of this parameter was by far the most consistent change found in the treated patients. Moreover, the study of minimum F-wave latency, which is the most sensitive motor conduction parameter in detecting early changes (21), disclosed a significant prolongation at the ulnar nerve in 3 out of the 13 patients tested (23%). This finding implies that, in addition to the sensory fibre dysfunction, there might be an involvement of at least some of the fastest conducting large myelinated motor fibres. In view of these minor motor changes and the complete absence of clinical weakness in all patients, needle electromyography was not performed.

The mechanisms by which retinoids can affect the development and function of the nervous system at the molecular and cellular level are currently under investigation (11–13). All-trans-retinoic acid is known to regulate proliferation and differentiation of a variety of cell lines, including neuronal precursors (13) and the antero-posterior patterning of the central nervous system, particularly of the hindbrain (22). Experiments on adult rats showed the presence of cellular retinoid-binding proteins in Schwann cells surrounding fine and large-calibre fibres of the spinal roots and the peripheral nerves (11). A sural nerve biopsy performed in a case of peripheral neuropathy associated with etretinate therapy (5) showed diminution of small and large myelinated fibres, macrophages, numerous axonal degeneration ovoids and abnormal Schwann cell complexes. The neurophysiological changes observed in this study under oral acitretin therapy point towards a typical distal, length-dependent and predominantly sensory polyneuropathy similar to that caused by diabetes mellitus, various drugs, such as thalidomide (9, 23), and industrial chemicals. In view of the pleiotropic effects of retinoids on nervous tissue in concert with protein growth factors (13), a metabolic rather than a toxic mechanism seems to better explain the early nerve conduction abnormalities found in our patients.

The exact clinical significance of the acitretin-induced neurophysiological alterations reported here remains to be determined in further studies of patients receiving long-term treatment with this compound. However, in view of the two cases of acitretin-induced peripheral neuropathy observed in our departments (unpublished data) and the findings of the present study, it seems reasonable to suggest that neurophysiological and neurological evaluation of peripheral nerve function should be added to the list of investigations that are routinely performed in patients treated with oral acitretin.

REFERENCES