# EXPERIMENTAL AND CLINICAL STUDY OF THE EFFECT OF NAFTIDROFURYL* ON THE RECOVERY FROM PERIPHERAL NERVE LESIONS

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After primary repair of lesions of nerves and vessels, patients who were administered a vasoactive drug, naftidrofuryl, postoperatively, had a better functional recovery than untreated patients. Evidence for the favourable effect of the drug on nerve regeneration was first obtained from experiments in the rat. The sciatic nerve was transected and repaired with standard microsurgical techniques. Results were evaluated by electromyography and histology. Data indicated that treated animals had better motor responses and distal latency than untreated rats. Fibre counts showed a greater number of nerve fibres in the distal stump of treated animals. The clinical study was undertaken in cases of carpal tunnel syndrome with muscle atrophy. Assessment was performed by electrophysiology: motor and sensory conduction was studied. Data showed that all treated patients recovered totally or partially from the thenar atrophy they presented before operation, whereas thenar atrophy persisted in 37% of the patients receiving placebo. In conclusion, naftidrofuryl has an experimentally and clinically favourable effect on nerve regeneration and on muscle trophicity, but the mechanism of action of this drug is not known.



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Plusieurs patients ayant bénéficié d'une réparation nerveuse et vasculaire en urgence et qui ont reçu en post-opération une molécule vas-active (la naftidrofuryl), ont présenté des résultats fonctionnels supérieurs à ce qui était classiquement observé. Apporter la preuve de l'efficacité de cette molécule sur la régénération nerveuse a nécessité, d'une part une étude expérimentale sur le nerf sciatique de rat sectionné puis réparé par technique microchirurgicale, et d'autre part une évaluation en double aveugle chez des sujets présentant une compression du nerf médian au canal carpien avec atrophie des muscles théariens. Lors de l'étude expérimentale, tous les rats ayant reçu le principe actif ont manifesté une activité motrice volontaire et une latence distale significativement supérieures à celles du groupe témoin. D'autre part, le nombre de fibres nerveuses compté à la partie distale de la suture est plus élevé dans le groupe traité que dans le groupe témoin. Les résultants de l'étude clinique font apparaître que les patients du groupe traité ont tous vu leur atrophie thénarienne rétrocéder partiellement ou totalement alors qu'il en persiste 37% dans le groupe placebo. En conclusion, sans que l'on puisse préciser le mécanisme d'action du naftidrofuryl sur la régénération nerveuse, il est démontré expérimentalement et cliniquement que ce produit agit directement sur la richesse de la régénération nerveuse et sur la trophicité musculaire.



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The functional prognosis of nerve injuries or chronic denervation by compression is often deceptive. Age, the type of injury, the level of the lesion, devascularisation and an unfavourable tissue environment are often the reasons put forward to justify poor results. In spite of the contribution of microsurgical techniques affecting the repair of both the nerve and surrounding tissue,[1] it has to be admitted that so-called useful functional results for adults are still limited.

Our surgical experience over the past 15 years has been directed towards urgent and systematic repair of the vascular axes which have suffered injury, and of the nerve. We found that where long-term vascular permeability was confirmed, nerve repair could be classified within the group of useful results in 80% of our cases.[1] Revascularisation of the nerve and its environment further promotes the regeneration of nerves. With this in mind, we systematically used a vasoactive molecule (naftidrofuryl) for postoperative treatment. The beneficial effect of this compound has been reported earlier[2]; its action was observed in vitro[3] and in diabetic patients.[4] Therefore, we began to use this drug before and after surgery for tunnel syndromes: compression of the median nerve in the carpal tunnel and of the ulnar nerve at the elbow. We observed that recovery of muscle

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function at the level of the intrinsic muscles of the hand after decompression of the nerves was improved in comparison to recovery in untreated patients. Several patients who underwent preoperative treatment with the product showed a regression, if not disappearance, of their symptomatology before surgical intervention, with reappearance of symptoms after discontinuation of the treatment.

These observations, which were unusual in the field of peripheral nerve pathology, led us to carry out detailed evaluation of naftidrofuryl. We undertook two studies; the first was an experimental study on rats and the second was a double-blind clinical study to closely observe this effect on the peripheral nervous system.

## I. EXPERIMENTAL STUDY ON RATS

### METHODS

In order to study the effect of naftidrofuryl on microsurgical repair of a complete section of sciatic nerve in the rat, three groups of rats were used. Group 1: 6 unoperated rats were used to calibrate the electromyographic method. Group 2, the control group. Ten rats were operated on but received no postoperative treatment. As one of the animals died, the study included only the remaining 9 animals. Group 3 was the experimental group. This included 13 rats, 2 of which died during the course of the experiments (nos. 1 and 7), thus leaving 11 rats used for evaluation.

#### Surgical Protocol

On the day of operation (D/0), each rat (mean weight 180 g) was anaesthetized by intramuscular injection of a mixture of Ketamine® and Meprobamate®. The two sciatic nerves were then successively approached by a longitudinal incision through the posterior aspect of each thigh. The sciatic nerve was sectioned using microscissors, then sutured under a surgical microscope (magnification × 16) with 5 to 7 epiperineural sutures using a nylon monofilament suture (10/0). This was a direct suture without the addition of fibrin glue or an interposed nerve graft.

The rats in group 3 received 30 mg/kg of naftidrofuryl by intraperitoneal injection from day 1 to day 21 (D/1 to D/21) postoperatively. On day 22, groups 2 and 3 were studied electromyographically and then sacrificed. The two sciatic nerves were removed through the same incision. A suture was used to mark out the proximal section of each sample. The nerve was then fixed for histomorphometric examination.

#### Electromyographic Protocol

Electromyographic evaluation was carried out on the 3 groups of rats without sedation.

Group 1 (6 normal rats) was used to determine the normal values for motor responses after electrical stimulation of the sciatic nerve and to determine the latency of appearance of the response and its duration.

All electromyographic studies were carried out by the same operator. This was important for homogeneity, given the difficulty in executing this technique.

**Detection EMG.** The electrical activity of the muscle was recorded at rest and on moving, and was collected by a bipolar, monofilament axial needle (diameter of 0.045 mm and length of 50 mm) at the level of the gastrocnemius of the rear paw of each rat in the series. Electrical activity was observed and recorded on a cathode screen. This part of the study shows that there is no spontaneous electrical activity at rest in normal muscle but is present in even partially denervated muscle. This spontaneous activity (called denervation activity) consists of fibrillation potentials and slow potentials.

The study of electrical activity triggered by voluntary movement is technically difficult in a nonsedated rat. Nonetheless, we were able to determine 5 levels of activity: (1) absence of voluntary activity; (2) poor activity, consisting of one or two motor unit potentials, most frequently mature without reinnervation potentials. These mature potentials often pulse at high frequencies and give a neurogenic atrophy plot of the severe peripheral type; (3) mediocre activity, which is not very abundant in polyphasic reinnervation potentials and poor in mature potentials, thus pointing to neurogenic atrophy; (4) average activity, moderate number of reinnervation potentials, few mature potentials, and (5) good activity, fairly abundant reinnervation potentials, associated with more or less mature potentials. A few signs of partial neurogenic atrophy may remain. This level of activity indicates a good reinnervation process.

**Stimulation EMG.** The sciatic nerve of each paw was stimulated electrically by a bipolar stimulation electrode at the level of the ilio-lumbar angle corresponding to the radical centre of the nerve. The motor response was obtained at the level of the gastrocnemius on the same side using a bipolar or bifiliary coaxial needle which had been used to record motor activity. This protocol determines: (1) the latency of appearance of the motor response after stimulation. This latency is expressed in milliseconds (ms) with respect to time constituted by stimulation; and (2) the duration of the response, which is also expressed in ms.

Increased latency with respect to the normal reference value indicates a slowing down in nerve conduction and thus, immaturity of fibres being reinnervated. An increased response time also points to this type of immaturity. Moreover, the abundance of reinnervation is greater the longer this time is. The presence of several responses to one stimulation is an indication of the extent of reinnervation. The more grouping together there is, the more abundant the reinnervation. Thus, 4 categories were determined depending on the character-

istics of the response to stimuli and the firing frequency: (1) no response, (2) poor response, (3) mediocre response, and (4) satisfactory response.

Analysis of the amplitude of plots and responses was not carried out. Interpretation of such plots would have been too complicated given the experimental conditions: the rats were not sedated in such a way as to allow collection of voluntary muscle response. Due to this, the pain caused by the needle and, particularly, by electrical stimulation made the rats aggressive and fidgety, thus moving the needle around in the muscle and greatly modifying the amplitude of the information collected.

### Histoquantimetric Protocol

**Samples–preparation of slides.** Each sciatic nerve removed was treated according to a technique similar to that used in electron microscopy: (1) fixation with a 2.5% gluteraldehyde solution for 12 hours, (2) rinsing with a buffer solution, (3) postfixation with a 1% osmic acid solution, (4) dehydration with alcohol solutions of increasing titre, (5) preimpregnation with "D" mixture (50% Epon and 50% Propoxide), and (6) impregnation with Epon.

At this stage, semifine cuts were made (1.5 μm) using an ultramicrotome. These cuts were stained with paraphenylene-dianine. Two cuts were made for each nerve: one passing about 0.5 cm above the suture area, easily located by the threads. This was called the proximal cut. The second was made below the suture area and was called the distal cut.

**Description of the photoquantimetric method.** Each cut was photographed on a Leitz® orthoplan microscope with a magnification of ×40. Calibration was carried out using a Zeiss® micrometric blade. For each cut, 4 photographs of the nerve section were taken at random. This was based on the assumption that, statistically, these 4 photographs constituted a representative sample of the whole nerve section. Nerve fibres were easily identified on these photographs. The photograph was read using a pen which the operator used to mark the smallest diameter of each nerve fibre. This pen was connected to a Hewlett-Packard® 98774A digital table. The digital table was coupled to a Tektronix 4054® calculator which recorded the number of nerve fibres counted in each photograph, their mean diameter, and standard deviation. After calibration, the measurements were given directly in micronmeters. It was thus possible with this method to obtain an evaluation of the number of nerve fibres and their diameter for each proximal and distal cut. At the end of counting, the total number of fibres found in the proximal segment and in the distal segment of the right nerve and left nerve was determined. The total number of fibres must be divided by the number of photos used to arrive at this total. Furthermore, knowing the surface area of each photo (23,408 $\mu m^2$), the number of fibres was adjusted to the surface area unit (in this case, $mm^2$). The number of nerve fibres per $mm^2$ counted in the proximal and distal cuts of the left and right sciatic nerves in experimental rats and control rats could thus be compared. A neurotisation quotient could be obtained.

**Table 1.** Results of the Study of Voluntary Motor Activity in the Rat.

| Group | n (rats) | n (paws) | Spontaneous denervation activity % | Voluntary motor activity (V.A.) Absent | Poor | Mediocre | Average | Good |
|---|---|---|---|---|---|---|---|---|
| Normal group 1 | 5 | 10 | 0 | | | | | |
| Control group 2 | 9 | 18 | 100 | 2 | 2 | 5 | 7 | 2 |
| Experimental group 3 | 11 | 22 | 100 | 0 | 3 | 5 | 59 | |

## RESULTS

These results were not submitted to statistical analysis.

### Electromyography

**Voluntary motor activity (V.A.).** The results (Table 1) show that all the rats in group 3 (naftidrofuryl-treated group) had voluntary activity, 41% of which obtained good scores (9 paws out of 22). Eighty-nine percent of rats in group 2 (control group) had voluntary motor activity of which 11% showed good scores (2 paws out of 18).

**Motor activity after stimulation (Table 2).** No response was observed in the two sciatic nerves of rat no. 2 belonging to group 2. Furthermore, no response was found in the sciatic nerve of rat no. 11 from group 3. In the two sciatic nerves of control rats (no. 6 right side and no. 7 left side), a second group of responses was recorded, whereas this type of response was found in 6 sciatic nerves of rats belonging to experimental group (nos. 2–6 and 13 left side, and nos. 5, 11 and 13 right side). Only rats in the experimental group showed 3 cases of a third group of responses indicating abundance of reinnervation.

The results also showed that the latencies were increased in the control rats (group 2, 7.66 ms) with respect to treated experimental group 3 (4.95 ms). This was also true for the duration of the motor response, 12.09 ms for control rats versus 10.48 ms for experimental rats.

**Table 2.** Motor Response After Stimulation of the Rat Sciatic Nerve.

| Group | No response | Poor response n (paws) | Poor response Mean latency (ms) | Poor response Mean duration (ms) | Mediocre response n (paws) | Mediocre response Mean latency (ms) | Mediocre response Means duration (ms) | Satisfactory response n (paws) | Satisfactory response Mean latency (ms) | Satisfactory response Mean duration (ms) |
|---|---|---|---|---|---|---|---|---|---|---|
| Normal group 1 | 0 | 10 | 1.63 | 3.38 | | | | | | |
| Control group 2 | 2 | 16 (72%) | 7.66 | 12.09 | 3 (16.6%) | 34.65 | 13.75 | | | |
| Experimental group 3 | 1 | 12 (54.5%) | 4.95 | 10.48 | 6 (27%) | 26.1 | 17.7 | 3 (14%) | 45.6 | 21.9 |

### Histoquantimetry

The results of the histoquantimetric study are shown in Table 3. The usual bimodal distribution of fibre diameters was found in the proximal sections, where small unmyelinated fibres and large myelinated fibres were observed. As usual, the majority of fibres in the distal specimens were small unmyelinated fibres or fibres in the process of myelination. In treated and untreated animals, the total number of fibres was greater in the proximal than in distal specimens. However, the ratio proximal/distal was better in the treated animals; in other words, treatment resulted in more abundant neurotisation. The number of fibres/mm$^2$ was also different in the two groups; the concentration of fibres per unit area was better in treated animals.

## DISCUSSION

This experimental study, based on evaluation by electromyography and histoquantimetry, points to improved reinnervation in rats treated with naftidrofuryl. All the treated animals showed voluntary motor activity with 41% obtaining good scores, whereas motor activity was found in only 89% of the control series with only 11% of cases with good scores. Similarly, motor response after stimulation showed that the latency increased less in the experimental rats with respect to the controls. Furthermore, rats with satisfactory responses to electrical stimuli all belonged to the experimental group; there were none in the untreated group. The histoquantimetric study showed that the greatest number of distal fibres was found in the group of treated experimental rats. These were smaller in diameter, but nonetheless indicate better neurotisation.

It is difficult to determine the mechanism by which naftidrofuryl enhances nerve regeneration. The vasomotor effect of the drug is probably not involved. We are currently testing two vasodilating drugs belonging to the same family as naftidrofuryl, using the same protocol. Preliminary results indicate that these drugs have no effect on regeneration, suggesting that sprout enhancement is not linked to a vasoactive action. Actually, naftidrofuryl seems to affect the abundance of reinnervation but not its speed. This action cannot be connected directly to haemodynamic phenomena observed with this molecule.

The experimental findings justified carrying out a double-blind clinical evaluation of the molecule.

## II. CLINICAL EVALUATION

## MATERIALS AND METHODS

### Choice of Protocol

Evaluation of functional results in the surgery of nerve injuries is complicated and requires long-term studies in order to identify technical or therapeutic progress. We decided not to undertake such a study in patients presenting with nerve injuries, as there are too many factors affecting the positive or negative effect of naftidrofuryl on the results. We thus chose to work on nerve regeneration in the median nerve in cases of carpal tunnel syndrome associated with thenar atrophy. This disease mainly affects female patients aged between 50 and 70 years. As the clinical symptoms and electromyographic studies of this syndrome are well recorded, this protocol seemed to be the most appropriate.

### Patients

The study was a double-blind study of naftidrofuryl versus placebo and included two random parallel groups of patients with an age limit of 70 years, presenting with clinically and electromyographically observed thenar atrophy with signs of denervation and without signs of ulnar involvement. Beginning on the first postoperative day, treated patients received 600 mg of the drug daily for 3 months. All patients had undergone a standard open carpal tunnel release without complementary neurolysis of the median nerve. Patients operated on gave their informed consent in accordance with legislation in force.

### Methods of Assessment

Evaluation was carried out according to clinical criteria and electromyographic recordings, the latter being carried

**Table 3.** Results of Histoquantimetric Study of Rat Sciatic Nerves.

| | | | Sum of fibres | Mean diameter (μm) | T | Number of fibres/photo | Number of fibres/mm² |
|---|---|---|---|---|---|---|---|
| Experimental group | Right nerve | Proximal | 8,304 | 4.18 | 2.05 | 267.87 | 11,493 |
| | | Distal | 2,722 | 2.31 | 0.70 | 70.48 | 3,011 |
| | Left nerve | Proximal | 8,524 | 4.16 | 2.07 | 236.77 | 10,114 |
| | | Distal | 3,684 | 2.67 | 1.00 | 92.82 | 3,965 |
| Control group | Right nerve | Proximal | 7,966 | 4.11 | 2.31 | 221.27 | 9,453 |
| | | Distal | 816 | 2.88 | 0.67 | 23.31 | 991 |
| | Left nerve | Proximal | 8,504 | 4.04 | 2.33 | 236.22 | 10,091 |
| | | Distal | 1,115 | 2.11 | 0.70 | 34.84 | 1,488 |

out and/or analyzed by the same specialist. The clinical signs are classical: (1) sign "0": this is defined as the inability to make an "0" shape using the thumb and index due to the absence of the thumb opposition; (2) atrophy of the thenar eminence, and (3) static two-point discrimination, regarded as pathological when > 5 mms.

**Electromyographic findings.** Examination of the thenar eminence muscles was carried out using a bipolar coaxial needle. The needle was implanted in the motor point of the opponens muscle, a little beneath the first half of the internal palmary edge of the axis of the first metacarpal. Evaluation by detection and stimulation EMG as well as study of sensory conduction was carried out as follows:

(i) EMG for detection of muscle activity was carried out by monofilament collection.

*At rest:* recording of spontaneous denervation activity in the form of slow denervation potentials and/or fibrillation potentials indicating acute or subacute peripheral neurogenic disorder.

–normal muscle: absence of spontaneous activity = 2 points

–acute or subacute peripheral neurogenic disorder: presence of spontaneous activity = 0 points.

*On maximum voluntary contraction of the muscle* (opposing movement of the thumb to the manual resistance of the operator): recording of the electrical activity of the muscle which was ± abundant depending on the degree of nerve injury.

–normal muscle: interferential activity = 4 points; mean amplitude of recordings 3 to 4 mV.

–partial denervation: intermediate activity = 3 points; the abundance of the recording was less. Motor unit potentials could be individually analyzed. Some were polyphasic whilst others were mature but predominant with amplitudes that were usually higher than the mean of the recording (5 to 6 mV), often seen as short and sometimes linked points which pulsed at a high frequency, characteristic of temporal summation.

–large-scale denervation: characteristic peripheral neurogenic activity.

Two stages:

1. Poor activity = 2 points: recordings showed at least 2 distinct motor unit potentials pulsing at high frequencies (temporal summation + + +).

2. Simple activity = 1 point: a single motor unit potential pulsing at a high frequency.

*The morphology of potentials varied:*

–normal, biphasic,

–polyphasic seen in either acute or subacute denervation in progress or in reinnervation.

*The amplitude could vary:*

–normal, 3 to 4 mV,

–increased, 5 to 15 mV, often with short points that were sometimes linked indicating the development of chronic neurogenic atrophy.

The greater the amplitude, the more established was the disorder.

–reduced or microvoltage: 150 to 500 μV indicating either acute or subacute denervation or reinnervation

–complete denervation: absence of voluntary activity, no recording = 0 points.

(ii) Study of the motor conduction of the median nerve in the carpal tunnel was carried out by bifiliary recording. The negative pole of the stimulation electrode was applied to the lower end of the forearm, between the large and small palmary muscles of the tendons, 7 cm above the point of insertion of the needle implanted in opponens muscle of the thumb. The earth electrode was attached to the wrist in the area between nerve stimulation and the reception needle in the muscle. A motor response was characterised by:

(a) its distal latency in the muscle after stimulation,

from the beginning of the response, (b) its duration, and (c) its morphology and amplitude.

*Distal latency:*

| | | |
|---|---|---|
| –normal | DL < 4.5 ms | = 3 points |
| –increased | 4.5 < DL < 6 ms | = 2 points |
| | 6 < DL < 7 ms | = 1 point |
| | DL > 7 ms | = 0.5 point |
| | | = 1 point if a response reappears after the operation (EMG at 90 days) |
| –absence of response | | = 0 point |

*Duration:*

| | | |
|---|---|---|
| –normal | D < 10 ms | = 2 points |
| –increased | 10 < D < 15 ms | = 1 point |
| | D > 15 ms | = 0.5 point |
| | | = 1 point if a response reappears after the operation (EMG at 90 days) |
| –absence of response | | = 0 point |

*Morphology:*

| | |
|---|---|
| –normal 2 to 4 phases, amplitude of 1 to 3 mV | = 2 points |
| –simple single biphasic motor unit potential 1 to 2 mV amplitude or polyphasic ± μV from 150 μV to 1.5 mV) | = 1 point |
| –heterogeneous 2 or more groups of response | = 0.5 point |
| | = 1 point if postoperative reinnervation |
| –absence of response | = 0 point |

(iii) *Study of the sensory conduction of the median nerve was carried out using a cut-by-cut antidromic stimulation method.*

The negative pole of the stimulation electrode was placed in the same position as that for motor stimulation. The electrodes for collection of sensory potential were skin electrodes (rings if possible) placed on the index finger at the level of the flexion points of the proximal interphalangeal joint for the negative electrode and at the level of the distal interphalangeal joint for the positive electrode. Sensory conduction was characterised by the rate of conduction of sensory fibres and by the morphology and amplitude of the potential recorded.

The rate of conduction is given in metres per second, calculated from the distance separating the negative stimulation electrodes at the wrist and receiver at the level of the proximal interphalangeal joint expressed in millimetres with respect to distal latency at the beginning of the sensory potential given in milliseconds.

$$\textit{Rate of sensory conduction m/s} = \frac{d\ (mm)}{dl\ (mm)}$$

(a) The rate of sensory conduction of the 2 median nerves was calculated comparatively:

| | | |
|---|---|---|
| –rate of conduction | | |
| | normal SCR > 40 m/seconds | |
| | equivalent to the other side | = 4 points |
| | reduced with respect to the other side | = 2 points |
| –reduced rate of conduction | 30 m/s < SCR < 40 m/s | = 1 point |
| | SCR < 30 m/s | = 0.5 points |
| | | = 1 point if reappearance of postoperative sensory response (EMG AT 90 days) |
| –absence of sensory response | | = 0 points |

(b) Morphology and amplitude of sensory potential:

| | | |
|---|---|---|
| –normal | | |
| | amplitude > 10 μV, biphasic morphology, | |
| | identical to other side | = 3 points |
| | reduced with respect to other side | = 2 points |
| –modified | | |
| | microvoltage < 10 mV or triphasic | = 1 point |
| –absence of response | | = 0 point |

A clinical examination was performed before surgical intervention. Treatment started on the day of the operation: one group of patients received 600 mg of naftidrofuryl, the other group received a placebo. The first EMG evaluation was carried out a few days before the operation. Then at 45 days after the operation, a clinical examination was carried out. A second EMG evaluation was performed on the 90th day after the operation.

### Statistics

Statistical analysis was carried out using an ISIS programme (version 2, 1991) on an IBM-compatible computer and BMDP installed on HP 3000 (LIPHA, Lyons, France, with a BMDP user's licence). In order to compare the 2 groups treated, we used the $\chi^2$-test for nominal and ordinal variables and the Student t-test for variables with one less interval scale. All Student t-tests used in the series were considered to be bilateral and the level of significance was fixed at 5%.

Analysis of efficacy took into account the type of vari-

**Table 4.** Patient Population (n = 56).

| | Naftidrofuryl | Placebo |
|---|---|---|
| | 4 male<br>23 female | 4 male<br>25 female |
| Total number of patients | 27 | 29 |
| Mean age (± S.E.) | 59.22 ± 12.4 | 51.14 ± 15.4 |
| Operation side | right: 15<br>left: 12 | right: 23<br>left: 6 |
| Handedness | right: 26<br>left: 1 | right: 28<br>left: 1 |

**Table 5.** Abnormal "0" Sign at Days 0 and 90.

| Day | Naftidrofuryl | Placebo |
|---|---|---|
| 0 | 18 | 20 |
| 90 | 12 | 19 |
| | $\chi^2$ NS | |

able. Binary criteria or criteria measured on a nominal or ordinal scale, such as zero signs and trophic disorders, were tested using the $\chi^2$-test, taking into consideration the limit of approximation of the $\chi^2$-test fixed by the percentage of the number of cells having an expected theoretical value of less than 5.[5] If this limit is exceeded, we recommend the use of the Kendall tau b or c test,[6] if the variable is ordinal. If the variable is nominal, the values are grouped together or, if the numbers available are less than 20, the $\chi^2$-test is replaced by the Fisher test 2 × 2.[7] The criteria studied and measured on an interval scale (Weber sign, electromyogram values) were studied by variance analysis of repeated measurements of two factors: the time factor (random) and the treatment factor (fixed). In simple cases, orthogonal resolution by the Winer unweighted means method was used.[8]

## RESULTS

Fifty-six examinations are reported.

### Distribution of Patients (Table 4)

A preponderance of female patients is noted. The mean age was higher (59 years) in the naftidrofuryl than in the placebo group (51 years). However, this did not affect the homogeneity of the groups. It should be noted that 97% of the patients were right-handed, but that operations on the injured side were carried out 38 times on the right-hand side versus 18 times on the left-hand side. This is of no great importance except in the case of subjective evaluation of functional recovery which may be overestimated in a right-handed person whose left side is operated on (16 times). It was also found that more "left sides" were operated on in the naftidrofuryl group (12 versus 6).

**Table 6.** Changes in Weber Sign.

| Patient group | Day 0 | Day 45 | Day 90 |
|---|---|---|---|
| Naftidrofuryl | 8 | 6.42 | 5.21 |
| Placebo | 6.83 | 5.38 | 4.21 |

**Table 7.** Muscle Trophicity at Days 0 and 90.

| Day | | Naftidrofuryl | Placebo |
|---|---|---|---|
| 0 | Moderate atrophy | 20 | 24 |
| | Complete atrophy | 6 | 5 |
| | | $\chi^2$ NS | |
| 90 | Normal trophicity | 11 | 9 |
| | Moderate atrophy | 8 | 6 |
| | Complete atrophy | | 9 |
| | | $\chi^2$ $P < 0.01$ | |

### Appraisal of Clinical Parameters

**"0" sign.** The presence of this sign was assessed on inclusion and after 3 months of treatment. Table 5 shows the results. It can be seen that the difference was not statistically significant but that the "0" sign was not present 6 times in the naftidrofuryl group versus only once in the placebo group.

**Weber sign.** Variance analysis by repeated measurements showed a highly significant development in each of the two groups ($P < 0.001$) but an absence of intergroup difference in spite of a greater differential in favour of the treated group (Table 6).

**Evaluation of trophicity.** A significant difference was found at D/90 ($P < 0.01$) in favour of the naftidrofuryl group, whereas there was no significant difference at D/0 (Table 7).

**Motor disorders.** The action of the drug on motor condition did not reach statistical significance. Most treated patients were ameliorated but the condition of one patient was unchanged and that of two others worsened.

### Electromyographic Parameters

We analysed the following parameters: rate of motor conduction of the median nerve in the carpal tunnel (Table 8); motor distal latency (Table 9); rate of sensory conduction (Table 10); amplitude of sensory conduction (Table 11); overall analysis (Table 12). In order to obtain an overall view, based on individual electrophysiological parameters, we gave each patient an overall score based on the electromyogram recording according to a scale and then appraised the development of each plot. Overall appraisal of progress by the electromyographist was based on the scale in Table 13).

**Table 8.** Changes in Rate of Motor Conduction From D/0 to D/90.

| Group | Day 0 | Day 90 |
|---|---|---|
| Naftidrofuryl | 30.80 | 46.15 |
| Placebo | 36.80 | 45.45 |
| | Effect of time $P < 0.01$–NS interaction | |

**Table 9.** Changes in Motor Distal Latency From D/0 to D/90.

| Group | Day 0 | Day 90 |
|---|---|---|
| Naftidrofuryl | 8.57 | 4.65 |
| Placebo | 5.26 | 3.81 |
| | Effect of time $P < 0.05$– NS interaction | |

**Table 10.** Changes in Rate of Sensory Conduction From D/0 to D/90.

| Group | Day 0 | Day 90 |
|---|---|---|
| Naftidrofuryl | 20.53 | 40.80 |
| Placebo | 20.95 | 36.92 |
| | Effect of time $P < 0.01$–NS interaction | |

**Table 11.** Changes in Rate of Sensory Amplitude From D/0 to D/90.

| Group | Day 0 | Day 90 |
|---|---|---|
| Naftidrofuryl | 6.67 | 20.40 |
| Placebo | 15.39 | 19.47 |
| | Effect of time $P < 0.001$–NS interaction | |

**Table 12.** Changes in Overall Score.

| Group | Day 0 | Day 90 |
|---|---|---|
| Naftidrofuryl | 6.65 | 12.44 |
| Placebo | 8.65 | 13.14 |
| | Effect of time $P < 0.001$–NS interaction | |

**Table 13.** Overall Appraisal.

| Condition | Naftidrofuryl | Placebo |
|---|---|---|
| Improved | 20 | 17 |
| Stationary | 0 | 2 |
| Worsened | 0 | 2 |

## DISCUSSION

It was interesting to observe that clinical improvement was much more evident in the treated group, both as far as the "0" sign and improvement in trophicity or motor disorders was concerned. At D/90, there was no complete atrophy of the opponens in the treated group, whereas this occurred in 9/24 of the placebo group. Motor disorders were still found in the placebo group (3/24), whereas they were absent in the treated group. These results were reinforced by the fact that the treated group had a higher mean age (59.22) than the placebo group (51.14), a factor which tends to have a negative effect.

The electromyographic study was not significant for the rate of motor conduction, whereas motor distal latency became normal under better conditions in the treated group, although this was more altered (8.57 ms) than in the control group (5.26 ms). In the same way, the rate of sensory conduction and sensory amplitude as better at D/90 in the treated group than in the control group. The same electromyographist gave each patient an overall score out of 20. The treated group had a very low score at D/0 (6.65), whereas the placebo group had a score of 8.65. The treated group obtained a score of 12.45 and the placebo group had a score of 13.14 at D/90. The differential was thus in favour of the treated group (Table 12). Finally, the electromyographist had given an overall evaluation of development (Table 13) which showed that all cases treated with naftidrofuryl improved, whereas in the control group, two cases showed no change and two cases became worse.

## CONCLUSION

This prospective double-blind trial confirms that naftidrofuryl prescribed at a daily dose of 600 mg has a direct effect on trophicity and muscle function. This fact was reinforced by the majority of the parameters of the electromyographic study.

The clinical study confirms the experimental study carried out on rats, and although naftidrofuryl does not influence the speed of nerve regeneration, it does affect the number of regenerated fibres.[8] However, the mechanism of action of naftidrofuryl still has to be elucidated.

## REFERENCES


1. Merle M, Amend Ph, Foucher G, Michon J: Playdoyer pour la réparation primaire microchirurgicale des lésions des nerfs périphériques. Etude comparative de 150 lésions du nerf médian et du nerf cubital avec un recul supérieur à 2 ans. *Chirurgie* 110:761–771, 1984.
2. Hauw JJ: Un nouveau promoteur de croissance nerveuse: Le Naftidrofuryl. *C.R. Académie des Sciences*, Paris, t. 302, série III, no. 14, 1986.
3. Louis JC: Effect of Naftidrofuryl on metabolism and survival of cultured neurons. *Neurochemical Research* 14:1195–1201, 1989.
4. Doucet J: Amélioration de la polynéurite diabétique sous naftidrofuryl. *Thérapie* 46:315–318, 1991.
5. Cochran, WG: Some consequences when the assumptions for the analysis of variance are not satisfied. *Biometrics* 2:22–38, 1947.
6. Kendall MG: *Rank Correlation Methods*. London: Griffin, 1955.
7. Siegle S: *Non-parametric Statistics for the Behavioral Sciences*. New York: McGraw-Hill.
8. Winer JB: *Principles of Experimental Design*. New York: McGraw-Hill, 2nd edition, 1972.