COMPARATIVE STUDIES OF THE EFFECTS OF
\(\alpha\)-TOCOPHERYL NICOTINATE AND THE
COMBINATION \(\alpha\)-TOCOPHERYL ACETATE
AND NICOTINIC ACID

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By conducting a cross administration of Toc. nic and the combination
of Toc. ace and 20\% nicotinic acid to cases with insufficient micro-
circulation and also by performing the cooling rewarming test during
the administration, it was found that Toc. nic is more effective than
the combination in reducing the MRT, and that the effectiveness of
Toc. nic was not due to the synergic action of tocopherol and nicotinic
acid but to the independent action of Toc. nic.

It has been reported that \(\alpha\)-tocopheryl nicotinate (Toc. nic) has a more im-
mediate and superior effect on the microcirculatory system than \(\alpha\)-tocopheryl
acetate (Toc. ace). However, it has not been clarified whether the superiority
of Toc. nic is due to inherent essential properties or to the synergetic effect of
tocopherol and the nicotinic acid produced by the hydrolysis of Toc. nic in the
body. In order to elucidate these properties the author conducted studies of
the cross administration of Toc. nic and the combination of Toc. ace and nicotinic
acid to patients with microcirculatory insufficiency and compared the results
using the cooling rewarming test (1).

EXPERIMENTAL METHODS

1. Drugs and the method of administration. One of the drugs administered
was Toc. nic 100 mg and the other, used for controls, was the combination of
Toc. ace 100 mg and nicotinic acid 20 mg. The drugs were put into different
capsules having the same outward appearance. Without telling the patients
about the differences of the two types of drugs used, 4 capsules a day were
administered, 2 in the morning and 2 in the evening when the patients were
hungry. One of the drugs was administered for 2–3 weeks, mostly 2 weeks, and
the other drug was continuously followed in the same way, and furthermore the drugs was alternately administered for every 2–3 weeks (cross administration of drugs).

2. **Subjects in the experiment.** As shown in Table 1, the subjects were 10 persons aged 24–60 (2 males and 8 females) and the diagnosed diseases were classified as 3 cases of scleroderma en plaque, 2 of feeling cold, 1 of hyperidorosis localis (palmar and plantar), 1 of acrocyanosis, 1 of sclerodactria, 1 of sclerodermia diffusa, and 1 of microcirculatory insufficiency after congelation. Two of these patients cases (case 5, 6 and 7, 8) were restudied after having discontinued the treatment once, and 1 patient (case 10, 11) with acrocyanosis was measured with the hand in both horizontal and vertical positions. Although no apparent disturbances were observed in the internal organs of the patients, microcirculation disturbances appeared to develop, and the mean rewarming time (MRT) in the cooling rewarming test (CR test) described in the following pages increased and showed Heidelmann’s contraction type except for the 27-year-old male with acrocyanosis (case 11) when the fingertip was measured in the horizontal position.

Moreover, as for the cross administration assortment of the two drugs, the administration of one drug was continued for about 2 weeks mostly, 19 pairs of readings were obtained with the administration of the combination drug followed by Toc. nic and another 18 pairs of readings with Toc. nic followed by the combination drug.

3. **Testing Method.** The CR test was performed before the administration of the drugs and 2 weeks after the administration of each drug, the MRT at the middle fingertip and at the center of the dorsum of the hand was obtained to make comparative studies. The CR testing method was based on the original plan devised by Heidelmann (2). The test was carried out from 9 to 11 o’clock in the morning. Before starting the test, the subject was made to sit on a chair in a relaxed position for more than 30 min at a constant room temperature of 21°C ± 1°C. While in the same posture the temperature at the middle fingertip and at the center of the dorsum of the hand as measured with a thermister every 10 sec to confirm the stability of the skin temperature. Then the hand, up to the wrist joint, was soaked in water maintained at 15°C for 5 min. The hand was then drawn out and wiped softly with a dry towel immediately. The skin temperatures at the two points mentioned above were quickly measured. The thermister was connected to a recorder and the alteration of the skin temperature was recorded on graph paper. The time required for the skin temperature to rise to 25°C after removal from the water was calculated on the basis of the recorded graph to decide the MRT at that time. Measurements were not conducted at the time of pyrexia or during menstruation periods, and especially the time of premenstruation was deliberately avoided. It is well known that the CR test is said to show the reserve capacity (reserve Kraft) of microcirculation in the best way (3).
Table 1. Mean rewarming time before and after administration of tocopheryl nicotinate and the combination of tocopheryl acetate and nicotinic acid.

| Patient                                      | No. | Portion | Before administration | After administration |
|----------------------------------------------|-----|---------|-----------------------|----------------------|
| Scleroderma en plaue                         | 1   | hand    | >40'                  | combination          |
| Feeling cold                                 | 2   | hand    | 49'10''               | 27'20''             |
| Feeling cold                                 | 2   | finger  | >50'                  | 14'20''             |
| Feeling cold                                 | 3   | hand    | >50'                  | 13'50''             |
| Feeling cold                                 | 34  | hand    | >50'                  | 11'10''             |
| Circulation insufficient after congelation   | 4   | hand    | >50'                  | 14'20''             |
| Scleroderma en plaque                        | 5   | hand    | 40'00''               | 16'10''             |
| Hyperidrosis localis                         | 7   | hand    | 38'00''               | 21'10''             |
| Hyperidrosis localis                         | 6   | finger  | 44'00''               | 4'30''              |
| Hyperidrosis localis                         | 26  | hand    | 44'00''               | 42'00''             |
| Hyperidrosis localis                         | 7   | finger  | 41'20''               | 24'20''             |
| Acrocyanosis (hanging down)                  | 8   | hand    | 50'00''               | 22'20''             |
| Scleroderma en plaque                        | 9   | hand    | 40'40''               | 26'00''             |
| Scleroderma en plaque                        | 25  | hand    | >40'                  | 28'10''             |
| Acrocyanosis (horizontal)                    | 10  | hand    | >50'                  | 34'00''             |
| Sclerodactyria                               | 11  | finger  | 25'30''               | 23'00''             |
| Sclerdermia diffusa                          | 12  | hand    | >40'                  | 12'10''             |
| Sclerdermia diffusa                          | 52  | finger  | >40'                  | 12'10''             |
| Sclerdermia diffusa                          | 13  | hand    | >40'                  | 13'30''             |
| Sclerdermia diffusa                          | 59  | finger  | >40'                  | 7'50''              |
RESULTS

1. The MRT before and after administration and during cross administration of drugs

The MRT of each patient before administration, after the initial administration, and 2 weeks after changing the drug is shown in Table 1. It can be seen from Table 1 that in most cases the MRT was reduced after the administration of both drugs, and the degree of reduction was more marked when Toc. nic was administered. There were several cases where the MRT continued to reduce after the combination was changed to Toc. nic, and an increase of MRT was observed in not a few cases to which the combination was administered. This tendency was more marked at the fingertip than at the dorsum of the hand. As shown in Table 2, the mean MRT in all the tests was reduced to approximately 60% after the administration of the combination, and to approximately 40% after the administration of Toc. nic when compared with the MRT before administration. In the comparison between the combination and Toc. nic, the MRT in cases to which Toc. nic was administered was more markedly reduced, to about 55% at the fingertip and to 59% at the dorsum of the hand.

| Table 2. Mean value of MRT before and after administration of tocopheryl nicotinate and combination of tocopheryl acetate and nicotinic acid. |
|------------------|------------------|------------------|
|                   | Before administration | After administration |
|                   |                   | combination       | tocopheryl nicotinate |
| Cases             | 13                | 24               | 26               |
| Fingertip         | 39‘13’”           | 21‘55’”          | 11‘54’”          |
| Dorsum of hand    | 42‘38’”           | 26‘13’”          | 15‘34’”          |

| Table 3. Relationship of MRT after cross administration of tocopheryl nicotinate and combination of tocopheryl acetate and nicotinic acid. |
|------------------|------------------|------------------|
|                   | Combination→Toc. nic | Toc. nic→combination |
|                   | fingertip         | dorsum of hand   | fingertip         | dorsum of hand |
| Combination > Toc. nic | 19               | 19               | 17               | 14               |
| Combination = Toc. nic | 0                | 0                | 0                | 0                |
| Combination < Toc. nic | 0                | 0                | 1                | 4                |

2. Correlation between the MRT obtained after the administration of Toc. nic and after the combination

The differing cross administration of both drugs provided 37 pairs of readings each for the fingertip and the dorsum of the hand. The relationship of the MRT for each pair of readings is shown in Fig. 1. In the dilatative type (MRT being within 10 min), there were readings where the difference between each pair was slight, but in many pairs of readings, that is 69 out of 74, the MRT was shorter.
Fig. 1. Relationship of MRT between tocopheryl nicotinate and combination of tocopheryl acetate and nicotinic acid (ホール, fingertip; オーバー, dorsum of hand).

Table 4. Relationship of numbers of cases classified from MRT after administration of tocopheryl nicotinate and combination (fingertip/dorsum of hand).

| Combination  | 0–   | 5–   | 10–  | 15–  | 20–  | 25–  | 30–  | 35–  | 40–  | Total |
|-------------|------|------|------|------|------|------|------|------|------|-------|
| MRT         |      |      |      |      |      |      |      |      |      | 5/8   |
| 0–          | 3/   | 2/   | 1/   | 5/   | 6/1  | 2/2  | 2/1  | 1/   | 17/4 |
| 5–          | 2/   | 2/3  | 1/1  | 2/1  | 1/1  | 2/   |      | 1/   | 6/9  |
| 10–         | 1/   | 1/   | 1/   | 1/   | 1/   | 1/   | 2/   |      | 4/4  |
| 15–         | 1/   | 2/1  | 2/   | 1/4  | 2/   |      |      |      | 2/9  |
| 20–         | 1/   | 1/   | 1/   | 1/   | 1/   |      |      |      | 2/2  |
| 25–         | 1/   | 1/   | 1/   |      |      |      |      |      | 1/1  |
| 30–         | 1/   | 1/   |      |      |      |      |      |      |      |
| 35–         | 1/   |      |      |      |      |      |      |      |      |
| 40–         |      |      |      |      |      |      |      |      |      |
| Total       | 3/   | 3/4  | 6/2  | 8/8  | 2/6  | 3/2  | 5/4  | 3/4  | 4/7  | 37/37 |

after administration of Toc. nic. As shown in Table 3, when viewed from the order of administration, in pairs where Toc. nic was administered first and followed by the combination, the MRT was reduced more sharply in 1 case at the fingertip and in 4 cases at the dorsum of the hand, based on observations on 18 pairs of readings. In 19 pairs of readings where Toc. nic was continuously administered, the MRT was reduced more sharply in all cases than at the time of administration of the combination. From the results, it can easily be inferred...
that there is a significant difference between the two drugs. Although in further assessments of the mean difference the risk was 0.1%, and the range of the non-significant difference was $t^o = 3.646$ for the 30 pairs of readings, the difference between the two in the present test was significant as shown in the mean difference of $t^o \geq 3.989$ at the fingertip and $t^o \geq 4.469$ at the dorsum of the hand in 37 pairs. The relationship between the two drugs MRT classified into 5 min each was shown in Table 4, in the contracture type (MRT being over 20 min), all the cases to which Toc. nic was administered showed a sharp reduction of the MRT, except for 1 case where the readings were recorded at the dorsum of the hand.

DISCUSSION AND SUMMARY

The ester of vitamin E currently used largely for clinical purposes is Toc. ace. In addition, such agents as tocopheryl succinate and tocopheryl phosphate were developed, but the usefulness of these agents has been limited because of the lack of specific features, hemolytic reaction, and other disadvantages. Under these circumstances, Toc. nic, which has sufficient tocopherol action and no shortcomings such as the flash and short duration of effectiveness observed in nicotinic acid, arrived on the scene and has attracted attention (4, 5). In a previous experiment, the author conducted the cross administration of Toc. nic and Toc. ace in the same way as in the present experiment and showed that with respect to the microcirculatory system Toc. nic had more immediate and higher effectiveness than Toc. ace (1). However, it was not clarified whether such effectiveness was due to the independent effect of Toc. nic or to the synergetic effect of tocopherol and nicotinic acid produced by the hydrolysis of Toc. nic in the body. Accordingly, in order to clarify this point, the author examined the effect of both drugs using the CR test and found a significant difference between the two by cross administering Toc. nic and the combination of Toc. ace and nicotinic acid. Although there are many problems regarding absorption, hydrolysis, dosage, and other aspects, it can be concluded that the effectiveness of Toc. nic is not due to the synergetic effect of tocopherol and nicotinic acid but to the independent effect of Toc. nic on the microcirculatory system. The results of the experiment are discussed below.

The arithmetic mean of MRT at the fingertip was more than 39'13'' before administration, and it was 11'54'' after administration of Toc. nic and more than 21'55'' after administration of the combination. For the dorsum of the hand, the mean MRT was more than 42'38'' before Toc. nic, 15'34'' after Toc. nic, and 26'13'' after the combination, showing that MRT was sharply reduced with Toc. nic. Even in the cases in which the MRT was not reduced by the administration of the combination, such as sclerodactyly and sclerodermia diffusa, the administration of Toc. nic markedly reduced the MRT. Moreover, in the cases where the MRT was reduced much more after the administration of the combina-
tion than after the previous administration of Toc. nic, the followup administration of Toc. nic further reduced the MRT. It can be understood that rather than disproving the stronger effect of Toc. nic for reducing the MRT than the combination, this shows the short duration of the administration. The above-mentioned results demonstrate that Toc. nic has a stronger effect in reducing the MRT than the combination.

In addition, based on a pair of MRT readings measured after the alternate administration of Toc. nic and the combination, 37 pairs of readings for the assortment were recorded at the fingertip and also at the dorsum of the hand in order to make comparative studies between the two drugs. In the 19 pairs of readings where the administration of the combination preceded, the MRT after the administration of Toc. nic was shorter in all the paired readings, and in 18 pairs of readings where the administration of Toc. nic preceded, the MRT after the administration of the combination was shorter in only 4 pairs at the dorsum of the hand and 1 at the fingertip. As mentioned above, the findings can be understood to have been obtained because of the insufficient duration of the administration, and cannot be taken as a problem of selecting drugs according to symptoms. Moreover, the values obtained by means of the modulus treatment of these assortments clearly show the significant difference between the two drugs. Furthermore, the marked superiority of Toc. nic in the extension of MRT implies not only a quantitative difference, but a qualitative difference. Recently, Toc. nic and Toc. ace have not only been separated pharmaceutically as an ester of vitamin E but also have attracted attention due to their different natures. For example, Toc. nic can easily be hydrolyzed in the body, leaving some portion as an ester type for quite a long time, and a difference in the condition of retention in the body between the two has been observed (6). Consequently as many more esters join the scene in the future, attention must be paid not only to the question of quantity but also to the question of quality.

The observations above describe, our findings that Toc. nic efficiently reduces the MRT in the CR test (thought to be the most accurate measure of the reserve capacity of the microcirculatory system) and that the effect of Toc. nic is not due to the synergetic action of tocopherol and nicotinic acid produced by hydrolysis but to the independent action of Toc. nic.

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