A Curative Effect of Carnosine (β-alanyl-1-histidine) on the Decubital Ulcer

by

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Summary

An effective dose of 1-carnosine (β-alanyl-1-histidine) for the restoration of inflammatory tissues (by formalin filter method) is known to be 8.8 μmol/100g rat ip. In the present paper, an application of this potent effect to the decubital ulcer is discussed. By spraying minute powder of 1 to 3g carnosine on an ulcerous wound, the necrotic layer is made to fall off and, through the formation of new granulations, the wound will become gradually cicatrized from the periphery.

1. Introduction

1.1 Healing of the wound

Healing of the wound, which is a primary concern in surgery, is currently effected by three measures of the hemostasis, prevention of an infection and antiphlogistic measure, so that conditions most favorable to a natural heal may result in. However, it is far from directly influencing the mechanism that restores a pathological physiologic state.

When something happens which interferes with this natural healing process, any clinical attempt at its cure will become correspondingly difficult. These cases may include the opening of postoperative wounds, keloidosis, decubital ulceration, alveolar pyorrhea and dry socket complaints in the dental domain. In recent years, in addition, interferences with the natural healing are recognized to come from an excessive administration of such drugs as tend to inhibit the vital defense reaction, including carcinostats, antiinflammatory drugs, steroid preparations and antimmunologic agents. A change in our philosophy of the healing process of a vital body is bound to come about, if we want to deviate from the current practice of having recourse to a healing of wound merely from a biochemical point of view.

Since the healing of wound is terminal to an inflammatory reaction, a major portion of the previous investigations has been addressed to this negative component of an inflammation, i.e., interference or inhibition of the manifestation of an inflammatory reaction. It is for this very reason that many steroid and non-steroid preparations which are screened in terms of inhibiting the granular process due to an inflammation.

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are marketed at present. An entirely new drug which will positively contribute toward the restoration of inflamed tissues needs, it is urgently felt, to be developed.

1.2 Carnosine

In connection with a series of researches in which the effect of ω-amino acid on an inflammation was attempted, the potent effect of 4-amino 3-hydroxy butyric acid (GABOB) and 4-hydroxy 3-amino butyric acid (GOBAB) against the edema due to carrageenine was discovered in 1967 [1, 2].

In view of the fact that an inflammatory granular process is influenced by both the quantity and quality of an exudate, a physiologic consideration came to the fore that some kind of chemical mediator might exist in these amino acids which would involve itself in the inflammatory granular process. This assumption was substantiated by our discovery of an action of carnosine in 1970, which proved to possess the same anti-inflammatory effect as GABOB and GOBAB.

Carnosine, which is a polypeptide discovered by Glew with from a meat infusion in 1900, has not been known to possess a physiologic significance at all. This substance, chiefly contained in the skeletal muscle of animals, has the following distribution in different species of animals, though certain variations are known from measurement method to measurement method, and from investigator to investigator.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Carnosine Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ox</td>
<td>230mg%</td>
</tr>
<tr>
<td>Swine</td>
<td>387</td>
</tr>
<tr>
<td>Whale</td>
<td>103–300</td>
</tr>
<tr>
<td>Dolphin</td>
<td>447</td>
</tr>
<tr>
<td>Domestic fowls</td>
<td>437</td>
</tr>
<tr>
<td>Seal</td>
<td>592</td>
</tr>
</tbody>
</table>

An effective dose of carnosine for the restoration of inflamed tissues has been determined at 2.0mg/100g rat ip., which corresponds to 1/35 of what is usually contained in a vital body, 308μmol/100g rat gastronemius.

A unique effect of this carnosine is seen when it is conjointly administered with either cortisone or ACTH in that it enhances the granular process and anti-edematous effect. However, the latter effect disappears in adrenalectomized animals but is restored again when cortisone is added. On the strength of these findings, one of the authors, Nagai, proposed a hypothesis that such substance as cortisone which is involved in a vital defense mechanism would need for its action a co-factor like carnosine.

It is beyond doubt that endogenous cortisone works in a vital defense mechanism but it seems also true that exogenous cortisone works similarly. This view is endorsed by the fact that an amount of carnosine which is far smaller than that contained in a vital body definitely works beneficially on the restoration of inflamed tissues or, at least, it works in the capacity of a chemical mediator.

So far, the following physiologic significances of carnosine are established:

1. It promotes the repair function of inflamed granulations.
2. It inhibits the retardation of the Arthus' phenomenon.
3. It prevents an anaphylactic shock by the blood serum or prolongs the length of survival.
4. 0.1 mm mol of carnosine inhibits the local anaphylaxy of sensitized Guinea pig intestinal ducts.
5. It prevents the abnormal permeability of blood vessels induced by bradikinin.
6. It acts inhibitively on the anti-granular effect of cortisone and thus promotes the granulation.

HORISAKA and his associates investigated these physiologic effects of carnosine in the light of pharmacology and confirmed its excellent curative action particularly in wounds.

In the present study, the authors concerned themselves with spraying of carnosine powder on 5 patients who suffered from the decubital ulcers of varying degree and, as a consequence, brought to light some interesting findings.

2. Clinical Findings

2.1 Experimental material

By way of experimental material, use was made of carnosine (β-alanyl L-histidine) synthetized for the purpose and, prior to an administration, it was made into very fine powder. Depending on the size of wounds, the amount anywhere from 1 to 3 g was sprayed on them on the daily basis. The wounds were subsequently protected from exposure by means of rivanol gauze.

To insure the accuracy of data, no other drugs or antibiotics than carnosine powder were employed throughout the experimental period. Five subjects studied were selected from among the patients suffering from the motor disturbance as a result of the cerebral hemorrhage and were hospitalized at St. Luke Hospital, Yugawara, Kanagawa.

Their clinical findings of our experiment are summarized in Tab. 2.

<table>
<thead>
<tr>
<th>Name</th>
<th>Sex</th>
<th>Age</th>
<th>Decubital area</th>
<th>Size of ulcer</th>
<th>Degree of necrosis</th>
<th>No. of days before cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y.M.</td>
<td>Male</td>
<td>65</td>
<td>Sphenoid area</td>
<td>8 × 8 cm</td>
<td>++ +</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Y.K.</td>
<td>Female</td>
<td>72</td>
<td>&quot;</td>
<td>5 × 3</td>
<td>+</td>
<td>6 days</td>
</tr>
<tr>
<td>S.M.</td>
<td>Male</td>
<td>68</td>
<td>&quot;</td>
<td>7 × 5</td>
<td>+</td>
<td>20 days</td>
</tr>
<tr>
<td>K.O.</td>
<td>Male</td>
<td>66</td>
<td>Median lumbus</td>
<td>4 × 4</td>
<td>-</td>
<td>15 days</td>
</tr>
<tr>
<td>O.A.</td>
<td>Male</td>
<td>74</td>
<td>&quot;</td>
<td>6 × 4</td>
<td>+</td>
<td>25 days</td>
</tr>
</tbody>
</table>

All of the subjects, who were advanced in age and complained of the motor disturbance as a retarded manifestation of the cerebral hemorrhage, could barely move just enough to roll in bed.

In about 10 days after the spraying of carnosine powder (4 days in the case of a light symptom), the necrotic layers or crusts that had attached themselves to the
Fig. 1  A female, 70 years old. A decubital ulcer was complained on the buttock and was hospitalized presumably after 50 days of the incidence. The wound was covered with necrotic layers and coagulated blood. The suppurative ulcer developed on the peripheral region, extending to the depth of 15cm at the deepest spot, and was drained by use of rivanol gauze. Carnosine powder, 3g per day, was sprayed on the wound together with rivanol gauze as a protective measure. No further drainage.

Fig. 2  18th day of carnosine spray. Much exudate and filth attached itself to the gauze from the second day onward, the wound surface becoming gradually cleaner. On 5th day, fresh granulations were observed to develop on the clean surface. By 18th day, necrotic layers were completely shed and the wound was completely covered with fresh granulations. No further attachment of exudate on the gauze. The wound perforation was so closed that gauze could not be inserted. As in all other cases, the wound became cicatrized and was much reduced in size. (The subject died of an acute heart failure on 32nd day and further observation of the wound was impossible).
wound surface began to fall off and gradually became replaced by fresh granulations. In some severe cases, the bony surface came to be exposed through the shedding of necrotic layers but, in several days of carnosine spray, even these came to have fresh granulations which covered the exposed bone.

A similar beneficial effect of 4-hydroxy 3-amino butyric acid (GABOB) on the decubitus had previously been reported by one of the authors. In that previous report, it was noted that the necrotic layer in question was resolved by the effect of GABOB but, as in the present case, it would be more exact to say that the necrotic layer comes to fall off through the formation of fresh granulations underneath it.

It is held to be commonplace that, in patients of advanced age suffering from the motor disturbance as a result of the cerebral hemorrhage, their nerves also suffer as well as pronounced decubital ulcers associated with the malnutrition and, therefore, are difficult of cure. However, as far as the findings of the authors go, the spraying of carnosine powder seems to have a potent healing efficacy regardless of the degree and malnutritive level of decubital ulcers involved.

3. Summary and Discussion

Carnosine, when used in the form of spray in an amount of 1 to 3g daily, proved quite beneficial to 5 patients of the decubital ulcers of varying degree. When a case is light enough without any necrotic layer, the formation of fresh granulations took place in about 2 weeks, reaching a complete cure. The physiologic significance of carnosine in the repair of inflamed tissues is now being explicated. That carnosine corresponding to 1/35 of what is usually contained in a vital body is sufficient to repair inflamed tissues, appears to indicate that carnosine is an important chemical mediator playing a major role in this healing process.

Our biochemical knowledge of carnosine alone will not solve the granular promotive mechanism on the part of carnosine and much future research is indicated in this direction.

At the present state of our knowledge, it may be concluded that, along with cortisone, carnosine is significant in that it is a co-factor in the vital defense mechanism.

4. Conclusions

In conjunction with 5 patients who suffered from the decubital ulcers of varying degree, an application of carnosine (β-alanyl 1-histidine) in the form of fine powder spray proved very efficacious.

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References


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