Effect of intralesional treatment with Lidocaine and Glucantime®
in hamsters infected with *Leishmania (Viannia) braziliensis*¹

José Yépez¹, Dalmiro Cazorla¹, Auristela Sánchez de Mirt², Néstor Añez³ y Ana Lugo de Yarbuh³

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Se estudia comparativamente el efecto por vía intralesional de la Lidocaina y el Glucantime® sobre lesiones de hámsteres experimentalmente infectados con *Leishmania (Viannia) braziliensis*. Los resultados revelan que todos los fármacos ensayados reducen significativamente (P < 0,01) los tamaños promedios de las lesiones de los animales experimentales en comparación con los animales controles sin tratamiento. Se demuestra que el efecto del Glucantime® aplicado por vía intralesional es similar al obtenido con la aplicación del tratamiento sistémico standard con Glucantime®, reduciendo el tamaño de las lesiones leishmánicas; produciendo ambos regímenes antimoniales mejores resultados clínicos que el de la Lidocaina. Con la excepción de los animales tratados localmente con Glucantime®, se detectaron amastigotes viables en nódulos palpables y/o cicatrices en un 75% de los hámsteres evaluados 75 – 195 días después de finalizados los tratamientos mediante frotis, histopatología convencional, cultivo en medio NNN y el método de inmunoperoxidasa. Las observaciones ultraestructurales mostraron que la Lidocaina causa fragmentación y la pérdida de definición morfológica en la membrana plasmática y en las de otras organelas. Los efectos sobre los parásitos leishmánicos expuestos al antimonial exhibieron un citoplasma desorganizado y picnótico, membrana plasmática alterada, más una electrondensidad aumentada que pareciera estar asociada con un empaquetamiento de los ribosomas. La significancia de los resultados obtenidos se discuten en relación a la evaluación de los esquemas quimioterapéuticos en la leishmaniasis cutánea experimental y clínica, y acerca de los posibles mecanismos de acción de los fármacos ensayados.

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**Palabras clave:** Quimioterapia, *Leishmania (V.) braziliensis*, hámster, microscopía electrónica.

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INTRODUCTION

Cutaneous leishmaniasis (CL) occurs from the southern United States to the North of Argentina (OPS., 1994). In Venezuela, CL is endemic and focal in virtually all territorial units, being recorded more than 4000 cases each year (Convit *et al.*, 1987; OPS, 1994). The disease, although usually benign, can cause considerable morbidity and may result in severe disfigurement with tissue damage, especially that due to *Leishmania (V.) braziliensis* (Marsden, 1986). Organic pentavalent antimonials, mainly represented by meglumine antimoniate (Glucantime®), are still the drugs of choice for the treatment of CL in Latin America, despite their cardiac and renal toxicity, high costs and difficulty of administration, especially when administered intramuscularly (IM) for long periods (WHO, 1990). Alternative drugs, such as penta-midine and amphotericine B, could also exhibit similar side effects as those of Sb⁵ (Olliaro & Bryceson, 1993). During recent decades, new chemotherapeutic schemes have been developed as an attempt to reduce the need
were inoculated subcutaneously in the base of the tail hamsters, 8 to 12 weeks old, weighing ca. 100 – 120 g. Outbred male passages in male hamsters. Venezuela, and has been maintained by continuous leishmaniasis at the city of Trujillo, Trujillo state, strain was isolated from a human case of cutaneous parasites of dermal lesions with 4 intralesional injections and a combined regimen (IM and IL) of Glucantime®. More recently, Yépez & Scorza, (1995) have taken into account an intralesional therapeutic test with patients from the Venezuelan Andes region. In these trials, the authors cured 37 out of 40 lesions in 30 patients treated with local injections of Glucantime®. Likewise, local application of a mixture of Glucantime® plus 1% lidocaine as well as the local anesthetic alone induced 100% and 98% of clinical resolution, respectively.

Attempts have been made in the present study to compare the action to attain clinical and parasitological cure with lidocaine and Glucantime® locally applied with that of Glucantime® IM in dermal lesions experimentally produced in male hamsters by L. (V.) braziliensis. Furthermore, the ultrastructural changes of this leishmanial parasite after treatment with assayed drugs were also evaluated.

MATERIALS AND METHODS

Parasites. L. (V.) braziliensis MHOM/V/82/ZC. This strain was isolated from a human case of cutaneous leishmaniasis at the city of Trujillo, Trujillo state, Venezuela, and has been maintained by continuous passages in male hamsters.

Animals and experimental infections. Outbred male hamsters, 8 to 12 weeks old, weighing ca. 100 – 120 g were inoculated subcutaneously in the base of the tail with 0.1 ml 0.85% saline containing 4 x 10^7 amastigotes, which were obtained from hind foot pad lesions of outbred male hamsters.

Drugs. N-methyl glucamine antimoniate (Glucantime®, specia) was manufactured by Rhône Poulenc, Francia, and 1% Lidocaine (hydrochloride form) by Palenzona Laboratories, USA.

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Protocol for drug therapy. In all trials, initiation of treatment schedules took place at about two months after inoculation when leishmanial nodules exhibited sizes (diameters) of 6 – 8 mm. The control group (13 nontreated hamsters) received daily IM injections of sterile 0.85% saline for 80 days; the systemic or standard group (n= 13) was treated with daily IM injection of 80 mg/Kg of Glucantime® for 20 days, in maximum of 4 series, 10 days rest between the series. Two other groups of animals had local treatment with weekly infiltrations for 7 weeks, receiving in one group of 17 individuals 20 mg/Kg of Glucantime®, and the other one of 14 animals 8 mg/Kg of Lidocaine.

Evaluation of treatments. After the first drug infiltration, the clinical evaluation of treatments was monitored weekly, during 24 weeks, by following the development of diameter of dermal lesions with a caliper. Two animals of each experimental group were randomly selected 75 – 195 days after cessation of treatment and killed with ether to assess parasitological cure by smears, conventional histopathology, culturing and the immunoperoxidase method. Peripheral blood samples and biopsies of skin lesion, liver and spleen were taken for culturing in NNN medium. At the same time, additional biopsies and smears were also taken from leishmanial skin lesions. Tissue impression smears were fixed in methanol and stained with Giemsa. For conventional histopathological studies and immunoperoxidase staining, biopsied tissues were fixed in 10% formaldehyde, embedded in paraffin and stained with Giemsa. For conventional histopathological studies and immunoperoxidase staining, biopsied tissues were fixed in 10% formaldehyde, embedded in paraffin and stained with the Giemsa-colphonium method proposed by Bray & Garhnam, (1962) and the methodology described by Sells & Burton, (1981), respectively. Furthermore, the effect of chemotherapeutic agents on the parasite ultrastructure was also evaluated as indicated below.

Electron microscopy. During infiltration periods, at the same time of weekly measuring of the size of lesions, two animals of each experimental group (excepting those treated with systemic Glucantime®) were randomly selected and killed with ether. Immediately, samples of granulomatous tissue were dissected, cut into small pieces (ca. 1 mm^3) with a razor blade and were fixed in 2.5% (v/v) glutaraldehyde in 0.2 M cacodylate buffer (pH 6.8) for three hours at 4 °C, washed three time in 0.2 M cacodylate buffer and postfixed in 1% (w/v) osmium tetroxide in 0.2 M cacodylate buffer for two hours at room temperature, and were subsequently rinsed in three changes of deionized water for 10 minutes each. After water rinse, the samples were dehydrated in ascendent ethanol and in three changes of propylene oxide for 10 minutes each. Three changes in a mixture of propylene oxide: araldite marker.
(3: 1; 2: 1 and 1:1) for one hour each preceded embedding in pure araldite for 48 hours. Polymerization was also made in araldite at 60 °C. Thin sections were cut on a Porter-Blume MT-2B ultramicrotome, stained with uranyl acetate and lead citrate and viewed on an Hitachi 7000 electron microscope at 75 kV.

**Statistical analysis.** Kruskal-Wallis one way analysis of variance and multiple comparison tests were used to determine the significance of the results.

**RESULTS**

**Development of CL due to *Leishmania (V.) braziliensis* in outbred male hamsters.** Outbred male hamsters inoculated in the base of the tail with $4 \times 10^3$ amastigotes of *L. (V.) braziliensis* developed palpable nodules at about 30-60 days post-inoculation. No spontaneous healing or recovery from infection was observed in any of these animals. In untreated hamsters, lesions grew progressively to reach maximum average diameters ($X= 28.6 \text{ mm } \pm 8.2$) at 16 weeks of clinical evaluations (Fig. 1), producing from 15-20 weeks post-infection on progressive ulceration and death. Two non-treated animals were evaluated 305 days post-infection, detecting viable amastigotes in granulomatous dermal lesions (Table I and II).

**Effect of chemotherapy on leishmanial infection.** It’s worth mentioning that, excepting pain at the infiltration site, drugs were well tolerated by hamsters with not apparent side effects.

**Glucantime® IM.** Hamsters parenterally treated with Glucantime® showed a rapid decrease in average lesion diameters (Fig. 1). This decrease persisted for up to 18 weeks, with a maximum mean lesion diameter of 6.7 mm ± 2.9. After treatment was stopped, lesions slowly increased again although averaging only reached up to 8.8 mm ± 7.6 at the end of the measuring period. Statistical significance ($P<0.01$) was obtained when evolution of mean lesion diameters between antimonial systemic regimen and non-treated animals were compared. 75 days after cessation of treatment, parasitological evaluation of two hamsters clinically cured with Sbv systemic regimen revealed viable amastigotes in their scar lesions, as shown in Tables 1 and 2.

**Glucantime® IL.** After the first local infiltration, mean lesion diameters were strikingly inhibited by antimonial regimen, reaching averages between 5.0 and 9.9 mm during six months of clinical evaluations (Fig.1). Statistical comparison of mean lesion diameters between Sbv local regimen and non-treated hamsters revealed

*Fig.1.- Effect of treatment with Lidocaine IL and systemic and local Glucantime® on the development of lesions in the base of the tail of outbred male hamsters inoculated with $4 \times 10^3$ amastigotes of *Leishmania (V.) braziliensis*. Excepting statistical comparison between antimonial regimens, remaining ones were significant ($P<0.01$). Bar indicates lidocaine and Glucantime® IL administration time. Arrows indicate Glucantime® IM administration time.*
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**TABLE 1**

<table>
<thead>
<tr>
<th>Hamsters (Nº Positive/Nº Examine)</th>
<th>Group</th>
<th>Days Post-treatment</th>
<th>Smears</th>
<th>Histopathology</th>
<th>Immunoperoxidase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>-</td>
<td>2/2</td>
<td>2/2</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td><em>Lidocaine IL</em></td>
<td>146</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td><em>Glucantime® IL+</em></td>
<td>140</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td><em>Glucantime® IM+</em></td>
<td>153</td>
<td>0/1</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td><em>Glucantime® IL+</em></td>
<td>75</td>
<td>2/2</td>
<td>2/2</td>
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</table>

Hamsters* excepting comparison between antimonial schedules, statistical significance (P < 0.01) was obtained when evolution of mean lesion diameters among regimens were compared. + Hamsters clinically cured.

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**TABLE 2**

<table>
<thead>
<tr>
<th>Hamsters (Nº Positive/Nº Examine)</th>
<th>Group</th>
<th>Days Post-treatment</th>
<th>Lesion</th>
<th>Liver</th>
<th>Blood</th>
<th>Spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>-</td>
<td>2/2</td>
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<td>0/2</td>
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<tr>
<td><em>Glucantime® IL+</em></td>
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<td>1/2</td>
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</tr>
</tbody>
</table>

* Excepting comparison between antimonial schedules, statistical significance (P<0.01) was obtained when evolution of mean lesion diameters among regimens were compared. + Hamsters clinically cured.

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**DISCUSSION**

In Venezuela for decades, meglumine...
Fig. 2.- Electron micrographs of amastigotes of Leishmania (V.) braziliensis in granulomatous skin lesions in the base of the tail of male hamsters not exposed to any drug (control). Typical ultrastructural morphology of a leishmanial parasite is shown in A, detailing into frames regularity of plasma (a), nuclear (b) and kinetoplast (c) membranes.

Abbrevations: (PM) plasma membrane; (mt) subpellicular microtubules; (F) flagellum; (P) flagellar pocket; (B) basal body; (K) kinetoplast; (m) mitochondria; (N) nucleus; (Nm) nuclear membrane; (n) nucleolus; (v) vacuoles; (M) megasomes.

antimoniate (Glucantime®) parenterally administered has been used as a first line drug, with daily doses of 50 mg/Kg for 20 days, in a maximum of 3 doses with 10 days rest between series (WHO, 1979; Convit et al, 1987). However, there is not complete agreement regarding an optimum regimen for treatment of CL. As an attempt to overcome this, Yépez & Scorza (1995) applied an intraleisonal chemotherapeutic regimen with Glucantime®, a local anesthetic (lidocaine) and mixture of both. In their clinical trials, the authors achieved a significant reduction to 7 infiltrations as a maximum, 4 as an average with 1 – 3 ml of the antimonial, that is to say, employing less than 1 ampule or 90% less than conventional treatment for achieving scarring. In order to reduce the inconvenience at the infiltration site, administration of a mixture of the antimonial with lidocaine (3:1 v/v) has achieved therapeutic success to more than 90%, with a mean of 4 infiltrations, and a maximum of 7, and reducing even more the amount of antimonial required to obtain a clinical cure. A remarkable fact is that with the application of local anesthetic alone, the clinical improvement can reach up to 97% of the cases with a mean of only 4 infiltrations, being this the same quantity as the mixture and the antimonial alone, therefore reducing considerably the cost in many cases and obtaining an healing efficiency comparable to antimonials, having the advantage of no serious side effects.

Our experimental results confirmed partially the findings of Yépez & Scorza (1995), after determining that a schedule of 7 injections, one weekly of 20 mg/Kg of IL Glucantime®, are as effective as the systemic application of standard therapy with Glucantime®, for reducing or healing lesions of infected hamsters. This fact indicates that with this therapeutic design the potential toxic systemic effects could be minimized as well as the cost of treatment. Also, with application of
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Fig. 3.- Electron micrographs of amastigotes of *Leishmania (V.) braziliensis* in granulomatous skin lesions in the base of the tail of male hamsters treated with Glucantime® II. In A and B cytoplasm is disorganized and its electron density is increased with a greater concentration of ribosomes and considerable amounts of pycnotic vacuoles and megasomes (especially in A); plasma membranes and microtubules were also altered (arrows). Framed magnifications of loss of nucleus envelope and packing ribosomes are arrowed in a and b, respectively.

Abbreviations: L: lipidic granule. mg: megasome. Remaining as indicated in Fig.2.
Fig. 4.- Electron micrographs of amastigotes of *Leishmania (V.) braziliensis* in granulomatous skin lesions in the base of the tail of male hamsters intralesionally injected with Lidocaine. Amastigotes are shown in A with loss of electron density and disintegration of plasma membrane and most organelles and their membranes (arrows). Within frames, arrowed magnifications of fragmentation and loss of morphological definition of plasma membrane and subpellicular microtubules (a, c), flagellum (a), nucleus and mitochondria (b, c) membranes.

Abbreviations: As indicated in Fig. 2.
our therapeutic schedule with relatively few days of intermittence there could be a reduction in a large scale of the possibility of resistance to the drug as expounded by Olliaro & Bryceson, (1993). Travi et al., (1993) found similar clinical results in IL treatment of male hamsters infected with L. panamensis, another species of the subgenus Viannia. However, these authors employed 4 injections of Glucantime®, and a combined IM and IL regimen of the antimonial, especially at low dosages.

Kellum, (1986) has summed up the advantages of IL antimonial treatment in the CL in the following aspects: i.- a lower quantity of the drug is required; ii.- undesirable side effects of the systemic treatment are diminished; iii.- a higher concentration of the chemotherapeutic agents is delivered directly into affected tissues; iv.- the costs of treatment are frankly lower than systemic treatment v.- response to medication is faster and more effective; vi.- Scarring period is noticeable reduced. All these factors are in agreement with our own observations with the experimental model used in this study. The aseverations of Kellum (1986) seem to be supported by the findings of Berman et al. (1987), Burguera et al. (1993) and Lugo et al., (1994), who detected a high accumulation of Sb into granulomatous infected tissues, being able in this way to accumulate the heavy metal by macrophages and/or amastigotes, which consequently would maintain a “parasitostatic effect” with a subsequent reduction of the inflammatory reaction in a shorter period during the clinical cure (Croft et al., 1981; Travi et al., 1993).

Even when the anti-leishmanial action mechanism of the pentavalent antimonials has not seen well established, it is known that they are able to inhibit in vitro the glycolytic enzymes of glycosomes, as well as furthermore affecting the process of fatty acid β-oxidation and the phosphorylation in Leishmania (Berman et al., 1985; Berman, 1988). However, being Sb a heavy metal, it is quite possible that this has other mechanisms of action as suggested by Olliaro & Bryceon, (1993). In fact, in the present work the most consistent ultrastructural effect of the pentavalent antimonials observed on L. (V.) braziliensis amastigotes was an increase in electron density of the parasite’s cytoplasm, which appeared to be associated to a greater concentration of the ribosomes. As appears likely, the detection of damage to the parasite plasma membrane and its subpellicular microtubules, disorganized cytoplasmatic and partial disintegration of various organelles also occurs. Similar results to ours have been found by other authors using other species of Leishmania. Thus, Langreth et al (1993) found a loss of definition in plasmatic and mitochondrial membranes of L. (L.) tropica amastigotes exposed to the action of Pentostam® in vitro before disintegration of the parasites. Chulay et al., (1985) and El- Shoura & Sheika, (1991) also detected in L. (L.) donovani, isolated from patients treated with Pentostam®, increase of the electron density of the cytoplasm associated with ribosomal condensation, disorder and loss of the cytoplasmic unity. Based upon previous observations pointed out, it could be speculated with almost certainty that it is possible that the Sb acts on the mechanisms of active transport and/or the permeability of the membrane(s), as judging by ribosomal condensation and the cytoplasmatic disorder observed in the parasite, which would unbalance, as well as other processes, the uptake and leakage of metabolites and nutrients and the mechanisms for extruding the Sb from the cytoplasmatic interior as sustained by Dey et al., (1994).

Forty years ago, Hughes & Stewart, (1957) focused on the inhibitory effects of local anesthetics on bacterial activity. Concerning leishmaniasis, these compounds have frequently been used as “placebos” by several authors, failing in most of the cases to recognize their anti-leishmanial activities. In Pakistan, Currie, (1983) attained a clinical cure of 73 out of 78 lesions in 30 patients with a single curettage; nevertheless, ulcers were previously infiltrated with 2% of Lignocaine (=Lidocaine). Experimental basis supporting Yépez & Scorza (1995) clinical trials are given in the present study, as demonstrated by the fact that 7 weekly intralesional injections with cainic anesthetic lidocaine (8 mg/Kg) significantly reduced mean lesional diameters of male hamsters infected with L. (V.) braziliensis. Likewise, the drug produced irreversible damage to the parasite ultrastructure, this being to our knowledge, the first use of an anesthetic tertiary amine on experimental CL.

It is a well documented fact that the amphiphilic molecules, such as local anesthetics, are able to modify membrane function (De Foresta et al., 1990). Even though it is still a matter of discussion, several studies suggested that local anesthetics interact with membrane proteins; nevertheless, workers are not in agreement whether membrane enzyme effects are due to direct interactions of anesthetic molecules with proteins or rather to indirect effects via lipid perturbation (García – Martín & Gutierrez – Merino, 1986; Tarba & Cracium, 1990). These last authors proposed that electron microscopy can be used for estimating, at least qualitatively, the relationship between ultrastructural morphology and functional effects of local anesthetics on cells.
Thus, taking into account all the aforementioned evidence and regarding the interpretation of our own ultrastructural electronmicrograph results, in which we detected among other effects, disruption and morphologic alteration of amastigote membranes (e.g., plasmatic, mitochondria and nucleous), one can not rule out the possibility that these structures, particularly their membrane enzymes, are the main targets of lidocaine on leishmanial parasites.

Some authors recommend measuring the diameter of the lesions as a valid criterion for evaluating the efficiency of the chemotherapy in experimental CL, especially in lesions produced by species of the subgenus Viannia, eg., L. (V.) braziliensis y L. (V.) panamensis (Ercoli & Coelho, 1967; Hanson et al, 1991). The detection of viable amastigotes in up to 75% in some cases 195 days after treatment suggests that even though as practical as it apparently looks, the recommendation of these authors, the criterion of measuring the lesion is not reliable for estimating the actual efficiency of the chemotherapeutic activity in experimental CL. Our observations seem to support previous trials on different models, in which several workers detected the persistence of parasites in scar tissues which became infective, not reducing its pathogenicity and being able to induce granulomatous lesions in susceptible animals (Rezzano et al, 1984; De Rossell et al, 1992). Likewise, viable parasites have been detected in patients clinically cured with chemotherapy or immunotherapy, even 30 years after clinical resolution (Schubach et al, 1988; Guevara et al, 1993).

Taking into account the foregoing mentioned evidence, it can be concluded that the evaluation of the chemotherapeutic activity in experimental and clinical CL, should not be done exclusively by measuring the size of the lesions; therefore, this should be complemented with the search of remanent parasites in scars and others tissues.

Based on the results obtained in the present work, it is considered pertinent to present the proposal of the intralesional scheme with Glucantime® and especially with Lidocaine, as alternative agents of the chemotherapeutic armamentarium in the clinical treatment of CL, with mild side effects and significantly lower costs. The last point is important for developing countries, and particularly for Venezuela, where according to Convit et al, (1987) the average costs of a conventional treatment per patient is about US $ 200.

SUMMARY

The effect of intralesional treatment with lidocaine and Glucantime® was compared with standard dosage of Glucantime® administered intramuscularly in male hamsters infected with Leishmania (Viannia) braziliensis. Results revealed that all drugs assayed reduced significantly (P< 0.01) average lesion sizes in experimental animals when compared with those untreated. Local treatment with Glucantime® was as efficient as systemic antimonial for clinical resolution. Both antimonial regimens were more successful in clinical improvement than the anesthetic schedule. With the exception of those animals locally treated with Glucantime®, viable amastigotes were detected in nodules and/or scars of 75% of the evaluated hamsters 75 – 195 days after the end of the treatments using smears, conventional histopathology, culture in NNN medium and indirect immunoperoxidase method. Ultrastructural observations showed that Lidocaine causes fragmentation and loss of morphological definition of plasma and other amastigote organelle membranes. The effects on Leishmania parasites exposed to SbV were disorganized and pycnotic cytoplasm, plasma membrane altered, plus an increase in the electron density that appears to be associated with a packing of ribosomes. The significance of these results are discussed in relation to the evaluation of chemotherapeutic schemes in experimental and clinical cutaneous leishmaniasis, as well as the possible mechanisms of action of the tested drugs.

Key words: Chemotherapy, Leishmania (Viannia) braziliensis, hamster, electron microscopy.

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REFERENCES


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