THERAPEUTIC EFFICACY OF ALLOPURINOL (ZYLORIC) IN CUTANEOUS LEISHMANIASIS

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ABSTRACT:
Present study was conducted to observe the therapeutic efficacy of allopurinol (Zyloric) to treat cutaneous leishmaniasis with the object of having a good alternate therapeutic agent of antimony compounds.
Cutaneous leishmaniasis is a major tropical and subtropical parasitic disease to which antimony compounds injections are generally accepted treatment. This is expensive and not readily available in developing countries, besides serious side effects and development of resistance. Allopurinol is an inexpensive, orally administered drug with less toxic and minimum side effects. This would be substantial advance in treatment. Previous studies in vitro have shown synergism between Allopurinol and antimony compounds (Martiniz & Marr, 1992).
We studied Allopurinol in a dose of 300 mg twice a day in 42 all adults, otherwise healthy patients for 14 days in two courses with a gape of 14 days in between. The cure response was 61% with mild side effects of pruritis in 4 patients, and nausea in 6 patients. The side effects were easily managed by 4mg of chlorpheniramine (Priton from Glaxo) and cyclizine (Marzine from - GSK) twice a day respectively. 8 patients who did not improve with Allopurinol, were given injections Glucantime (Antimony compound) intra-muscular for 14 days, among them 5 improved and 3 did not report back. This result however indicates superiority of therapeutic efficacy of antimony compounds over allopurinol.

INTRODUCTION

Leishmaniasis is a complex and widespread human disease that has been recognized through out history. The disease is of high prevalence with 12 million cases worldwide and 1.5 million new cases occurring each year. WHO has estimated 4,00,000/- new cases every year in the world (WHO 1984).

In human it may exist often as asymptomatic carriers of leishmaniasis. The clinical syndrome occurs in two forms cutaneous or mucocutaneous and visceral. Cutaneous is most common, of which 50 to 75% cases annually typically caused by leishmania Major, leishmania Tropica, leishmania Mexicans and leishmania Brazillances.

Cutaneous leishmaniasis has worldwide distribution with different local names (1982). Common transmission is by the bite of sand fly (Phlebotomus), rarely by direct contact, congenital or by blood transfusion. Incubation period is few days to several weeks (Kubba, 1989). Children and youth with unfavorable socio-sanitary conditions are maximally predisposed.

The aim of therapy is two fold namely clinical healing and disappearance of parasite. Very few well-documented and scientifically
designed clinical trials have been carried out or have been reported (Alkhawja). Cutaneous leishmaniasis is self-limiting within 1-5 years in most cases, however treatment is justified in a variety of cases, namely, early lesions, multiple lesions, lesions involving cosmetically important areas, disseminated lesions and in patients with significant immunosuppression (Stratigos, 1980).

The assessment of efficacy of any therapeutic agent in a self-limiting disease such as cutaneous leishmaniasis is very difficult. Cure rates have been reported varied from 0 to 100% in different areas of the world (Stratigos, 1980). 30 years back vaccines were tried to develop but despite many attempts remained unfruitful (Khalil et al., 2000). Unfortunately its control is hampered by ignorance of its prevalence (Alkhawja).

Recently autoclaved leishmania major vaccine for prevention of visceral leishmaniasis has been tried Hashmi et al., 1980). Pentavalent antimony compounds still are standard drugs in the management of all types of Leishmaniasis but there are still controversies and unanswered questions regarding to these drugs, in addition treatment failure have been observed (Max, 2000). According to WHO recommendations the dosage of PVAs (pentavalent Antimony compounds) for cutaneous leishmaniasis is 20 mg / kg body weight per day, at maximum 600 mg per day for 10 to 14 days. This can be repeated after a period of 14 days in resistant cases (WHO). 15% of patients die from injection of pentostam (PVAs) according to Professor Wemsdofer of Vienna, while 40% of infected patient in India are already resistant to this drug. Similar observation in Sudan supports this report (Alkhawja).

Various drugs have been tried to overcome the resistance and minimize the toxic effects of PVAs. Rifampicin gives inconsistent result and resistance emerges regularly. Isoniazid was combined in a dose of 300 mg + Rifampicin 1200 mg - per day for 2 to 7 weeks, in patients with cutaneous leishmaniasis caused by leishmania Mxicania and leishmania Major (Jacinto, 1987).

Rifampacin with intraleosomal sodium stibogluconate was reported to produce good results in cutaneous leishmaniasis in Saudi Arabia (Jacinto, 1987).

Liposome encapsulated PVA and amphotericin - B recombinant interferon, cyclosporin and monoclonol antibodies are some of the modulaties under evaluation (Martinez, 1997).

Amphoterin-B has been used rarely because of its severe toxicity (Kamau et al., 1985). Metronidazole still is used despite of its inefficiency in American leishmaniasis by Walton and Griffith's report investigations. The incidence of treatment failure with sodium stibogluconate is increasing dramatically in endemic areas (Martiniz, 1992). Resistance to sodium stibogluconate has been well documented in both laboratory derived strains and clinical isolates (Kubba, 1989). These facts led the workers to use pantamidin in combination of sodium stibogluconate with paramomycin (Kamau et al., 1985).

The introduction of Allopurinolol by Hitching, Elion and associate (Goodman & Gilman), provides an example of the development of a drug on a rational biochemical base. Originally synthesized as candidate for an antineoplastic agent but was found to lack this activity while proved to be a substrate for and an inhibitor of Xanthine Oxidase. Some degree of inhibition of denovo purine synthesis also occurs. The drug is available for oral use in tablets of 100 mg and 300 mg with famous commercial name of Zyloric by Glaxo Welcome Company.

Drug is well tolerated by most of the patients. The most common adverse effect is hypersensitivity reactions. They may occur even after months and years (Goodman & Gilman). Cutaneous reactions include
pruritic, erythematus maculopapular eruptions and occasionally the lesion may exfoliate. Such effects are noted only in 3% of patients with normal renal function but more frequent in those with renal impairment. Hepatomegaly and elevated level of aminotransfirse activities in plasma and progressive renal insufficiency also may occur (Goodman & Gilman).

**Object:**

We selected allopurinol to observe it’s therapeutic efficacy in cutaneous leishmaniasis in our country (particularly Sindh/Balochistan) with a view to find a better substitute of antimony compounds, since it is of low cost, easy to administer and with less serious side effects in comparison to later.

**PATIENTS AND METHODS**

45 patients varying from 21 to 58 years of age were included in the study although patients from 8 month to 65 years were seen. Out of 45 patients – 31 were male and 14 were female. The patients belonged to districts Malir, Lyari and Central areas of Karachi. 6 of them belonged to Balochistan and 2 belonged to Bangladesh who have migrated and settled in Karachi for more than 2 years.

These patients were collected from the private clinics of dermatologist of the city and from skin and social hygiene center Karachi (institute of Skin diseases). The included patients were examined physically and screened for not having any gross or major illness related to C.V.S.- respiratory system-G.I.T. and renal functions by having their normal laboratory tests of lipid profile, urea, uric acid, creatinine and Liver Function tests. Patients having at least 2 characteristic nodules with history of at least 2 months duration were selected. Apart from clinical diagnosis direct smears for LD bodies was done and found positive in 33 cases out of 42 (78.5%). Irrespective to their age and weight all of them were given allopurinol (Zyloric) in a dose of 300mg – twice a day which is close to the recommended dose of 10 mg/kg body weight.

**RESULT**

Out of 45 patients 3 (2 females 1 male) did not report back and so they were excluded from the study. Out of 42 patients 26 patients completely improved after receiving 2 courses of the above-mentioned drug for 14 days with a gap of 14 days (Table 1). While 16 did not improve, among them 8 were advised for a 3rd course of allopurinol, among them 5 did not improve and 3 refused to take the treatment (Table 3 - Group A). 8 patients out of 16 who did not improve with allopurinol were given glucantime intramuscular injections daily for 14 days, 6 of them completely improved and 2 refused to take the treatment (Table 3 Group B).

**DISCUSSION**

The prototype allopurinol is non-toxic to human beings as the metabolic pathways for purines in parasitic protozoans differ significantly. In Leishmania and Trypanosoma cruzi particular enzymatic reactions halt protein synthesis and cause break down of RNA. Studies in vitro and vivo have demonstrated the anti-parasitic action of allopurinol and led to its development as a chemotherapeutic agent for diseases caused by these organisms (Marr 1991).

Allopurinol was shown to be effective in vitro against Leishmania maxicana and Leishmania donovani as well as against Leishmania braziliensis. The major metabolic derivative of allopurinol in humans, oxipurinol, is also antileishmanial for Leishmania donovani. Antileishmanial effect of allopurinol and oxipurinol can be reversed specifically by adenine and its metabolic precursors and derivatives, but no other purines or their derivatives. It is proposed that adenylosuccinate synthetase or the adenine
phosphoryltransferase may be sites of action for these agents (Marr, 1997).

In our study 26 patients all adults out of 42 exhibited 61% cure of cutaneous leishmaniasis by an oral dose of allopurinol 600mg per day in 2 equally divided doses. In another study result of allopurinol were compared to placebo indicated cure rate up to 80% (P<0.001) (Martiniz, 1992). This study was conducted in American population suffering from leishmania maxicana, and variation in the result rate may be due to difference in parasitic species.

The side effect were observed only in 10 patients and also not very serious, except that 4 of them complained of itching all over the body with no obvious signs and were managed by symptomatic drug therapy of 4mg of chlorphenaramine twice a day while 6 patients complaining of nausea were also able to complete their therapy with change in diet, encouragement and the symptomatic therapy of one tablet of marzin twice a day. 6 patients who did not show cure with allopurinol, got improved with injection of Glucantime intramusculax daily for 14 days. This indicates better therapeutic effect of glucantime in our population.

### Table 1
Total number of patients with age and sex

<table>
<thead>
<tr>
<th>S. No.</th>
<th>n</th>
<th>Age</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>21 – 58 years</td>
<td>30</td>
<td>12</td>
</tr>
</tbody>
</table>

n = Total number of patients.

### Table 2
Therapeutic efficacy of Zyloric in total number of patient

<table>
<thead>
<tr>
<th>S. No.</th>
<th>n</th>
<th>Treatment</th>
<th>No. of patients recovered</th>
<th>% of patients recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>Tab. Zyloric 300 mg – B.D. for 14 days in (2 course) with gape of 14 days</td>
<td>26</td>
<td>61%</td>
</tr>
</tbody>
</table>

n = Total number of patients.

### Table 3
Therapeutic efficacy of glucantime and 3rd course of Allopurinol

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Group</th>
<th>n</th>
<th>Treatment</th>
<th>No. of the patients received the treatment</th>
<th>No. of the patients refused the treatment</th>
<th>No. of the patients recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>8</td>
<td>3rd course of Zyloric 300mg B.D. for 14 days</td>
<td>5</td>
<td>3</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>8</td>
<td>Glucantime I/m injections O.D. for 14 days</td>
<td>6</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

n = Total number of patients.

In our study 26 patients all adults out of 42 exhibited 61% cure of cutaneous leishmaniasis by an oral dose of allopurinol 600mg per day in 2 equally divided doses. In another study result of allopurinol were compared to placebo indicated cure rate up to 80% (P<0.001) (Martiniz, 1992). This study was conducted in American population suffering from leishmania maxicana, and variation in the result rate may be due to difference in parasitic species.
CONCLUSION

The aggregate data support the use of allopurinol as an inexpensive orally administered drug that can be used alone or in combination with pentavalent antimonial compounds and perhaps much better than any other orally administered compounds tried so far (Martiniz, 1992). Combined therapy of Glucantime with allopurinol has also been found effective with no side effect observed in LR (Leishmania recidivans) not responding to any other therapeutic agent with no recurrence reported (Momeni, 1995).

REFERENCES

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