NEW APPROACH TO CURB THE TRANSMISSION OF LEPROSY

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ABSTRACT - The effect of local treatment of nose of lepromatous type of patients with different formulations of rifampicin nasal drops/sprays was investigated in a large number of patients. The preparations were either sprayed or instilled into the nostrils after flushing the nostrils with normal saline at 37° C. It was observed that 10 mg/ml of rifampicin was effective in reducing the BI and MI to zero in nose in seven days in majority of the patients. No untoward effect was seen in any of the patients. It is suggested that nasal sprays/drops may be able to prevent the transmission of hanseniasis, as nose is recognised to be an important portal of exit of *M. leprae.* **Further** when rifampicin drops/sprays are used as soon as the diagnosis is made, the nasal deformity may be prevented. It is believed that local treatment along with systemic therapy would go a long way in controlling the transmission of hanseniasis.

Keywords: Hanseniasis, Rifampicin Nasal Drops and Sprays, Local Treatment.

1 - INTRODUÇÃO

Hanseniasis is a chronic infectious disease caused by the bacteria *Mycobacterium leprae.* The main Source of *M. leprae* are the patients suffering from the lepromatous type of hanseniasis and also the lepromatous borderline type of hanseniasis.

In lepromatous patients nose forms a dangerous and potential reservoir of *M. leprae* from where they disseminate readily to infect contacts (Barton, R.P.E.2; *Davey,* T.F.6; Davey, T.F. & Rees R.J.W.9; Pedley, J.C.14; Pedley, J.C. & Geater J.G.16; Shepard, C.C.20. In spite of realizing that nose is the most important source of infection, nose does not receive due importance during the treatment of leprosy.

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By our earlier studies we have established that in spite of longterm, single and multi-drug therapy, the nose of lepromatous patients continues to harbour large number of *M. leprae* (Prabhakar, M.C. *et al.*17) which has been corroborated by others (Green, C.A. at al.[10]; Padma, M.N. & Bhatia, V.N.13). In view of these findings it was felt that, in addition to the systemic therapy, local treatment of the nose of lepromatous patients is very much warranted in order to kill the bacilli of the nose in the shortest possible period. Local treatment of the nose of lepromatous patients had been recommended as early as in Barton, R.P.E.[2] (1973).

The present study was aimed at investigating the importance of local treatment with rifampicin nasal drops in making the patients non-infectious.

2 - MATERIAL AND METHODS.

This study comprised of only untreated lepromatous patients. The nasal flushings were collected (about 100 ml) by the Jalaneti technique (Appa Rao, A.V.N. *et al"")* in stoppered glass cylinders. Each sample was shaken with 10 ml of a mixture of chloroform and xylol (19:1) for 5 min and was allowed to settle for 10 min. The chloroform layer (a white emulsion that settled at the bottom of the cylinder) was transferred to a centrifuge tube using a Pasteur pipette and spinned for 15 min at about 2 000 rpm. There were three layers distinctly separated from one another. The top aqueous layer, the bottom chloroform layer and a middle cotton-like pellet. The aqueous and chloroform layers were carefully removed using a Pasteur pipette and were discarded. The sediment (cotton-like mass) was carefully transferred to a smaller (5 ml) tube and dried at room temperature under vacuum. After evaporating the chloroform completely, 0,05 to 0,1 ml of 0,1% bovine serum albumin was added and mixed thoroughly on a vortex mixer. By introducing a sterile ground glass rod in the tube while mixing on the vortex mixer, the mucus was more finely ground. A loopful of this suspension was spread (8 mm diameter) on a clean microscope slide (four spots were made on each slide), dried and fixed by heating over a spirit lamp. The slides were then stained using carbol fuchsin (hot-method, 15-20 min) and decolourized with 1% hydrochloric acid in 70% ethyl alcohol for 2 min. They were then counterstained with 0,3% methylene blue for 1 min. Morphological index (MI i.e., the percentage of solid staining bacilli) was determined using a binocular microscope. On each slide at least 350 fields were examined for AFB. This forms the initial MI.

All the patients were put on DDS monotherapy. These patients were supplied with the nasal drops and were advised to instil then into their nostrils (a dropper was supplied along with the nasal drops). The intra-nasal treatment was given for 2 weeks with formulation number 1 while it was given for only 3week w th formulation number 2. Systemic therapy with DDS continued even after the local treatment was stopped. After the local treatment, the nasal flushings were collected and MI was determined again to study the effectiveness of the local treatment.

Formulation number 1: 1 mg/ml of rifampicin solution in phosphate buffer at pH 7.4.

Phosphate buffer was made by mixing 39,5 ml of 0,2N solution of sodium hydroxide and 50,0 ml of 0,2N solution - of potassium dihydrogen orthophosphate, made up to 200 ml with distilled water. Finally the pH was confirmed using a sensitive pH meter. To this solution was added 0,1% ascorbic acid which

acts as an antioxidant.

Formulation number 2: 10 mg/ml rifampicin in 0,2% sodium carboxymethyl cellulose in distilled water, plus 0,1% ascorbic acid.

Mode of administration: Three drops into each nostril 3 times a day.

Note:

(a) The above mentioned formulations have to be shaken well before use.

(b) The approximate amount of rifampicin that is delivered into each nostril with the formulation number 1 is 0,1 mg and with the formulation number 2 is about 0,5 mg at a time.

(c) The formulations should be kept in well closed, amber-coloured containers.

(d) The formulations must be used within 10 days of preparation.

Formulation number 3: Spraying of rifampicin powder (40 mg) once into each nostril, soon after the nasal wash with normal saline at 37°C. It was felt that solid rifampin will have sustained effect and that just one spray may be sufficient to make the patient non-infectious in a short period.

Some of the patients were re-examined at different time intervals (after stopping the local treatment) to see if AFB reappear in the nose.

3- RESULTS.

Table 1 shows the effect of rifampicin nasal drops (2 mg/ml) on the *M. leprae* of the nose in LL patients. In a majority of patients (8 out of 12), it was observed that the MI was reduced to zero in nose in 2 weeks of local treatment. In three other patients also there has been remarkable fall in MI. In one patient (MN), however, there was a slight reduction after the second week, while after three weeks of local treatment there was appreciable reduction in MI in this patient also. The follow up examination of the nasal flushings of the patients, after the local treatment was stopped, was done at different time intervals (Table 1). It can be seen that in a good majority of the patients AFB could be seen but their (MI) values are extremely low when compared to the original values. Globi disappeared in the first week of treatment itself and never reappeared in any of the patients who had the globi initially.

Table 2 shows the effect of formulations number 2 (10 mg/ml solution) instilled into the nostrils of the patients. It can be seen that the MI was reduced very significantly in all the cases except in two (BN and RN) by one week's local treatment. No globus was seen in any of the patients after one week's treatment.

Table 3 shows the effect of solid rifampin sprays on *M. leprae* of the nose. This was sprayed only once into the nostrils of each patient. It was very convenient, as it was to be sprayed only once. The results are very encouraging but the exact amount that stayed in the nostrils could not be assessed as the rifampicin powder when sprayed into one nostril some of it was coming out through the other nostril.

TABLE 1 - Formulation number 1: patients were advised to instil formulation number 1 three drops into each nostril tds. for 2 weeks. Nasal drops were not given during the follow up.

Patient	* Morphological Index			Subsequent examination (period after which the nose was re-examined)	
	Initial	After			
		1 week	2 weeks		
VK	59(many globi)	12 (no globi)	0	0	(4 months)
AK	66	13	0	13/26	(2 months)
KK	38	66	25/28	3/23	(5 months)
MN	77	65	55	17	(1 week)
VR	68	4/9	0	0/5	(2 months)
GR	58	4/4	0	1/1	(6 months)
VR	51	33	5/11	3/5	(4 months)
RB	73	42	0	3/20	(7 months)
SJ	13/3 (many globi)	12/6 (no globus)	0	-	-
SH(a) did not turn up- (b) for 2 months	72 81	43 0	0	8/24	(6 months)
AV	3/6	0	0	0	(4 months)
GV	69	3/1	2/2	0/2	(2 months)

* About 350 fields were examined. When less tham 50 AFB were seen in 350 fields, total number of AFB are given as solids/granules.

TABLE 2 - Formulation number 2: patients were advised to instil three drops into each nostril tds. for one week.

Patient	Morphological Index	
	Initial	one week after Instillation
KC	17/16	4/13
CE	7/10	0/13
JK	45	0
KS	22/28	14/14
KK	11/11	1/9
AK	40 (many globi)	3/10 (no globus)
CL	64	2/10
JM	7/10	0
BN	38	24
KN	21/11	0/1
RN	42	35
TR	46 (many globi)	16 (no globus)
SS	10/24	5/15
SG	15/17	2/31
PS	54	15/27
MS	54 (many globi)	4/8 (no globus)
KU	37	0
MV	32	1/1
SK	28	1/5
BJ	54	1/1

TABLE - Formulation number 3: rifampin powder was sprayed (40 nags) into each nostril, soon after nasal wash with normal saline at 37ºC (sprayed only once).

Patient	Morphological Index	
	Initial	one week after the spray
RL	21.5	0
VR	18/20	2/2
VV	31.0	3/0
ND	15.0	0.6
AP	37.0	4/25

4 - DISCUSSION

The presence of a large number of AFB in the nostrils of lepromatous patients is well known and it was demonstrated that a large number of these organisms are disseminated into the atmosphere readily (Schaffer, 119). This was re-established by various other research workers 2.3.4.5.6.7.9.11. 12.13.14.15.16.17.19 and now it is an established fact that millions of AFB are harboured in the nostrils of LL patients which are dissipated into the atmosphere. The daily discharge of the viable bacilli runs into millions[8].

It is custom in India and perhaps in many other countries for the people to clear their nose as a part of their early morning ablutions. The quantum of infection let out by this practice by infectious patients may well be enormous.

We have reported that patients continued to harbour a large number of *M. leprae* in their nostrils in spite of regular treatment for considerable length of time with both single and multi-drugs (Prabhakar, M.G. et al., 1974)[8]. Our findings have been corroborated by others 10.13.

In view of the above mentioned facts local treatment of the nose of lepromatous patients is perhaps inevitable. R.P.E. Barton2 suggested the intranasal use of anti-leprotic drugs as early as 1973. Local treatment of the nose will eliminate the bacilli of the nose at the earliest possible period. Further if such a treatment is given as soon as the cases are detected, it will enormously reduce the quantum of infection. Systemic therapy will take care of the bacilli found elsewhere in the body.

Using 2 mg/ml of rifampicin solution the nostrils of the patients were freed from bacilli in 2 weeks and with 10 mg/ml solution the bacilli disappeare d in one week. In three of the patients there was no appreciable reduction in MI (Table 2 - MN, Table - BN & RN). It is likely that these patients would not have used the nasal drops regularly. From our studies, formulation number 2 appeared to be the most suitable and convenient one for practical reasons. The only limitation that it has is that rifampicin is unstable in aqueous medium. It is absolutely necessary to make the solution fresh. Our results show that in the presence of ascorbic acid, rifampicin solution can be used for about ten days after preparation. The container should be air-tight and must be protected from light (amber-coloured glass containers can be used). Solid sprays are quite effective. The problem of stability of rifampicin will not arise if it is used in a solid form. A micronized powder of rifampicin sprayed into the nostrils will perhaps give the best results. The duration of local treatment will also be very much reduced.

We followed up some of the cases for a period ranging from 2 to 7 months, after the local treatment was stopped. It can be seen from the results that the nasal flushings of some of the patients contained a very small number of bacilli when tested during this period, while the MI was zero when tested immediately after the local treatment. In any case these bacilli are to be found in over 350 fields and their number is too small to give any credence. We could follow up only a limited number of patients as they were spread over in far off places.

We have tried the intranasal treatment on a larger number of patients. We tried different formulations like rifampin in propylene glycol, rifampin in polyethylene glycols etc. in different concentrations. Further we used these as sprays in some patients and as nasal drops in others. For this reason we are unable to incorporate the results of these trials. Nevertheless these experiments have given us

the same results. The nostrils are getting freed from *M. leprae* in 8-15 days.

We feel that local treatment of the nose in conjunction with systemic therapy goes a long way in controlling the transmission of hanseniasis, while the systemic therapy will take care of the bacilli of the body in general, local treatment will most effectively kill the bacilli of the nose. There are three distinct advantages if the local treatment is implemented on a large scale. They are: (1) it would enormously reduce the quantum of infection which will prove beneficial in controlling the transmission of HD in general; (2) it would prove especially beneficial to the close contacts; (3) it would prevent the deformity of the nose. Thus chemotherapy of infectious patients. of hanseniasis would be more meaningful if their nostrils are made free of *M. leprae* at the earliest with the help of concurrent local treatment

Sensitization and resistance development are two likely disadvantages of the local treatment. We have treated a large number of patients and we have not observed any ill-effects like irritation, allergic reactions etc. As regards the possible development of rifampicin resistance, we have no comments to offer at this stage.

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RESUMO O efeito do tratamento local do nariz de paciente do tipo lepromatoso com diferentes formulações de rifampicina em gotas ou "sprays" nasais, foi investigado em um grande número de pacientes. As preparações foram ou aspergidas ou instiladas dentro das narinas depois de sua limpeza por jato com solução salina normal a 37°C. Observou-se que 10 mg/ml de rifampicina eram eficazes na redução do BI e do MI a zero no nariz em sete dias na maioria dos pacientes. Não foi visto efeito desagradável em qualquer dos pacientes. Sugere-se que "sprays"/gotas nasais possam prevenir a transmissão da hanseníase, uma vez que o nariz é reconhecido ser uma importante porta de salda de *M. leprae.* Além disso a deformidade nasal pode ser prevenida quando a rifampicina "sprays"/gotas é usada tão logo o diagnóstico é feito. Acredita-se que o tratamento local juntamente com a terapia sistémica contribuiriam muito no controle da transmissão da hanseníase.

Palavras chave: Hanseníase. Rifampicina em gotas e "sprays" nasais. Tratamento local.

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