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MINOCYCLINE VERSUS CO-TRIMOXAZOLE IN CHANCROID : A DOUBLE-BLIND RANDOMISED STUDY

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This double-blind randomised parallel-group study comparing the efficacy and side effects of minocycline with that of cotrimoxazole in chancroid, had 56 analysable cases, 28 in each group. All admissible cases were assessed clinically on a scale of 0 to 3 for number and size of ulcers, pain, discharge, surrounding erythema and bubo. Each drug individually showed significant improvement in all clinical parameters. Minocycline showed significantly better improvement than cotrimoxazole in all parameters. Minocycline had 43% cure rate, and no failures, against 36% cure and 25% failure for cotrimoxazole. Both the drugs were well tolerated. We conclude that minocycline is a superior alternative to cotrimoxazole in the therapy of chancroid.

Key Words : Minocycline, Co-trimoxazole, Chancroid

Introduction

The exact incidence of chancroid is unknown, owing to inaccurate diagnosis and incomplete reporting. It is common in S.E. Asia and Africa, and is more prevalent than syphilis in many countries. Furthermore, almost one half of bidirectional heterosexual transmission of HIV-1 may be attributed to chancroid in some countries. Control and eradication of chancroid is now recognised as an urgent priority to curtail heterosexual transmission of HIV-1.[1]

Chancroid is the most common cause of genital ulcers in India.[2] Kar[3] in a study on 2300 males between 1971 to 1980 noted that chancroid (35.5%) was the highest, followed by syphilis (26.2%) gonorrhoea (10.3%), LGV (9.3%).

Many isolates of *H. ducreyi* possess plasmids which mediate resistance to sulphonamides, tetracyclines, chloramphenicol, ampicillin with a somewhat similar picture in India.[4] Today erythromycin and trimethoprim sulfamethoxazole (160/800 mg twice daily) have become established as the treatment for chancroid.[1,5,6]

Minocycline is a superior tetracycline with better absorption, and fewer gastrointestinal side effects than tetracyclines. Being more highly protein bound it can be utilised in a bid dosage regimen. It has a higher activity than other tetracyclines against most gram positive bacteria.[7] *H ducreyi* resistant to tetracycline have shown sensitivity to minocycline, with MIC reported between 0.25-2.0 mcg/ml.[8,9]

In clinical studies, minocycline has produced complete healing in all patients with chancroid.[10,11] The recommended dose is 100 mg bid for 10 days. In this study the efficacy and safety of minocycline has been compared with that of co-trimoxazole in chancroid.

Materials and Methods

It was planned to randomise 60 cases, however, on completion, we had a unequal number in both groups and 9 dropouts, so 6 more cases were randomised, of which one dropped out. We were left with 56 evaluable

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cases, 28 in each group. These were otherwise healthy young adult males with clinical signs and symptoms suggestive of chancroid. The study had a double-blind, randomised parallel-group design. Patients with systemic diseases like TB, leprosy, malignancies, diabetes were excluded so were patients who had history of hypersensitivity to sulfonamides or tetracyclines, or those that had been treated with an antibiotic one week before inclusion in the study.

All the patients passing the above criteria, had their blood collected for VDRL and material from the ulcer sent for smear and culture. A basal clinical assessment was done wherein details of the genital lesions and associated features were noted. The number, site of ulcer, associated pain, discharge, inguinal lymphadenopathy were scored on a scale of 0 to 3.

The patients were randomly assigned to one of two treatment groups. The patients were given orange capsules, which contained either minocycline or cotrimoxazole. The dose ingested was 100mg bid for minocycline and 160/800 of cotrimoxazole bid for 10 days. No concomitant use of antibiotics or analgesics antiinflammatory drugs was permitted. Bubos were aspirated to drain pus.

Patients were evaluated on day 7, day 14 and again on day 21. Cure was judged as complete healing of ulcer and resolution of lymphadenopathy. Reduction in size of ulcer, with healthy granulation tissue and epithelisation at the margins was considered improvement, while no change or worsening of lesions was considered failure. The time taken for complete healing was also recorded.

Side effects volunteered by the patient were recorded at each visit. In addition a non leading question was asked to each patients "Have you had any new complaints after starting the treatment?" The response to this question was recorded separately.

Analysis was carried out using non parametric tests like Wilcoxon rank test for within group evaluation, and Mann Whitney test for between group evaluation. Chi Square test was also used wherever applicable.

Results

In this study treatment was given for 10 days, but patients were called for follow-up on days 14 and 21. However very few patients reported on day 21 so the data analysed is only upto day 14. Of the 66 cases included we had 56 analysable cases, the rest being lost to follow-up. Although the initial entry into the trial was clinical, patients were tested for VDRL. Only 9 of the 56 patients had concomitant syphilis.

Both the drugs showed significant improvement over basal, on day 7 and day 14, for all parameters like size of ulcer, pain, discharge and surrounding erythema. However between groups minocycline was significantly superior to cotrimoxazole on all counts except

Table I. Comparison of Response Minocycline (M) Vs. Cotrimoxazole (C)

A. Between Group Comparison- Mann. Whitney test.

Parameters	Day 7	Day 14
Number of Ulcer	M=C	M=C
Size of Ulcers	M>CP <0.002	M<C P<0.001
Pain/Tenderness	M>C P<0.001	M>C P<0.002
Discharge	M>C P<0.002	M>C P<0.002
Surroundings Erythema	M=C	M=C

B. Within Guoup Comparison : Wilcoxon Signed Rank Test

Both Minocycline and Cotrimoxazole showed significant improvement on day 7 day 14 for all parameters (P<0.001), except number of ulcers on day 7.

erythema (Table 1).

On day 14, for minocycline, 12 (43%) patients were cured and the remaining 16 (57%) had improved, with no failures, while for cotrimoxazole 10 (36%) were cured and 11 (39%) improved and 7 (25%) showed failure (Table 2). There was no significant difference between drugs for number of days required for healing, or the reduction in size and tenderness of inguinal lymph nodes. There were no drop outs due to side effects. Both the drugs were well tolerated. All the drop outs were due to lack of timely follow-up visits by the patients.

Table II. Number of responders (percentage in brackets)

	Minocycline*	Cotrimoxazole
Cured	12 (43%)	10 (36%)
Improved	16 (57%)	11 (39%)
Failure	0 (0%)	7 (25%)
Total	28 (100%)	28 (100%)

* $P<0.05$ Chi square test comparing number of patients cured and improved against failure

Comments

Individually, both minocycline and cotrimoxazole, showed a significant change over basal, for all clinical parameter. However, the improvement was significantly better for minocycline than cotrimoxazole as shown in the between group comparisons. Furthermore the cotrimoxazole group also had a 25% failure rate.

Kucers[12] states that treatment of chancroid with cotrimoxazole is highly effective if the strain is sensitive. Use of the drug in our country for over two decades must have led to development of resistance,[4] which could possibly explain the high failure rate. Minocycline is an advanced tetracycline, and is new in India, hence could be an ideal alternative to the earlier drugs.

In this study the admission to the study was on clinical grounds, yet the VDRL test was conducted on all cases. Only 9 cases (4 in the minocyline group and 5 in cotrimoxazole group) had a positive VDRL. This only speaks of the accuracy of clinical diagnosis of chancroid. Of these only two patients failed to respond, but that did not affect the statistical results. Again it is accepted that in about 15% cases chancroid may co-exist with syphilis.[12]

It is interesting to note that there was no difference between groups for time taken to healing. Dangor[3] states that clinical cure should ultimately be based on reepithelisation, which is usually complete by day 10, but may be delayed upto 28 days. In view of this fact follow-up of patients for upto 21 days would have given a clearer picture.

We conclude that minocycline is an effective and superior alternative to cotrimoxazole in the therapy of chancroid.

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