

TREATMENT OF CHANCROID WITH SINGLE-DOSE DOXYCYCLINE COMPARED WITH A TWO-DAY COURSE OF CO-TRIMOXAZOLE

by

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Summary — Patients with chancroid (based on clinical diagnosis and negative dark-field examination) were allocated randomly to treatment with either a single-dose of 300 mg doxycycline or 4 tablets of co-trimoxazole twice a day for two days.

Exclusion from the study of those patients with a possible combined or alternative etiology (based on viral cultures and serological tests) such as herpes, lymphogranuloma venereum or syphilis, left 11 patients in the doxycycline group, 11 in the first co-trimoxazole group and 30 in the second. An inadequate response to treatment was seen in 6 of 9 patients followed after doxycycline, nil of 7 followed in the first and 2 of 24 followed in the second co-trimoxazole group. Treatment response after co-trimoxazole was significantly better ($P < 0.01$) than after doxycycline treatment.

It may be concluded from this study that a single dose of 300 mg doxycycline is inadequate treatment for chancroid in Swaziland. Co-trimoxazole 4 tablets twice daily for two days is effective but other co-trimoxazole regimens should be studied in order to determine the most suitable schedule.

KEYWORDS : Chancroid; Doxycycline; Co-trimoxazole; Swaziland.

Introduction

Chancroid has a high incidence in South-East Asia as shown in reports from Korea (Asin, 1952), Vietnam (Kerber *et al.*, 1969) and Singapore (Tan *et al.*, 1977).

Thirty years ago, Willcox (1949) mentioned the high incidence of chancroid also in Africa, but the disease continued to be misdiagnosed very often as syphilis. Recent data from Zimbabwe (Holland, 1976), Swaziland (Meheus *et al.*, 1979) and Kenya, where an average of 3,800 cases of chancroid a year are seen at the Nairobi Special Treatment Clinic (Nsanze *et al.*, 1979), show that chancroid is second only to gonorrhoea amongst those sexually transmitted diseases seen in Central, Southern and East Africa. The recommended treatment of chancroid is usually sulfonamides, tetracyclines or streptomycin (Willcox, 1975), but no schedule based on these antibiotics is really satisfactory in African countries. Streptomycin, 1 g daily for seven days, causes problems of patient compliance with daily injections, work load on the medical staff and a risk of increasing *Mycobacterium tuberculosis* resistance in populations where the prevalence of this infection might be high. Sulfonamides and tetracyclines have to be taken in multiple dosages for at least one week, again a problem of patient compliance.

Single-dose or short-term treatment of chancroid would ease considerably the work of the health services and allow for better control of the disease. A report from Zimbabwe (Stamps, 1974) indicated that single-dose doxycycline is very efficacious in chancroid. We report here a random clinical trial comparing single-dose doxycycline with a two-day course of co-trimoxazole in the treatment of chancroid in Swaziland.

Material and Methods

Patients seen at the Outpatient Department of the Mbabane Government Hospital in Swaziland during the period 17th January - 13th February 1979, with a clinical diagnosis of chancroid plus a negative dark-field examination of the genital ulcer(s) were included in the clinical trial. Patients were randomly assigned to one of two treatments groups (A and B) if they were not pregnant and not allergic to sulfonamides or tetracyclines. Group A received doxycycline 300 mg as a single-dose, taken under supervision in the consultation room. Group B received co-trimoxazole 4 tablets twice daily for two days; the first four tablets were taken under supervision.

Data were gathered on patient identification, age, sex and duration of genital ulceration. The number, localisation, clinical appearance and size of the largest ulcer were noted. Patients were examined systematically for inguinal lymphadenopathy.

A specimen was taken for dark-field examination with a platinum loop after thoroughly cleaning the ulcer with sterile saline. Calcium-alginate swabs were used to collect material for isolation of various organisms. Two media were inoculated for *H. ducreyi* culture (first medium : DST-agar plus 5 per cent horse blood plus 1 per cent isovitalax plus 3 $\mu\text{g/ml}$ vancomycin; second medium : GC-agar plus 5 per cent hemoglobin plus 1 per cent isovitalax plus 3 $\mu\text{g/ml}$ vancomycin).

Two additional specimens were placed in transport medium (MEM plus 10 per cent FCS) kept at -70°C and subsequently cultured for *Chlamydia trachomatis* and *Herpes simplex virus*.

A blood specimen was obtained from each patient and kept at $+4^{\circ}\text{C}$ until centrifugation later the same day. The Rapid Plasma Reagin test (RPR) for syphilis and the micro-immunofluorescence (micro-IF) test using pooled antigens for chlamydia were performed using standard procedures.

Patients were asked to attend for follow-up examination after 7 days when the clinical response to treatment was noted as adequate (lesions cured or much better) or inadequate (lesions unchanged or worse). Response to treatment was analysed using the χ^2 test. At a second follow-up visit after 14 days a further blood sample for serological tests was taken.

After an interim evaluation it was decided to stop the random clinical trial due to the inadequate results obtained with doxycycline. The clinical trial with co-trimoxazole was continued and these patients were classified as Group C.

Results

The characteristics of the patients, the results of diagnostic tests and the outcome of treatment in patients with « clinical chancroid - dark-field

negative » genital ulcers are summarised in Table 1, for the three different groups.

TABLE 1
Patient characteristics and results of treatment in each chancroid treatment group
(chancroid is defined as « ulcer(s) diagnosed as clinical chancroid and dark-field negative »)

	(A) Doxycycline N = 15	(B) Co-trimoxazole N = 15	(C) Co-trimoxazole N = 40
Age (range)	16-36	17-44	14-47
Age (median)	25 years	20 years	24 years
Sex	10 males, 5 females	4 males, 11 females	29 males, 11 females
Duration of ulcer(s) (median)	7 days	7 days	7 days
Number of lesions	3 single, 12 multiple	3 single, 12 multiple	8 single, 32 multiple
Large ulceration(s) \geq 10 mm	4 patients	5 patients	12 patients
Inguinal bubo absent	7 patients	11 patients	20 patients
unilateral	6 patients	4 patients	
bilateral	2 patients	0 patient	6 patients
Herpes culture pos.	0/15	1/14	3/40
Chlamydia culture pos.	1/13	0/12	1/35
<i>H. ducreyi</i> culture pos.	0/15	0/15	0/40
Chlamydia serology :			
Micro-IF \geq 1 : 8	14/15	14/15	35/39
\geq 1 : 512	1/15	3/15	1/39
Syphilis serology :			
RPR positive	4/15	3/15	9/40
\geq 1 : 4	3/15	0/15	5/40
Treatment :			
adequate response	4 patients (1)	8 patients (1)	29 patients
inadequate response	9 patients	0 patient	2 patients
not followed	2 patients	7 patients	9 patients
Number of follow-up visits (mean)	2.2 visits	1.6 visits	1.5 visits

(A) and (B) Random clinical trial with Doxycycline 300 mg single-dose and co-trimoxazole four tablets twice daily for two days.

(C) Group further treated with Co-trimoxazole four tablets twice daily for two days after random clinical trial was stopped.

(1) Difference statistically significant ($P < 0.01$).

Fifteen patients were given doxycycline (Group A) and another fifteen co-trimoxazole treatment (Group B) in the random clinical trial. No differences were seen in the characteristics of the patients and the clinical picture of chancroid in both groups, except for a higher proportion of females in Group B. No important differences were seen between the groups in the diagnostic tests : *Chlamydia trachomatis* was cultured from the ulcer of one patient in Group A and *Herpes simplex* virus from one patient in Group B. High titres in the chlamydia and syphilis serological tests were found in one and three patients in Group A and three and nil patients in Group B respectively. No positive cultures for *Hemophilus ducreyi* were obtained from any of the patients.

Nine (69 per cent) of the 13 patients followed had an inadequate response to doxycycline treatment, whereas all 8 patients followed after co-trimoxazole treatment responded. This difference is statistically significant ($P < 0.01$). The trial was continued with co-trimoxazole alone, 4 tablets twice daily for two days. An inadequate response was found in only 2 (6 per cent) of 31 patients treated. Table 2 summarises the data after excluding from consideration those patients with a positive *Herpes simplex* or *Chlamydia trachomatis* culture, or a high titre in the chlamydia or syphilis serological tests (micro-IF \geq 1 : 512; RPR \geq 1 : 4).

TABLE 2

Patient characteristics and results of treatment in each chancroid treatment group (chancroid is defined as « ulcer(s) diagnosed as clinical chancroid and which are dark-field negative plus exclusion of patients with positive Herpes or Chlamydia culture and positive serology for Chlamydia or Syphilis (Micro-IF \geq 512; RPR \geq 1 : 4) »).

	(A) Doxycycline N = 11	(B) Co-trimoxazole N = 11	(C) Co-trimoxazole N = 30
Age (range)	16-28	17-35	14-47
Age (median)	25 years	19 years	24.5 years
Sex	7 males, 5 females	3 males, 8 females	22 males, 8 females
Duration of ulcer(s) (median)	7 days	6 days	7 days
Number of lesions	3 single, 8 multiple	3 single, 8 multiple	5 single, 25 multiple
Large ulceration(s)	3 patients	4 patients	9 patients
Inguinal bubo absent	6 patients	8 patients	16 patients
unilateral	4 patients	3 patients	10 patients
bilateral	1 patient	0 patient	4 patients
Treatment :			
adequate response	3 patients (1)	7 patients (1)	22 patients
inadequate response	6 patients	0 patient	2 patients
not followed	2 patients	4 patients	6 patients
Number of follow-up visits (mean)	1.9 visits	1.7 visits	1.5 visits

(A) and (B) } See table 1.
(C) }

(1) Difference statistically significant ($P < 0.01$).

Doxycycline treatment was inadequate in 6 out of 9, whilst co-trimoxazole was successful in all 7 patients in the random clinical trial, a result which shows a statistically significant difference ($P < 0.01$); 22 out of 24 patients in Group C had an adequate response to treatment.

At the follow-up examination after 14 days recurrent lesions were seen in 2 of the 7 patients in Group B who had been considered much better after 7 days and this was the case in 6 of the 22 patients in Group C. Half of these patients admitted recent sexual contact, so probably most of these « recurrent » lesions were reinfections, but it can not be excluded that a number of these were treatment failures.

Discussion

Although still mentioned in some textbooks as a benign and self-limiting disease, a recent review text on genital ulcerations clearly states that untreated chancroid usually progresses to serious inguinal abscesses, enlarging genital ulcers and often to destructive erosive lesions (Wiesner *et al.*, 1979).

It is also our experience in Swaziland that untreated or badly treated chancroid develops into severely infected and painful ulcerations, paraphimosis and inguinal buboes.

For this reason, although the failure rate of 66 per cent occurred in a small sample of 9 followed patients, we decided to interrupt the clinical trial with single-dose doxycycline. In contrast, the two-day schedule of co-trimoxazole was highly effective in the random trial (no treatment failure in 7 cases followed), and this was confirmed by only 8 per cent treatment failures in the extended co-trimoxazole trial.

Two reports on 300 mg single-dose doxycycline in the treatment of chancroid are available : in Zimbabwe, Stamps (1974) found only one failure out of 32 patients treated and all ulcers healed within one week. During

a chancroid outbreak in Canada (Hammond *et al.*, 1979) a 27 per cent failure rate was noted with doxycycline, with vomiting as a frequent side effect, and a slower rate of healing than reported by Stamps. We also found that in cases with large ulcers or buboes it takes two weeks for the lesions to heal.

Females represented 38 per cent of the total patients in this study and 27 per cent in that Hammond *et al.* (1979). These figures disagree with others that clinical chancroid is predominantly a male disease (Morel, 1974; Stamps, 1974).

Our data suggest that chancroid in Swaziland might have developed tetracycline resistance, while the disease still remains susceptible to sulfonamide treatment. This should be substantiated by antibiotic susceptibility tests. It was recently shown that *H. ducreyi* strains from Swaziland and Johannesburg are indeed tetracycline resistant *in vitro* (Ballard, unpublished observation). Unfortunately we were unable to culture *H. ducreyi* under field conditions although using comparable methods to those which were successful in Canada (Hammond *et al.*, 1978). Two lyophilized *H. ducreyi* strains from Winnipeg were successfully used as controls to test the media and culture conditions used in Swaziland. After termination of this study, it was found that isolation of *H. ducreyi* in Southern and Eastern Africa requires media containing serum or albumin (Albritton *et al.*, 1980).

Sulfonamides are the recommended first-line treatment of chancroid, except in areas where there is more than 10 per cent resistance to this group of drugs (Wiesner *et al.*, 1979). Our study indicated that a sulfonamide (sulphametoxazole) combined with trimethoprim is highly efficacious in Swaziland. A further clinical trial comparing different sulfonamides (sulphadimidine, sulphamethoxypyridazine, co-trimoxazole) in varying doses should determine the most appropriate schedule to be recommended.

Recent data from the Netherlands (Nayyar *et al.*, 1979) indicated the high efficacy of co-trimoxazole in doses of two tablets twice daily and three tablets twice daily given for 10-14 days.

Our study has shown that co-troxazole in a dose of 4 tablets twice daily for two days is effective in the treatment of chancroid. Besides efficacy of treatment other factors must be considered such as cost, side effects and efficacy in curing gonorrhoea, an infection which is often associated with chancroid.

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Traitement comparé du chancre mou avec une dose unique de doxycycline et un traitement de deux jours de co-trimoxazole.

Résumé — Une étude thérapeutique faite au hasard sur des patients présentant un chancre mou (diagnostic clinique accompagné d'un examen négatif au microscope à fond noir) a été pratiquée en utilisant soit une dose unique de 300 mg de doxycycline, soit quatre administrations de 4 comprimés de co-trimoxazole réparties sur deux jours.

Les patients relevant d'une autre étiologie (herpès génital, lymphogranulome vénérien, syphilis) ou présentant une infection mixte ont été identifiés sur base de cultures virales et de tests sérologiques, et exclus de l'étude. Dans ces conditions, il restait 11 patients dans le groupe doxycycline et respectivement 11 et 30 patients dans les deux groupes traités par le co-trimoxazole.

Un échec de traitement a été constaté chez 6 patients sur les 9 qui ont pu être revus après traitement à la doxycycline, tandis que dans les deux groupes traités par le co-trimoxazole, respectivement 0 sur 7 et 2 sur 24 patients revus constituaient des échecs. Les résultats du traitement avec co-trimoxazole sont significativement meilleurs ($P < 0,01$) qu'avec la doxycycline.

Nous pouvons conclure que 300 mg de doxycycline en dose unique est un traitement inefficace pour le chancre mou au Swaziland. Le co-trimoxazole à raison de 4 comprimés deux fois par jour pendant deux jours est très efficace mais d'autres schémas de co-trimoxazole devraient être étudiés afin de déterminer le plus approprié.

Behandeling van weke sjanker met een éénmalige dosis doxycycline in vergelijking met een tweedaagse kuur met co-trimoxazole.

Samenvatting — Patiënten met weke sjanker (klinische diagnose en negatief bij donker-veld onderzoek) kregen at random ofwel doxycycline 300 mg in éénmalige dosis, of co-trimoxazole 4 tabletten tweemaal daags gedurende twee dagen.

Een reeks virale kulturen en serologische testen werden uitgevoerd. Patiënten met een andere of een gemengde etiologie zoals herpes genitalis, lymphogranuloma venereum of syphilis werden uitgesloten uit de studie, zodat er 11 overbleven in de doxycycline groep, 11 in de eerste co-trimoxazole groep en 30 in de tweede co-trimoxazole groep. Een onvoldoende genezing werd vastgesteld bij 6 van de 9 patiënten gevolgd na doxycycline, nul van de 7 patiënten gevolgd in de eerste en 2 van 24 patiënten gevolgd in de tweede co-trimoxazole groep. Behandeling met co-trimoxazole was significant beter dan met doxycycline ($P < 0,01$).

Er kan worden besloten dat een éénmalige dosis van 300 mg doxycycline geen goede behandeling is voor weke sjanker in Swaziland. Co-trimoxazole in een dosis van 4 tabletten tweemaal daags gedurende twee dagen is wel een goede behandeling. Maar andere doseringen van co-trimoxazole dienen uitgetest teneinde het optimale schema te bepalen.

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