

Meningococcal meningitis epidemic

A new role for single-dose oily chloramphenicol

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ABSTRACT

Objectives: To compare the orthodox use of 5 days crystalline penicillin and an alternate regime of single intramuscular injection of long acting oily chloramphenicol during the 1999 cerebrospinal meningitis epidemic that occurred in Abu Jubeha, South Kordofan, Sudan.

Methods: All 793 patients with meningococcal meningitis admitted to Abu Jubeha hospital in the eastern parts of South Kordofan State, were investigated. Through a quasi-experimental design some 140 patients were treated with crystalline penicillin for 5 days while the remaining majority, after the exhaustion of penicillin stocks, were put on single-dose intramuscular injections of oily long-acting chloramphenicol.

Results: Males were slightly more affected than females (1.3:1), mean age affected was 17.2 years, the majority being below 20 years of age (68%) while 27.3% were

below 10 years. The peak of the epidemic was during late March and early April namely 9th and 10th epidemic weeks. In the penicillin group 87.1% recovered uneventfully, 6.4% died, 2.1% developed blindness and 1.5% partial deafness. In the chloramphenicol group, full recovery was reported in 92.8%, 5% fatalities, blindness in 0.5%, partial deafness in 0.3% and skin necrosis in 0.1%.

Conclusion: The study suggests the use of single-dose intramuscular injections of oily chloramphenicol as a nationwide antibiotic of choice for future meningitis epidemics in view of not only its efficacy, but also its low cost, easiness of use, stability and safety.

Keywords: Cerebrospinal meningitis epidemic, African meningitis belt, long-acting chloramphenicol.

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Meningococcal infection continues to be a major public health problem in the Northern Savanna region of Africa. Violent epidemics of meningococcal cerebrospinal meningitis, occasionally referred to a cerebrospinal meningitis (CSM), occur every 6-12 years in the Savanna (Sahelian) zone of North Africa which lies between latitudes 5-15 N and the 300-1100 mm rainfall lines (Isohyets).¹ This region, which was named the "African Meningitis Belt" by Lapeyssonie,² is characterized climatically by long dry seasons (October to May) during which epidemics nearly

always start, reaching a peak when it is dry and dusty and subsiding at the onset of the rains.^{3,4} With each of the meningitis belt countries, an epidemic extends for 2-4 years and an attack rate of more than 900 per 100,000 population might be reached at its peak.⁵ Certain waves of major epidemics (for example, 1934-41, 1943-46, 1949-51, 1959-62) have spread across the African continent.^{2,3} Some of these reached Central and Southern Ethiopia⁶ and have such been considered as an extension to the African meningitis belt,⁷ forming a crescent-shaped area around Lake

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Victoria. Cerebrospinal meningitis epidemics were noted to strike mainly in the rural areas although they may occur in large towns and cities.² Cerebrospinal meningitis epidemics in Sudan have been known from time immemorial,^{8,9} and used to be termed in the Sudanese vernacular as "Abu Farrar" "the disease with the axe". Meningitis has been notifiable in Sudan since the turn of this century and the earliest definite records of the disease started in 1899 when an outbreak occurred in Omdurman, then the national capital and largest town.⁸ Notified cases from various national sources were estimated to be 258,388 between 1900 and 1988.¹ An important landmark in the history of CSM in Sudan as well as worldwide was the drop in mortality following the first worldwide field application of sulphonamides in the treatment of meningitis in 1939 from 53-79% in the pre-sulphonamide era to 21% following the immediate introduction of sulphonamides and to reach further to as low as 9.2% in the years 1978-1987.¹⁰ Another landmark was the successful field use of active immunoprophylaxis with meningococcal polysaccharide vaccine.¹¹ Sulphonamides, being safe, effective, cheap and easy to administer, fulfilled conditions of scarcity, poor staffing and lack of financial resources that characterize health care systems of developing countries. Later development of meningococci resistance to these drugs has, however, become a widespread phenomenon in Africa¹²⁻¹⁴ and has led to the introduction of penicillin since the early seventies. The use of single-dose intramuscular injections of long-acting (oily suspension) chloramphenicol during meningitis epidemics is a recent suggestion, the efficacy of which has been assessed in several studies.^{15,16} The Abu Jubeha CSM epidemic in the Eastern Nuba mountains of South Kordofan State, Southern Central Sudan offers a new opportunity. Besides outlining the general epidemiological feature of the 1998/1999 Abu Jubeha meningitis epidemic, our study will therefore assess the use of long-acting oily chloramphenicol during that epidemic and the potentialities it may pose a future nationwide antibiotic of choice for CSM epidemics.

Methods. Seven hundred and ninety three patients with meningococcal meningitis were admitted consecutively to Abu Jubeha Province Hospital between the 2nd day of February 1999 (first patient) and the 5th of May of the same year (last patient). The epidemic was initially confirmed by carrying out lumbar puncture to suspected individuals who all showed turbid specimens of cerebrospinal fluid (CSF) and gram negative (gm-ve) diplococci on gram-staining; further direct agglutination tests revealed type A meningococci which was then declared as the causative organism responsible for the epidemic. The first 140 patients

received the routine regime of 5-days crystalline penicillin, then exhausting the stocks to be replaced by stocks of long-acting oily chloramphenicol provided by a non-governmental organization working in the area (Medicines San Fronteirs, France), which to their previous experience was an effective alternate regime. The remaining 653 patients were put on single-dose oily chloramphenicol, providing us an opportunity for a comparative seemingly quasi-experimental study between the 2 regimes of therapy.

Results. Out of the 793 patients with meningitis, 140 (17.7%) were put on intravenous injections of crystalline penicillin for 5 days while 653 (82.3%) received single intramuscular injections of long acting oily chloramphenicol. Compliance with both therapies was 100% since all patients were under direct inpatient nursing care. Fifty seven percent of patients were males while 43% were females with a male:female ratio of 1.3:1. **Table 1** shows the age distribution of all patients: majority were below 20 years of age (68%) and patients of less than 10 years constituted 27.3% of the total. The mean age of the sample was 17.24 years (standard deviation (SD) 13.08). **Table 2** represents the weekly incidence of the Abu Jubeha meningitis epidemic. The first week started on the 2nd day of February 1999 and the last, and 14th week, on the 5th day of May of that year. It is clear that week 9 (20.7%) and 10 (18%) showed the highest incidence of occurrence. Indeed, 50% of all cases occurred during week 9, 10 and 11

Table 1 - The age distribution of Abu Jubeha hospital meningitis patients, February to May 1999.

Age group	Patients	
	N	(%)
0 to <6 years	109	(13.7)
6 to <10 years	108	(13.6)
0 to <10 years	217	(27.3)
10 to <20 years	232	(40.7)
20 to <30 years	151	(19)
30 to <40 years	54	(6.8)
40 to <50 years	15	(1.9)
50 to <60 years	11	(1.4)
60 years and above	22	(2.8)
Total	793	(100)
N - number		

Table 2 - Weekly incidence of meningitis cases, the Abu Jubeha cerebrospinal meningitis epidemic, February to May 1999.

Weeks	Patients	
	N	(%)
1	20	(2.6)
2	27	(3.4)
3	21	(2.6)
4	42	(5.2)
5	38	(4.8)
6	26	(3.3)
7	54	(6.8)
8	61	(7.7)
9	164	(20.7)
10	143	(18)
11	99	(12.5)
12	61	(7.7)
13	35	(4.4)
14	2	(0.3)
Total	793	(100)
N - number		

Table 3 - Comparing recovery, sequele, case fatality rate and mean hospital stay in the crystalline and chloramphenicol treatment groups.

Recovery, sequele, case fatality and mean hospital stay	Patients on 5 days crystalline penicillin		Patients on single dose crystalline penicillin	
	N	(%)	N	(%)
Recovery	122	(87.1)	606	(92.8)
Blindness	3	(2.1)	3	(0.5)
Partial deafness	2	(1.5)	2	(0.3)
Skin necrosis	0	(0)	1	(0.1)
Minor complications	4	(2.8)	8	(1.3)
Case fatality	9	(6.4)	33	(5)
Total	140	(100)	653	(100)
Mean hospital stay	4.33 days (SD 1.79)		1.9 days (SD 1.32)	
N - number, SD - standard deviation				

collectively namely late March and the first half of April. While 601 of the patients did not give recent history of vaccination (75.8%), 192 had meningitis vaccination the previous year (24.2%). The response to the 2 types of treatment as well as the mean hospital stay is compared between the 2 groups and shown in **Table 3**. Out of the 140 patients treated with intravenous injections of crystalline penicilline, 122 made an uneventfull recovery (87.1%), 3 patients developed blindness (2.1%), 2 ended up with partial deafness (1.5%) and 4 had minor non-disabling disturbances (2.8%). Nine patients died from that group scoring a case fatality rate of 6.4%. Of the 653 patients put on oily chlormphenicol injections, 606 fully recovered (92.8%), 3 had blindness (0.5%), 2 partial deafness (0.3%) and one developed skin necrosis at the injection site (0.1%), a known complication of parentral chloramphenicol. In 8 patients (1.3%) some complications were observed but soon resolved without leaving any sequele. Thirty-three patients succumbed and died in this group scoring a case fatality of 5%. As for the mean hospital stay between the 2 groups, in **Table 3** we observe that patients in the penicillin group stayed a mean time of 4.33 days (SD 1.79) compared with 1.94 mean days (SD 1.32) in the chloramphenicol group.

Discussion. The epidemiological features identified in the Abu Jubeha CSM epidemic resembles those characteristic of African meningitis in many respects. In accordance with the African meningococcal disease where more males were reported^{2,4,17,18} and with the Sudan CSM epidemics of 1988 and 1989 where sex distribution showed a male to female ratio of 3:1 and 2:1,¹⁹ our study again shows slight male-female preponderance particularly in the higher age group. Our peak age of incidence was observed to be late childhood and adolescence (10-20 years of age) (40.7% of all cases) followed by children below 10 years of age (27.3%) half under 5 (13.7%). This is similar to the reported data from Nigeria, Ghana and Gambia where the age group 10-14 years was reported to be mostly affected,⁴ ours deviates slightly from those reported from the meningitis belt where most of the studies showed a peak attack rate among children below 5 years (20-35% of reported cases).^{5,17,18} The seasonability of the Abu Jubeha epidemic was in line with outbreaks occurring in countries within the meningitis belt where late January to late June is the favorite period for both seasonal peaks and periodic epidemics of meningitis.²⁰ The Abu Jubeha epidemic scored a peak number of cases during late March and most of April, typical to that reported during Sudan meningitis epidemics of 1988 and 1989.¹⁹ Seventy-five percent of our patients were found to be not vaccinated in contrast with 24.2% who gave history of vaccination in the last year. It is estimated that up to 75% of

acute bacterial meningitis in the developing world is potentially preventable by immunization,²¹ in fact mass immunization is to be considered as an efficient and cost effective means for the control of serogroup A and C meningococcal disease in Europe and within the meningitis belt.^{11,22} However, due to the need for haste during the flare of MC epidemics, enough vaccine supplies to curb an outbreak should be available at the regional centres of the meningitis belt zone: the experience of extended program for immunization in vaccine storage and maintenance of cold chain can form a successful model for emulation or cooperation.²³ The study though revealing high recovery rate in both groups, the rate is however higher with the chloramphenicol group (92.8% versus 87.2%). Sequele, particular cranial nerve palsis, were less recorded with patients on chloramphenicol (0.8%) than with those on penicillin (3.5%). Cumulative case fatality rate among the chloramphenicol group was 5% compared with 6.4% in the penicillin group. In addition, the mean stay in the hospital was found to be much shorter on patients with single-dose chloramphenicol. It is estimated that on average, the cost of 5 days course of penicillin is approximately 8 dollars as compared to 3.5 dollars for one injection of oily chloramphenicol (for example, 3gm of Tifomycine-Roussel).²⁴ This is an extra incentive for using long-acting chloramphenicol, which when coupled with the easy administration of just one single intramuscular injection and the almost 2.5 less time stay in hospital in our study compared with the penicillin group, are positive merits for developing countries where massive epidemics are to be dealt with within settings of limited and constrained resources including scarce and untrained staff. For some practitioners chloramphenicol is a dangerous drug but research has shown that the risk of a serious blood disorder for example aplastic anemia following the administration of chloramphenicol is very small and has been computed at 1:20,000 or less and even smaller when it is given only by parental route.²⁵ It is believed by many workers in the field that the very occasional serious side-effects of chloramphenicol should not be a major consideration in deciding whether or not to use this drug in the treatment of a condition which has a significant mortality and morbidity.²⁴ Our study does not only suggest long-acting chloramphenicol as an effective and safe form of treatment for meningococcal meningitis thus confirming previous similar remarks from Francophone West Africa,^{15,16} it also supports similar recommendation by experts in the field like the World Health Organization and MSF France suggesting it as a first line and antibiotic of choice in the management of meningococcal epidemics.²⁶

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