antibiotic therapy versus antibiotic prophylaxis are needed to assess possible advantages of selective decontamination.[23]

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Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis

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In most developing countries, bacterial meningitis (BM) is associated with a high case-fatality rate. The search for a simple, convenient, and inexpensive antibiotic treatment remains a priority. In this study, a non-blinded, multicentre, randomised clinical trial of 528 cases of BM was done in two hospitals in Mali and Niger, between March, 1989, and May, 1990, to see whether a double injection of long-acting chloramphenicol (on admission to hospital and 48 h later) is as effective as a course of intravenous ampicillin (8 days, 4 times a day). The cumulative case-fatality rate on day 4 (principal end-point) among the chloramphenicol (254 patients) and ampicillin (274) groups were, respectively, 28% and 24·5% (relative risk 1·14, 95% confidence interval 0·86–1·52). No outbreak occurred during the study period. The hospital case-fatality rate was 33·1%. Main risk factors for death were associated with clinical condition on admission—ie, altered consciousness, convulsions, or dehydration. The case-fatality rates were 13% (21/161) for *Neisseria meningitidis*, 36·1% (48/133) for *Haemophilus influenzae*, and 67% (77/115) for *Streptococcus pneumoniae*. In a multiple logistic regression model, controlling for the differential distribution of potential risk factors (including bacterial species), there was no difference between treatment groups. Our findings suggest that long-acting chloramphenicol is a useful first-line presumptive treatment for BM in high-incidence countries.

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Introduction

Bacterial meningitis (BM) is a serious public health issue in the developing world.[1] Three species of bacteria—

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namely, *Haemophilus influenzae* type b (Hib), *Neisseria meningitidis* (Mnc), and *Streptococcus pneumoniae* (Pnc), cause more than three-quarters of all cases of acute BM in these countries.[1] In hospital conditions, the case-fatality rate varies between 10 and 70% according to the organism,[2-5] especially in the northern savanna region of Africa. In this area, health institutions are scarce, poorly staffed, and financial resources for health care are often inadequate. Therefore, it is important that drugs used to treat BM are not only safe and effective, but also inexpensive and easy to administer.

Use of chloramphenicol for the treatment of BM is of interest because of its low cost, its efficacy, and its low level of adverse effects.[6,7] The efficacy of long-acting (oily suspension) chloramphenicol for BM has been assessed in several studies[8-10] but to our knowledge the only controlled clinical trial assessed the antibiotic during an outbreak due to Mnc.[11] The reference treatment, ampicillin, is not practicable under most field conditions; moreover, it is over ten times more expensive than long-acting chloramphenicol. Ampicillin is still regarded as the gold standard treatment for BM in the developing world where current strategies using third generation cephalosporins are not affordable.

We here report the results of a randomised clinical trial in which we compared intramuscular long-acting chloramphenicol with intravenous ampicillin for treatment of BM.

Patients and methods

Patients

A non-blinded multicentre controlled trial was carried out in two hospitals. Patients were enrolled in Mali between May, 1989, and May, 1990, at Gabriel Touré Hospital, Bamako; and in Niger from March, 1989, to May, 1990, at the National Hospital of Niamey. Patients were eligible if there was a clinical suspicion of BM associated with one of the the following criteria: cerebrospinal fluid (CSF) culture or gram-stain indicative of BM, more than 500 white cells/ml of CSF, or a positive latex agglutination test for Mnc, Hib, or Pnc (Biomérieux, Lyon, France).

Patients less than two months old, pregnant women, patients with a history of antibiotic use for more than 24 h after onset of symptoms, patients with history of allergy to beta-lactam antibiotics, cases of recurrent meningitis, and patients with purpura fulminans were excluded. The study was approved by the Ministries of Health of Niger and Mali.

Treatment allocation

A table of random numbers was used to prepare sealed, numbered envelopes. After a patient had been admitted to the trial, the next envelope was opened to decide which treatment (chloramphenicol or ampicillin) had to be given. The investigators were aware of the treatment given to each patient. Patients assigned to the chloramphenicol group were given 100 mg/kg (maximum 3 g) of long-acting chloramphenicol by intramuscular injection (half in each buttock) at hour 0 (hour of admission in hospital) and 48 h later. Patients assigned to the ampicillin group had an intravenous drip inserted from day 0 (hour of admission) to day 7. A solution of isotonic sodium chloride was infused. Ampicillin was given intravenously every 6 h (200 mg/kg per day) for 8 days. All treatment information was recorded.

Methods

Laboratory procedures—CSF was collected on admission and 48 h after the start of treatment. Isolates were identified by standard methods, and antimicrobial susceptibilities were done by the disc diffusion method (Pasteur Diagnostics, Paris, France).

TABLE I—DISTRIBUTION OF BASELINE VARIABLES ACCORDING TO TREATMENT GROUP

Variables	Treatment	
	Chloramphenicol (n=254)	Ampicillin (n=274)
Age group		
<1 yr	39·8% (101)	38% (104)
1–2 yr	10·2% (26)	12% (33)
3–9 yr	27·2% (69)	25·2% (69)
⩾10 yr	22·8% (58)	24·8% (68)
Previous antibiotic treatment (<24 h) (n=441)	31·3% (67/214)	27·8% (63/227)
Duration of symptoms > 4 days (n=516)	39·6% (98/249)	40·8% (109/267)
Body temperature ⩾40°C (n=522)	15·2% (38/250)	17·8% (48/270)
Consciousness (n=515)		
Normal	35·4% (90)	33·2% (91)
Impaired	38·6% (98)	38·7% (106)
Reactive coma	14·2% (36)	19·7% (54)
Unarousable coma	9·4% (24)	5·8% (16)
Convulsions (n=511)	29·6% (73/247)	31·4% (83/264)
Irritability (n=444)	76·9% (166/216)	76·3% (174/228)
Focal signs (n=492)	22% (52/236)	22% (56/555)
Hydration status (n=523)		
Moderately dehydrated	27·4% (69/252)	27·3% (74/271)
Severely dehydrated	3·2% (8/252)	4·8% (13/271)
Respiratory symptoms (n=524)	13% (33/254)	13·7% (37/270)
Petechiae (n=522)	2% (5/248)	2·2% (6/269)

Follow-up—Baseline data and initial physical examination were recorded by a physician. Patients were assessed daily by a physician; the results of a standardised clinical evaluation at day 2, day 4, and discharge were recorded. According to clinical findings and CSF results, the investigator was allowed to change the treatment at day 4.

End-points—The principal end-point of the study was the cumulative case-fatality at day 4. Secondary end-points were day 4 failure rate (deaths up to day 4 or one of the following clinical symptoms: impaired consciousness, convulsions, focal signs, purpura, or dehydration) hospital failure rate (deaths or serious neurological sequelae at discharge), and hospital case-fatality rate (CFR) defined as cumulative CFR at discharge.

Sample size and analysis—The sample size was calculated with an estimated day-4 mortality rate of 20% (based on retrospective data from the two hospitals), an absolute precision of 10% (absolute difference accepted), a type I error of 0·05, and a type II error of 0·20 (n=251 for each group).[12] Mortality rate ratio between the two treatment groups was assessed by multiple testing procedures.[13] Differences in the distribution of base-line characteristics between the two treatment groups were tested by the chi-square test and when appropriate by the *t* test. Incidence rates of adverse outcomes were compared according to the treatment originally assigned. A stepwise logistic regression model ('Epilog-plus', version 2.0, Epicentre software, California) was used to identify interaction and to control for potential confounding factors.

Results

Patients

575 patients were admitted to the trial, of whom 394 were enrolled in Niamey (158 [40·1%] less than 3 years old) and 181 in Bamako (129 [71·3%]). After allocation to treatment (293 ampicillin, 282 chloramphenicol), 47 patients (6·3%) were excluded from the analysis; 39 did not meet any of the biological criteria for BM (16 ampicillin group, 23 chlorampenicol group), and 8 were excluded for other reasons (absconded, 4; shortage of ampicillin, 1; pregnancy, 1; cerebral bleeding, 1; previous treatment with chloramphenicol, 1). The final series consisted of 528 patients (274 ampicillin group, 254 chloramphenicol group). Compliance with the two treatments was 100% in terms of

TABLE II—CHLORAMPHENICOL VS AMPICILLIN IN THE TREATMENT OF BACTERIAL MENINGITIS ACCORDING TO AETIOLOGY AND TREATMENT GROUP

Aetiology	Treatment group		
	Chloramphenicol	Ampicillin	Total
*Neisseria meningitidis**	80 *(31·5)*	81 *(29·6)*	161 *(30·5)*
Haemophilus influenzae	69 *(27·2)*	64 *(23·4)*	133 *(25·2)*
Streptococcus pneumoniae	50 *(19·7)*	65 *(23·7)*	115 *(21·8)*
Others†	10 *(3·9)*	7 *(2·6)*	17 *(3·2)*
Unknown	45 *(17·7)*	57 *(20·8)*	102 *(19·3)*
Total	254	274	528

Data are no of patients *(%)*.
*Group C = 40, group X = 4, non-groupable = 5.
†*Salmonella* spp = 10; *Klebsiella* spp = 3; *Proteus mirabilis* = 1; *Enterobacter cloacae* = 1; group A haemolytic streptococcus = 1; *Staphylococcus aureus* = 1.

TABLE III—OUTCOME ACCORDING TO ANTIBIOTIC TREATMENT

Outcome	Chloramphenicol (n = 254)	Ampicillin (n = 274)	Total (n = 528)	RR (95% CI)
D4CFR	28%	24·5%	26·1%	1·14 (0·86–1·52)
Day-4 failure rate	50·4%	43·4%	46·8%	1·16 (0·97–1·39)
Hospital CFR	36·6%	29·9%	33·1%	1·22 (0·96–1·56)
Hospital failure rate	45·3%	39·1%	42%	1·16 (0·95–1·42)

D4CFR = case-fatality rate at day 4.

dose administered. However, for 123 (44·9%) patients treated with ampicillin, the intravenous drip had to be discontinued and the drug was injected intramuscularly. Clinical and laboratory features on admission were equally distributed among the two groups (table I).

Laboratory findings

A microorganism was recovered from 80·7% (426) of patients (table II). Among children less than 3 years old, isolates from 48·5% (128) were identified as Hib, 27·3% (72) as Pnc, 10·6% as Mnc, and 4·5% (12) as other bacteria. Among patients aged 3 years or more, isolates from 50·4% (133) were identified as Mnc, 1·9% (5) as Hib, 16·3% (43) as Pnc, and 1·9% (5) as other organisms. 238 antibiograms were done. 17·6% (12/68) of Hib isolates were resistant to ampicillin and 7·3% (5/68) to chloramphenicol. For Pnc the data are 1·5% (1/66) and 9·1% (6/66), respectively. 55% (5/9) of *Salmonella* spp were resistant to ampicillin and 11% (1/9) were resistant to chloramphenicol. Resistance by Mnc was not found for either treatment. Resistance to both antibiotics was encountered in 1 case each of Hib, Pnc, *Klebsiella pneumoniae*, and *Proteus mirabilis*. After 48 h of treatment, 11 out of 135 (8·1%) cultures were still positive in the chloramphenicol group compared with 1 out of 143 (0·7%) in the ampicillin group (relative risk [RR] 11·6, 95% confidence interval [CI] 1·5–89). There were no cases of blood dyscrasia after administration of chloramphenicol among 109 blood samples examined before discharge.

TABLE IV—CASE FATALITY RATE AT DAY 4 ACCORDING TO DELAY BETWEEN ONSET OF SYMPTOMS AND ADMISSION

Delay (days)	No of cases	No of deaths	CFR
1	3	1	33·3%
2	46	10	21·7%
3	139	30	21·6%
4	116	23	19·8%
5	73	20	27·4%
6	28	10	35·7%
7	20	7	35·0%
8	27	13	48·1%
>8	51	18	35·3%

CFR = case-fatality rate.
χ^2 for trend = 10·7; p = 0·001.

TABLE V—RISK FACTORS FOR DAY-4 CASE-FATALITY RATES

Factor	CFR day 4	RR (95% CI)	RR after logistic regression (95% CI)
Treatment			
Chlor (254)	28%	1·14 (0·9–1·5)	1·40 (0·9–2·1)
Amp (274)	24·5%		
Organisms			
Mnc (161)	10·6%	1	1
Hib (133)	30·1%	2·9 (1·7–8·1)	3·9 (2–7·7)*
Pnc (116)	53%	5 (3·1–8·1)	9·1 (4·6–18)*
Others (17)	29·4%	2·8 (1·2–6·6)	2·7 (0·8–9·3)
Unknown (102)	14·7%	1·4 (0·7–2·7)	1·5 (0·7–3·3)
Delay in admission to hospital			
>4 days (207)	33·3%	1·6 (1·2–2·1)	
≤4 days (309)	20·7%		
Consciousness			
Normal (181)	5·5%	1	
Impaired (234)	26·5%	4·8 (2·5–9·1)	6·3 (3–13·4)†
Reactive (90)	46·7%	8·5 (4·4–16·1)	12·7 (5·7–28·6)†
Unarousable (40)	72·5%	13·1 (1·9–3·3)	20 (9–50·1)†
Convulsions			
Yes (108)	44·9%		
No (156)	17·7%	2·5 (1·9–3·3)	
Focal signs			
Yes (108)	47·2%		
No (383)	20·1%	2·4 (1·8–3·1)	
Hydration status			
Normal (359)	19·8%	1	1
Moderately dehydrated (143)	36·4%	1·8 (1·4–2·5)	1·6 (0·9–7·4)
Severely dehydrated (21)	57·1%	2·9 (1·9–4·4)	2·9 (1·2–7·4)‡
Temperature on admission			
<40°C (436)	23·2%		
≥40°C (86)	39·5%	1·7 (1·3–2·3)	
Acute respiratory infection			
No (454)	23·6%	1·6 (1·2–2·3)	
Yes (70)	38·6%		

Chlor = chloramphenicol; Amp = ampicillin; CFR = case-fatality rate.
*p = 0·0001; †p < 0·0001; ‡p = 0·02.

Case-fatality

The cumulative case-fatality rate at day 4 (D4CFR) was 28% in the chloramphenicol group compared with 24·5% in the ampicillin group (table III). Among children less than 3 years old, the D4CFR was 35·4% and 32·8%, respectively (RR 1·08, 95% CI 0·77–1·51), and that among the patients more than 3 years old, was 20·5% and 16·1%, respectively (1·27, 0·76–2·13). Day-4 failure rate, hospital CFR, and hospital failure rate were also higher among patients treated by chloramphenicol (table III).

The organism-specific hospital CFRs, irrespective of treatment group, were 13% (21/161) for Mnc, 36·1% (48/133) for Hib, 67% (77/115) for Pnc, and 64·7% (11/17) for the other bacteria (8 deaths in 10 cases of BM due to *Salmonella*). Frequencies of serious neurological sequelae, irrespective of treatment group, were 4·9% (7/140), 28·2% (24/85), 21% (8/38), and 0% (0/6), respectively.

D4CFR increased the longer the delay between onset of symptoms and admission to hospital (chi square for trend = 10·7, p = 0·001) (table IV). D4CFR was higher among patients with the following base-line clinical signs: impaired consciousness, convulsions, focal signs, body temperature above 39·9°C, dehydration, and acute respiratory tract infection (table V). Logistic regression

showed that bacterial species, degree of consciousness, and hydration status on admission had an independent predictive effect on D4CFR (table v). If the 40 patients with unarousable consciousness are excluded from the analysis, the adjusted RR of death at day 4 in the chloramphenicol group compared with the ampicillin group was 1·14 (95% CI 0·68–1·92).

Discussion

We have not been able to show any statistically significant difference between long-acting chloramphenicol and ampicillin for treatment of BM under hospital conditions with respect to CFRs and D4CFRs. Excluded cases did not modify the results because there was a low CFR among these patients (8·5%).

The main finding of our study was the very high hospital failure rate (42%) irrespective of treatment. This failure rate was similar to that described in Papua New Guinea[4] (failure rate 37%), and in Dakar, Senegal (January, 1965, to April, 1970, CFR 39·2%;[5] February, 1983, to February, 1988, CFR 33%). There is a striking contrast between these rates and those found in developed countries (about 5%; 20–30% for Pnc).[14] However, our findings should be interpreted in an endemic context because there was no outbreak of meningococcal meningitis in either place during the study. Therefore, the high hospital failure rates are mainly due to the high proportion of Hib and Pnc cases among the patients included. In this respect, our study confirms the CFRs due to infection and the very high rate of serious neurological sequelae due to Hib recorded in developing countries.[2,5] Because of the types of organisms isolated, children less than 3 years old had a higher risk of death than did the patients over 3 years old. Among the former age group, Hib was present among half the cases, which is a higher proportion than previously described.[2,5] The clinical status of our patients on admission was serious (25% of the patients were unconscious compared with only 7% in Peltola et al's[14] study); it is likely that a delay in admission to hospital is a serious problem in Africa. In a review of published work, Gedde-Dahl et al[15] concluded that early antibiotic treatment even before admission to hospital improved outcome of BM. Management of dehydration seems to be another way of decreasing the CFR.

The rates of antibiotic resistance to Hib in our study are similar to those found by Diop Mar and Cadoz[3] and by Cisse et al[2] (between 10 and 20% for ampicillin). The slight improvement in survival in our ampicillin group could be due to the intravenous route via infusion rather than to the antibiotic effect. Because of the sample size we could not draw any conclusions about efficacy of the two antibiotics against the different organisms isolated. However, even if the sample is small, the rate of ampicillin resistance in *Salmonella* suggests that this antibiotic is not an appropriate treatment for BM due to this organism.

The lower success rate of long-acting chloramphenicol in sterilising the CSF at 48 h may be due to its bacteriostatic effect whereas ampicillin is bactericidal; it also raises the question of the concentration of chloramphenicol in CSF after one intramuscular injection of oily suspension. Wali et al[11] showed a concentration in CSF of 0·6 (SD 0·7) mg/ml at 48 h, which is weak in view of the MICs against the organisms and specifically Pnc (0·8 mg/ml).[3] Therefore, further data in pharmacokinetics of oily chloramphenicol will be useful in developing treatment methods.

The risk of a serious blood disorder after the administration of chloramphenicol is very small (none in our study). The risk of aplastic anaemia developing after chloramphenicol treatment has been calculated as 1 in 20 000 or less and it has been suggested that the risk is even smaller when chloramphenicol is given by the parenteral route only.[7] Despite the widespread use of chloramphenicol, a study of aplastic anaemia in Nigerians during a 14-year period revealed only 4 cases in which chloramphenicol was thought to play a causative role.[6] We do not believe that the very occasional serious side-effects of chloramphenicol should be an important consideration in deciding whether to use this drug in the treatment of a condition that has substantial mortality and morbidity, even when treated under the most advantageous circumstances.

Long-acting chloramphenicol is cheap and easy to administer; both factors are especially important in the context of limited medical resources. Despite the improved conditions provided by the logistic assistance set up for the study, ampicillin was not given appropriately in 43% of cases. We believe that in field conditions treatment with intravenous ampicillin for 8 days is not practicable. The cost of treatment of an adult with long-acting chloramphenicol is about US$8 compared with US$80 for ampicillin. The relative difference in cost is even higher for children. These costs do not take into account the duration of stay in hospital, which can be shortened if chloramphenicol is used. In most developing countries, the patient's family has to buy the medicine before its administration, but most families cannot afford appropriate ampicillin treatment. The use of a single injection of an oily suspension of chloramphenicol in the treatment of patients of all ages with meningococcal meningitis has already been recommended by WHO.[16] Under most field conditions, microbiological diagnosis of meningitis is not possible. Thus, starting an antibiotic treatment as early as possible for all suspected cases of BM is the only way to prevent secondary mortality and morbidity. For such a strategy, long-acting chloramphenicol seems to be the antibiotic of choice as first-line treatment. A second injection of long-acting chloramphenicol has to be given at 48 h, or earlier if indicated by drug assay. After 3 or 4 days, the treatment can be modified if necessary according to the antibiotics available, or continued with oral chloramphenicol. Meanwhile, the search for more effective, long-acting antibiotics that are easy to administer and are accessibly priced must be developed.

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Effects of in-utero exposure to oral hypoglycaemic drugs

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The observation that several Mexican-American women were taking oral hypoglycaemic agents while pregnant led to a study to confirm reports of associations between these agents and congenital abnormalities. 20 non-insulin-dependent (NIDDM) pregnant diabetic women with exposure to oral hypoglycaemic drugs during embryogenesis and 40 pregnant NIDDM women matched for age, race, parity, weight, and glycaemic control but not exposed to oral hypoglycaemic drugs were followed up. 10 infants (50%) in the exposed group had congenital malformations, compared with only 6 (15%) in the control group ($p < 0.002$). 5 (25%) infants in the exposed group had ear malformations, anomalies not commonly described in diabetic embryopathy. Hyperbilirubinemia ($p < 0.04$), polycythaemia, and hyperviscosity requiring partial exchange transfusions ($p < 0.03$) were commoner among babies in the exposed than in the control group. 3 babies in the exposed group but none in the comparison group had severe prolonged neonatal hypoglycaemia lasting 2, 4, and 7 days; 2 of the 3 had been exposed for 22 and 28 weeks during gestation, whereas the third had been exposed throughout the first trimester. Although exposure to oral hypoglycaemic drugs during fetal life seems to be associated with congenital malformations and neonatal hypoglycaemia, a large, prospective study is needed to exclude the confounding effect of maternal metabolic derangement secondary to diabetes.

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Introduction

In the USA oral hypoglycaemic agents are contraindicated during pregnancy because of the possibility of fetal teratogenesis and prolonged neonatal hypoglycaemia. The sulphonylureas readily cross the placenta but their metabolic fate and dose-response relations in the fetus have not been determined.[1] The most important adverse effect of these drugs in non-pregnant individuals is long-lasting hypoglycaemia.[2] There have been scattered case-reports of congenital malformations associated with oral hypoglycaemic agents taken by the mothers,[3–7] and two papers have described profound neonatal hypoglycaemia in children whose mothers took sulphonylureas until delivery.[8,9]

In 1985 we noted that several older Mexican-American women with non-insulin-dependent diabetes mellitus (NIDDM) who had become pregnant were still receiving oral hypoglycaemic agents. Concern about possible adverse effects of these drugs on the fetus and newborn infant led us to collect cases of fetal exposure to oral hypoglycaemic agents during embryogenesis for comparison with an appropriately matched, contemporaneous comparison group from the same clinic population.

Subjects and methods

In 1985–90 20 pregnant NIDDM women with first-trimester exposure to oral hypoglycaemic drugs were identified in the Diabetes and Pregnancy Clinic at the University of California San Diego (UCSD) Medical Center. In this clinic most women are obese, indigent Mexican-Americans with a high prevalence of NIDDM. This population has the highest birth rate in America and conception is not infrequent after age 40. For all but 1 woman exposed to oral hypoglycaemic agents the drug was identified. Fetal exposure occurred during embryogenesis[10] in all cases; the duration of exposure ranged from 3 to 28 weeks. Oral hypoglycaemic drugs were discontinued at the first prenatal visit.

Each exposed woman was compared with 2 NIDDM women matched for age, race, parity, and glycaemic control ($n = 40$). Obstetric care and diabetic management were identical in the two groups. All women received multiple daily doses of short-acting and intermediate-acting insulin and were followed up by weekly clinic visits and frequent telephone contacts. In addition, all were given meters for blood glucose monitoring four times a day, prescribed a diabetic diet for pregnancy, and had HbA_{1c} measured at the first prenatal visit and monthly thereafter. Obstetric care included ultrasonographic examinations for fetal growth, fetal

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