Chloramphenicol Pharmacokinetics in African Children with Severe Malaria

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Summary

The objective of this study was to determine if the current dosage regimen for chloramphenicol (CAP) administered to children with severe malaria (SM) for presumptive treatment of concomitant bacterial meningitis achieves steady state plasma CAP concentrations within the reported therapeutic range of 10–25 mg/l. Fifteen children (11 male, 4 female) with a median age of 45 months (range: 10–108 months) and having SM, were administered multiple intravenous doses (25 mg/kg, 6 hourly for 72 h) of chloramphenicol sodium succinate (CAPS) for presumptive treatment of concomitant bacterial meningitis. Blood samples were collected over 72 h, and plasma CAPS, CAP and CSF CAP concentrations determined by high performance liquid chromatography. Average steady state CAP concentrations were approximately 17 mg/l, while mean fraction unbound (0.49) and CSF/plasma concentration ratio (0.65) were comparable to previously reported values in Caucasian children. Clearance was variable (mean = 4.3 l/h), and trough plasma concentrations during the first dosing interval were approximately 6 mg/l. Simulations indicated that an initial of loading dose of 40 mg/kg CAPS, followed by a maintenance dose of 25 mg/kg every 6 h would result in trough CAP concentrations of approximately 10 mg/l and peak concentrations <25 mg/l throughout the treatment period. The current dosage regimen for CAP needs to include a loading dose of 40 mg/kg CAPS to rapidly achieve plasma CAP concentrations within the reported therapeutic range.

Introduction

Severe falciparum malaria is a major cause of childhood mortality in sub-Saharan Africa,[1,2] Bacterial infections often complicate severe malaria in children. In Kenyan children admitted to hospital with malaria, 7.8 per cent have been shown to have a bacteraemia and this is associated with a three fold increase in mortality.[3,4] Furthermore, it is difficult to clinically distinguish between cerebral malaria and bacterial meningitis, and antimicrobials are often administered until the results of the lumbar puncture are known.[5] Thus, in resource poor countries (RPCs), presumptive treatment with chloramphenicol and benzyl penicillin is often started until the cultures of blood and cerebrospinal fluid (CSF) are available.

In severely ill children, chloramphenicol is administered intravenously as the inactive prodrug, chloramphenicol sodium succinate, which has no antibacterial activity, and must be hydrolysed in the liver to generate the active chloramphenicol. The bioavailability of chloramphenicol from the intravenously administered prodrug is determined both by the extent of hydrolysis and renal excretion of the prodrug.[6] Studies in children[6,7] and adults[8] have shown that hydrolysis of chloramphenicol succinate to chloramphenicol *in vivo* is often incomplete and variable. In infants and children, the clearance of chloramphenicol and chloramphenicol

Acknowledgements

We are very grateful to the Director of the Kenya Medical Research Institute for permission to publish this work. We are also grateful to Prof. Kevin Marsh (Director, KEMRI-Wellcome Trust Collaborative Research Program) and Dr Norbert Peshu (Director, KEMRI-Center for Geographic Medicine Research-Coast) for their support. We also wish to thank all our clinical, nursing and laboratory staff both in Kilifi and Nairobi, who contributed immensely to this work.

This study was supported by a Collaborative Research Initiative Grant from The Wellcome Trust of Great Britain (grant no. 057978/Z/99/Z) and a Research Capability Strengthening Grant from WHO (TDR/MIM grant no. 980074) to Gilbert Kokwaro. Charles Newton is funded by the Wellcome Trust (Grant no. 050533) and Dr Ogutu was a trainee in Clinical Pharmacology supported by WHO (TDR/MIM) and KEMRI.

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doi:10.1093/tropej/fmi082 Advance Access Published on 26 August 2005

succinate has been reported to exhibit wide inter-individual variability. Furthermore, there is evidence suggesting that hepatocellular dysfunction associated with infections could impair metabolism of chloramphenicol.[9] The therapeutic range for chloramphenicol is thought to be between 10–20 mg/l,[10,11] and dose-related toxicity is associated with peak concentrations >25 mg/l.[12]

Chloramphinicol is included in the WHO list of essential drugs, and is still widely used in many RPCs because it is cheap and readily available. Its pharmacokinetics have been described in African infants <3 months[13] but detailed pharmacokinetics in older African children have only been reported in two studies in malnourished children.[14,15] Thus, the current dosage regimens for chloramphenicol in many RPCs have not been evaluated in many of the populations in which they are used. In particular, malaria infection in children may be associated with a degree of hepatic dysfunction[2] that may affect the pharmacokinetics of chloramphenicol. Children with malaria also receive other concurrent drugs such as phenytoin, phenobarbitone and paracetamol which have been reported to interact with chloramphenicol.[16–19]

We have studied the pharmacokinetics of intravenous chloramphenicol succinate in children with SM to assess whether the current dosage regimen rapidly achieves plasma chloramphenicol concentrations within the range of 10–25 mg/l.

Methods

Setting

The study was conducted at the Kenya Medical Research Institute (KEMRI) Unit, Kilifi District Hospital (KDH), on the Kenyan coast. The study formed part of a larger study on the effect of concomitant administration of chloramphenicol on pharmacokinetics of phenytoin in children with severe malaria and bacterial infections,[20] and was approved by the KEMRI Ethics Committee.

Patients

Children admitted to the KEMRI paediatric ward at the KDH were recruited into the study if: (i) they were aged 9 months to 13 years; (ii) they had features of severe falciparum malaria[1] and; (iii) if the parents/guardian gave a written informed consent. Details of the clinical management have been described elsewhere.[20]

Chloramphenicol administration and blood and CSF sampling

Chloramphenicol sodium succinate (Lincoln Pharmaceuticals Ltd., Nirav Complex, Ahmedabad, India) was administered intravenously (25 mg/kg, 6 hourly for 72 h) as a bolus over 1 min. Blood samples (0.4 ml), from which plasma was obtained for measuring chloramphenicol and chloramphenicol succinate concentrations,[21] were collected at various times over 72 h. In those patients who had a lumbar puncture performed for clinical purposes, an aliquot (100 µl) of CSF was obtained and stored at −20°C until assayed for chloramphenicol.[21]

Pharmacokinetic analysis

Plasma chloramphenicol and chloramphenicol succinate concentration-time data during the first 6 h dosing interval were simultaneously fitted to the model shown in Fig. 1, using the pharmacokinetic programme TopFit.[22] Simulations of plasma chloramphenicol concentrations were also performed using TopFit. Estimated pharmacokinetic parameters were

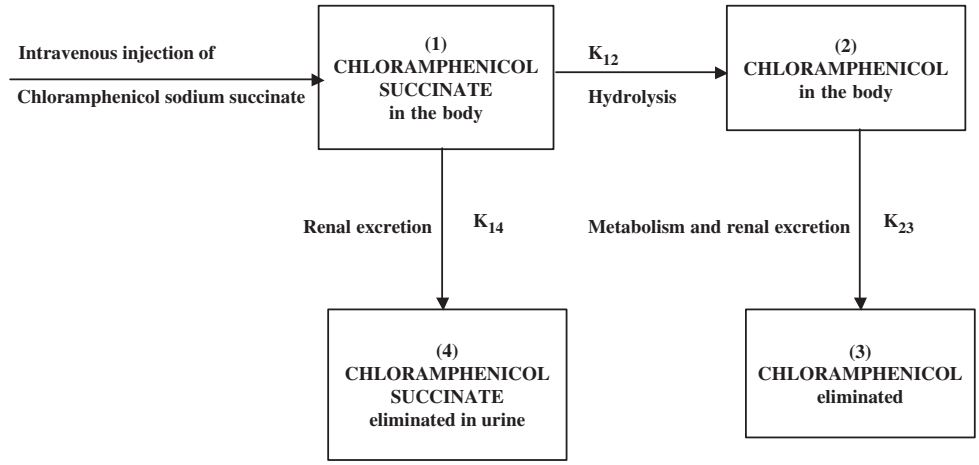

FIG. 1. Schematic representation of *in vivo* disposition of chloramphenicol sodium succinate.

summarised as mean [95 per cent confidence interval, (CI)] or median (range). The 95 per cent CI was estimated using the statistical program CIA.[23]

Results

Fifteen children (4 females and 11 males) were recruited into the study (Table 1).

Estimated mean steady state total chloramphenicol concentrations (C_{ss}) were within the reported therapeutic range of 10–25 mg/l (Table 2), although trough concentrations were <10 mg/l after the first dose. Simulations indicated that a loading dose of 40 mg/kg, followed by a maintenance dose of 25 mg/kg every 6 h would rapidly achieve and maintain plasma chloramphenicol concentrations within the therapeutic range throughout the treatment period (Fig. 2). Lumbar punctures were performed within a median time of 5 h (range: 2–6 h) after administration of the last dose of chloramphenicol succinate. Concentrations of chloramphenicol in CSF ranged from 4.4 to 13.2 mg/l (Fig. 3), above the MIC for all the isolates *Streptococcus pneumoniae,* the main cause of bacterial meningitis in this hospital.[24]

TABLE 1
Demographic and biochemical parameters. Values are mean (95 per cent confidence interval, CI)

	Chloramphenicol ($n=15$)
Demography	
Sex (M/F)	11:4
Age (months)	49.4 (33.9, 64.9)
Weight (kg)	14.3 (12.2, 16.4)
Rectal temperature (°C)	38.7 (37.9, 39.5)
WAZ (weight for age) score	−20.2 (−2.64, −1.4)
Laboratory measurements	
Haemoglobin (g/dl)	8.20 (6.95, 9.45)
WBC ($\times 10^6$)/l	11.6 (8.4, 14.8)
Parasite count (/μl); geometric mean	84 800
Total plasma proteins (g/l)	62.1 (57.3, 66.7)
Plasma albumin (g/l)	32.3 (29.8, 34.8)
Sodium (mmol/l)	132.7 (129.4, 136.1)
Potassium (mmol/l)	4.31 (3.85, 4.76)
Creatinine (μmol/l)	74.4 (46.6, 100.2)
pH	7.32 (7.27, 7.37)
Blood glucose (mmol/l)	5.84 (3.94, 7.73)
Base excess	−9.15 (−10.9, −7.4)

Discussion

Chloramphenicol is still routinely used in resource-poor countries (RPCs) for treatment of bacterial infections including bacterial meningitis despite concerns about its adverse effects, since it is cheap, widely available and a broad-spectrum antibiotic. The regimen we studied is recommended by the WHO and the British National Formulary, and is widely used in health facilities in rural Africa. It does not include administration of a loading dose. Based on the pharamcokinetic data generated from this study, we recommend that an initial loading dose of 40 mg/kg be administered to ensure that chloramphenicol trough and peak concentrations of approximately 10 and 20 mg/l, respectively, are achieved during the first 6 h when such children are most critically ill. Most children in this study received paracetamol for treatment of fever. In addition, all children received phenytoin. Although these drugs have been reported to interact with chloramphenicol,[16,18,19] we did not find any significant effect of concomitant administration of these drugs on the clearance of chloramphenicol.

The mean CSF: plasma chloramphenicol concentration ratio estimated in this study (0.62) was similar to previously reported values in Caucasian children and infants.[25] In addition, concentrations of chloramphenicol in CSF from different children at different times after drug administration were all ≥4 mg/l (Fig. 3). The MIC for *Streptococcus pneumonia*, the main causative agent for bacterial

TABLE 2
Pharmacokinetic parameters of chloramphenicol (CAP) and chloramphenicol succinate (CAPS) in children with severe malaria

Parameter	*n*	Mean (SD) or median (range)	95 per cent confidence interval
AUC (μg/ml×h)	13	99.6 (22)	86.6–113
C_{SS} total (μg/ml)	13	16.7 (3.7)	14.4–18.9
C_{SS} free (μg/ml)	9	8.7 (2.3)	6.9–10.5
C_{max} total (μg/ml)¶	13	14.1 (11.8–20)	12.8–16
Fraction unbound	9	0.49 (0.15)	0.38–0.60
CSF/plasma CAP ratio	13	0.65 (0.19)	0.54–0.76
CSF CAP conc (μg/ml)	13	7.6 (2.7)	5.9–9.2
T_{max} (h)¶	13	0.58 (0.25–1)	0.46–0.67
$T_{½}$ (h), CAP	13	4.1 (0.7)	3.6–4.5
$T_{½}$ (h), CAPS	13	0.16 (0.004)	0.14–0.19
CL_{TOTAL} (l/h), CAP	13	4.3 (1.5)	3.34–5.16

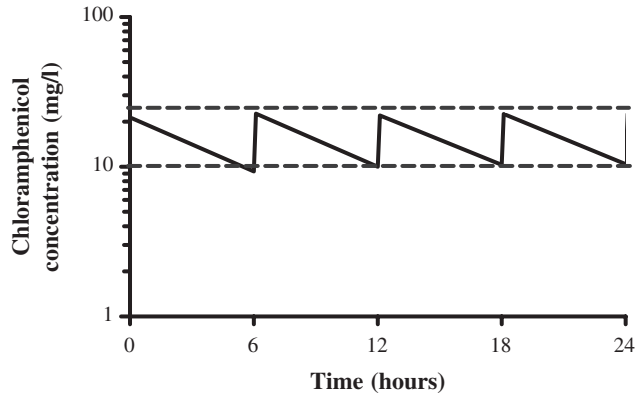

FIG. 2. Simulations of plasma chloramphenicol concentration-time profile that would be obtained after administration of a 40 mg/kg chloramphenicol sodium succinate loading dose followed by 25 mg/kg maintenance dose every 6 h for 72 h. For clarity, the 95 per cent confidence intervals are not shown in the figure.

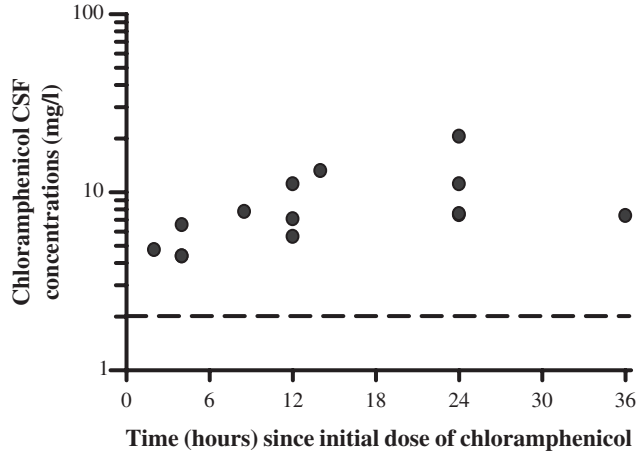

FIG. 3. Chloramphenicol concentrations in CSF at various times in different patients ($n = 12$). The dotted line is the MIC for *Streptococcus pneumoniae* isolates from the hospital where the study was carried out (Kilifi District Hospital, Kenya).

meningitis in children admitted to this hospital,[24] was estimated to be 2 mg/l, while the National Committee for Clinical Laboratory Standards criteria for sensitive isolates is an MIC $\leq$4 mg/l. Taken together, these results support the use of chloramphenicol for presumptive treatment of pneumoccocal meningitis in our setting.

Conclusions and Recommendations

We have shown that the pharmacokinetics of chloramphenicol in African children with severe malaria are broadly similar to previous reports in Caucasian children. Concomitantly administered paracetamol and phenytoin do not appear to have any effect on chloramphenicol pharmacokinetics. To achieve and maintain therapeutic chloramphenicol concentrations rapidly and throughout the treatment period, we recommend that a loading dose of 40 mg/kg chloramphenicol sodium succinate, followed by a maintenance dose of 25 mg/kg every 6 h should be administered.

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