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Ciprofloxacin in Multi-Resistant Infections in Childhood: An Audit

Pages with reference to book, From 147 To 150

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Abstract

Ciprofloxacm is a new orally administrable fluoroquinolones, with considerable efficacy against multi-resistant organisms. Its use in the paediatric age group however, is controversial because of the risk of potential articular toxicity. We retrospectively reviewed ciprofloxacin usage over a 32 week periods (June, 1991- September, 1993) in paediatric inpatients at The Aga Khan University Hospital. Ciprofloxacin was used in 21 cases, singly in 11 (52%) and in combination with other antibiotics in a further 10 (48%). The response to therapy was adjudged as 'good' or 'fair' in 13(62%) cases. Ciprofloxacin was the only sensitive antibiotic in 4(19%) and resistance to it was detected in another 4(19%) cases. Despite all efforts, adequate follow-up could only be achieved in a third of the patients. Although no toxic or side effects were detected, in view of poor follw-up and emergence of ciprofloxacin resistant strains, our experience highlights the need to regulate ciprofloxacin use in the paediatric age group (JPMA 45:147, 1995).

Introduction

Ciprofloxacin (CPX) is a new synthetic fluorinated carboxyquinolone with broad spectrum activity against aerobic gram positive organisms especially methicillin-resistant staphylococci and gram negative organisms such as Klebsiella, Enterobacter, Pseudomonas and Salmonella species[1,2]. CPX has thus been used extensively in adults for infections with resistant organisms. It offers considerable advantages over other antibiotics because of its broad spectrum, effective tissue penetration and ease of oral administration. In the developing world scenario, the emergence of multi-resistant strains of several organisms has begun to pose major health problems[3]. In view of the prohibitive costs of newer parenteral antibiotics, this has led to widespread quinolone and CPX usage in these countries, for reasons of cost and ease of ambulatory therapy.

The safety of CPX in the pediatric age group however, is controversial, as experiments with juvenile animals have shown quinolones to be toxic to weight bearing joints[4-8]. However, CPX has been used recently in multi-drug resistant typhoidal infections in children[9] with considerable benefits, Its use therefore, in other paediatnc severe infections has also begun to increase. The Aga Khan University Hospital (AKUH) is a 400 bed teaching hospital with a 80 bed pediatric ward and a 15 bed Neonatal Intensive Care Unit. At AKUH, CPX is not used routinely in the pediatric age group, but canbe prescribed under special circumstances, at the discretion of the attending physician. This audit of CPX use in the pediatric age group was conducted with a view to determine the frequency of CPX usage, its efficacy, patterns of resistance and potential side effects.

Materials and Methods

This is a retrospective case review of all hospitalized children (<16 years) at AKUH, who were treated as inpatients with CPX for _24 hours, over a 32 months period (January, 1991 - September, 1993).The charts were analyzed forpatient characteristics, presenting complaints, diagnosis, microbiological data, indications forCPX usage, side effects, toxicity or interaction with other drugs, response to therapy,

final outcome and follow- up. Response to therapy was judged by defervescence, loss of toxicity and the eradication of organisms as proved on negative cultures. Defervescence was defined as body temperature remaining <37.7°C for _24 hours. Resistance was determined by the disc diffusion method and graded according to the zone of inhibition[10]. Minimal inhibitory concentrations of antibiotic were determined in selected cases by standard methods[11].

Results

A total of 21 children (15 boys and 6 girls) received intravenous and oral CPX over this period, alone (52%) or in combination with other antibiotics (48%). The mean age was 13 months witha range of day to 12 years. Nineteen (91%) of the patients were infants, out of whom 10 (48%) were neonates.

Table I. Diagnoses in children receiving CPX (n=21).

Sepsis	7	(33%)
Meningitis	6	(29%)
Infected ventriculo-peritoneal shunt	3	(14%)
Pneumonia	3	(14%)
Sepsis with pneumonia	2	(10%)

Table I shows the diagnoses of the children who received CPX.

Table II. Microbiological spectra of organisms (n=20)*.

Organism	Sites of isolation				
	Blood	CSF	Sputum/ Trach. Asp	Stool	Total
Klebsiella pneumonia	4	0	1	0	5
Staphylococcus species	1	2			3
Enterobacter species	3		2		3
Salmonella paratyphi B	2	1		2	2
Flavobacterium meningosepticum		2	1		2
Pseudomonas aeruginosa			1		1
Enterococcus	1				1
Escherichia coli	1				1
Serratia	1				1
Bacillus species	1				1
Total					20

Table II describes the microbiological spectmm of isolates in these cases, while the resistance pattern to various antibiotics is shown in Table III.

Table III. Resistance of organisms (n=20) to commonly used antibiotics (%).

Organisms	Antibiotics										
	AMP	AUG	CFTX	CRO	CHLOR	GENT	AMIK	AZTR	PIPR	CLOX	CPX
Klebsiella	100	60	100	100	80	100	80	100	80	100	0
Staph	100	66	66	66	66	33	66	100	100	66	33[a]
Enterobact	100	100	100	100	66	66	66	66	100	100	33
Salmonella	100	50	100	100	100	100	50	100	100	100	50[b]
Flavobact	100	100	100	100	100	0	0	100	50	100	0
Pseudomonas	100	100	0	0	100	100	0	0	0	100	0
Enterococi	100	100	100	100	100	100	100	100	100	100	100
E. coli	100	100	0	0	100	100	0	100	100	100	0
Bacillus species	100	100	100	100	100	100	0	100	100	0	0

Note: AMP=Ampicillin, AUG=Augmentin, CFTX=Cefotaxime, CRO= Ceftriaxone, CHLOR=Chloramphenicol, GENT=Gentamycin, AMIK= Amikacin, AZTR=Aztreonam, PIPR Piperacillin, CLOX=Cloxacillin, CPX=Ciprofloxacin.
a : Developed resistance on therapy; b : Partial resistance; c : Sensitive only to Vancomycin.

There was one patient with an infected ventriculoperitoneal (VIP) shunt, in whom no organism could be isolated from either blood orCSF cultures. Resistance to CPX was detected in four patients. Two (10%) of the organisms showed full resistance to CPX at initial presentation One of the patients had meningitis with enterococcus, while the other had pneumonia with enterobacter cloacae. One patient with a VP shunt infection with staphylococcus epidermidis, was initially sensitive to CPX, but developed resistance after 5 days of therapy. One patient with salmonella paratyphi B meningitis also

showed partial resistance to CPX on MIC determination.
CPX was initially started empirically in 5 cases (24%). In one of these cases with an infected VP shunt, the organism could not be isolated, while in another child with meningitis the organism isolated at the referring hospital was knownto be Serratia, but no sensitivities were available. In the other cases CPX was initiated alone, or in combination with other antibiotics, as the patients were critically ill. In the rest of the 16 cases (76%), CPX therapy was initiated after the availability of the culture/sensitivity results. In 4 (19%) of the cases, the organisms were resistant to all antibiotics except CPX. These included two cases of Klebsiella sepsis and one case each of Salmonella paratyphi sepsis and enterobacter sepsis. In another 6 cases (29%), CPX was used when there was no clinical improvement on other sensitive antibiotics. In the rest of the patients CPX was used as the alternative sensitive antibiotics did not have good CSF penetration.
The mean duration of therapy was 11 days with a range of 2 to 21 days. The response to therapy was judged to be 'good' in 10 patients (48%) and 'fair' in another 3 patients (14%). The response was 'poor' in 6 patients (28%) and the antibiotic had to be changed, while in 2 (10%) of the patients the efficacy could not be determined from the records. The meantime-to-clinical response when efficacy was goodor fair was 2.5 days, with a range of ito 5 days. There was only one death (5%) of a newborn with pseudomonas pneumonia who was receiving multiple antibiotics.
All patients were given outpatient appointments on discharge from AKUH. However, of the twenty survivors, seven (3 5%) were being followed-up to date, with an average duration of 7 months. Eight (40%) of the patients returned initially, but were lost to follow-up afteran average duration of 2 months, while five (25%) failed to return after discharge. No toxic or side effects such asjoint pain,joint swelling, skin rashes, abdominal discomfort, headaches, dizziness, or signs of CNS dysfunction were noted at any stage.

Discussion

Development of resistance is a major problem with antibiotic therapy in developing countries where inappropriate antibiotic use is rampant and over-the-counter antibiotics are freely available. CPX is a new antibiotic that acts by inhibiting DNA gyrase, an enzy me which is essential for replication in prokaryocytes[1,6,12]. CPX has broad spectrum bactericidal activity, effective tissue penetration and can be administered orally. It is therefore, not surpnsing that CPX has become an attractive choice in the developing world for treating multidrug resistant infections. Development of resistance to CPX is slow and usually develops by altering the membrane proteins or the structure of DNA gyrase (especially its subunit A proteins) [13-15]. There have been some reports of CPX resistance in methicillin resistant staphylococcus and pseudomonas recently[16-23]. There were 4 cases in our series that were treated with CPX initially but the organism was subsequently found to be resistant. Two organisms (enterococcus and enterobacter) were fully resistant, one (salmonella paratyphi) was partially resistant, while one organism (staphylococcus epidermidis) was initially sensitive, but resistance developed to CPX on therapy.
The efficacy of CPX in several series of children with bacteremic infections has ranged from 94~100%[12,24,25]. CPX has been shown to be more effective than conventional antibiotics in the treatment of typhoid and salmonellosis[6,8,26,27]. The response to therapy to CPX in our series is however, lower than that reported by other workers. This could be related to a higher proportion of complicated referral cases at AKUH as compared to other hospitals. In our audit, CPX was clinically efficacious in 50% of the 6 meningitis patients and in all of the 3 patients with infected VP shunts. CPX penetration into CSF is approximately20- 30%[28] and is enhanced with meningeal inflammation[29]. Schonwald found its efficacy in gram negative bacillary meningitis to be 90%[23]. CPX has been shown

to cause damage to cartilage/joints in experimental animals[3,5-8]. This effect however, may be species specific. Nalidixic acid also causes cartilage damage in animals but inspite of extensive pediatric usage, no such effect has been reported in children. CPX has been used in children in the West, mostly for exacerbations of resistant pseudomonas infections in cystic fibrosis[22], but todate no overtcartilage damage has been reported mover 1500 patients treated worldwide[3,5,12,24]. There have been two published reports ofjoint symptoms on CPX therapy, a 16 year old girl and a 10 1ear old boy, who developed joint pain on CPX therapy[30,31] The symptoms however, resolved in both cases on stopping the antibiotic. In our experience todate, no significant side effects or toxicity were observed during therapy and in those followed up. CPX related chondrotoxicity may be acute and show up withindaysofstartingthernpy,butitmay sometimes eventake long as to manifest. On a cautionary note, despite all efforts, our follow- up was incomplete in 65% of the cases. This underscores the difficulty in securing longterm follow-up in similar circumstances in the developing world. Our data indicates that CPX usage can be life saving in many suspected/proven multidrug resistant infections in children. However, the recent emergence of drug resistance to CPX and the poor follow-up in our environment, highlights the urgent need to regulate and restrict its widespread pediatric use and 'over-the- counter' sales. We recommend that CPXbe used in children only for life threatening infections orwhen all alternative agents have failed, atleast until larger controlled clinical trials determine its efficacy and adverse effects in this age group.

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