

Evolutionary Aspects of Newborns Under 1500g Treated with Fluoroquinolones in Libreville, Gabon

Kuissi Kamgaing Eliane^{1,2*}, S Minto'o Rogombe¹, R Koumba Maniaga^{1,2}, A Lembet Mikolo^{1,2}, E Mintsu Mi Kama^{1,2}, I Busugu Bu Mbadinga^{1,2} and S Atebo^{1,2}

¹Department of Pediatrics, University of Health Sciences, BP, Libreville, Gabon

²Children Pole, Mother-Child Hospital-University Center Jeanne Ebori Foundation of Libreville, BP, Libreville, Gabon

*Corresponding Author: Kuissi Kamgaing Eliane, Professor, Department of Pediatrics, University of Health Sciences, BP, Libreville, Gabon.

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Abstract

Introduction: The resistance of germs responsible for neonatal infections sometimes requires the use of fluoroquinolones that are not indicated at this age. Our goal was to assess the short- and medium-term fate of newborns under 1500g treated with fluoroquinolone in Libreville.

Methodology: Case control study, over a period of 3 years (January 2015 - December 2018). The cases consisted of newborns under 1500g treated for neonatal infection with fluoroquinolones. Controls were newborns under 1500g treated for neonatal infection with other antibiotic families. The parameters studied were urea, creatinine, blood glucose of cases at Day0, Day10 and Day30 post-treatment. We compared anthropometric parameters and motor acquisition at 3, 6 and 12 months of the two groups.

Results: In the fluoroquinolones group, sepsis was the most observed localization (60%) and E. coli the most found germ (28%). The average time to the introduction of fluoroquinolones was 15d ± 7d. The most widely used molecule was Ciprofloxacin (68%). The most observed side effect was hypoglycaemia (28%) and an increase in serum creatinine (p = 0.006) and uremia (p = 0.0013) was observed on Day10 post-treatment. We did not observe any musculoskeletal manifestations. The evolution of anthropometric parameters and motor development was comparable in the 2 groups.

Conclusion: Fluoroquinolones motivated by the consideration of benefit/risk are well tolerated in newborns under 1500g.

Keywords: Low Weight Newborn; Fluoroquinolones; Libreville-Gabon

Introduction

Bacterial resistance is a growing threat to public health and a global scourge. It leads to difficulty, or even to the impossibility of treating certain infections. This phenomenon, stated since 1945 [1,2], is today one of the most complex health challenges in the world according to the World Health Organization (WHO) because it threatens the very heart of modern medicine [3] by being responsible for the deadliest infections in the world, such as nosocomial infections (NIs). These secondary infections affect hundreds of millions of people with a higher incidence in developing countries according to the WHO. In these countries, about 25% of patients will have NIs with a risk of 2 to 20 times higher than in developed countries [4]. Among the most affected services, neonatal services figure very prominently, where

NIs are a major safety problem with a mortality rate ranging from 23 to 57.3% depending on the hospital and country [5]. In Gabon, the hospital prevalence was 25.7% with a mortality rate of 23.3% in 2018 at the Angondjé University Hospital Center [5]. The most frequently identified germs are often highly resistant, sometimes requiring the use of certain antibiotics (ATB) outside the marketing authorization (MA) for the newborn in general and more specifically in the newborn of low birth weight such as fluoroquinolones, whose side effects can sometimes be serious and irreversible. Very few studies assess the risk of using this molecule in this segment of the population.

Aim of the Study

The aim of our study was therefore to assess the short- and medium-term fate of newborns under 1500g, treated with fluoroquinolone in Libreville, Gabon, secondly to analyze the motor development of its patients by comparing them to a control group (children under 1500 g not exposed to fluoroquinolones).

Patients and Methodologies

This is a control, prospective, descriptive, and analytical case study carried out in the neonatology departments of 3 private health structures in Libreville (El Rapha Polyclinic, Océane Clinic and Chambrier Clinic) and the Angondjé University Hospital Center over a period from January 2015 to December 2018.

The studied population consisted of newborns with a birth weight of less than 1500g, presenting a secondary neonatal infection caused by a germ resistant to usual antibiotics and treated with fluoroquinolone. Ciprofloxacin and ofloxacin were the molecules used according to their availability at dosages ranging from 8 mg/kg/12h ($\leq 1000g$) to 10 mg/kg/12h ($> 1000g$) in a 30 min slow intravenous (SIV) for 10 days. The control population were newborns with a birth weight of less than 1500g, also presenting a secondary neonatal infection and who did not receive fluoroquinolones as a means of treatment. The parameters studied included:

Clinically,

- The appearance of side effects (convulsions, vomiting, rashes, jaundice, joint swelling, decreased movement....).
- Anthropometric parameters at 1, 6 and 12 months and motor acquisition at 12 months of corrected age of newborns treated with fluoroquinolone were compared with those of newborns not treated with this molecule.

At the paraclinical level, creatinine, uremia, blood glucose and transaminases of Day₀ (start of treatment), Day₁₀ (end of treatment) in children set under fluoroquinolone and 1 month of discontinuation of treatment were assessed.

Data analysis

The data collected on a standardized sheet was entered on the MS Excel 2016 software, analyzed by P-value software (www.pvalue.io). The means were compared by student's T-test, the means variations were compared by the Anova test, the proportions by the Khi-2 test, with a significance threshold of p less than 0.05.

Results

A total of 801 newborns were hospitalized during the study period, 214 had a secondary infection, a prevalence of 26.7% with a proportion of newborns under 1500g of 32.2% ($n = 69$). Those treated with quinolones were 35 (50.7%), in this group, 7 died and 3 records were incomplete, so 25 were included. Newborns, less than 1500g not treated with fluoroquinolone were 34, there were 5 deaths and 25 were included in the study.

Study population characteristics

There was no statistically significant difference between the 2 study population groups. Table 1 shows the characteristics of the study population.

Parameters	Cases (n = 25)	Controls (n = 25)	p
Features of newborns			
Average age (SA)	31 SA ± 2 SA	31SA +1 J ± 3SA	NS
[extremes]	[27 SA - 37 SA]	[27SA; 38SA]	
Average weight (g)	1204 ± 210	1278g ± 164	NS
[extremes]	[910g - 1496g]	[910; 1490]	
Medium size (cm)	38 ± 2.5 cm	37.8 ± 2.4 cm	NS
[extremes]	[39 - 44]	[34; 41.8]	
Head circumference (cm)	28.8 ± 2.1 cm	29 ± 2.3 cm	NS
[extremes]	[28 - 34.5]	[26; 33.7]	
Sex ratio	1.27	1.5	
Reasons for hospitalization (alone or in associates)			
Prematurity	18/25 (72%)	14/25 (56%)	NS
Respiratory distress	7/25 (28%)	10/25 (40%)	NS
Perinatal asphyxia	6/25 (24%)	9/25 (36%)	NS
IUGR	6/25 (24%)	3/25 (12%)	NS
MFI	3/25 (12%)	4/25 (16%)	NS

Table 1: Study population characteristic.

Diagnostic aspects

Escherichia coli was the germ observed in 28% of cases and sepsis the localization of the infection in 60% of cases (Table 2).

Parameters	Numbers (n = 25)	Percentages (%)
Site of infection		
Sepsis	15	60
Urinary	3	12
Digestive	3	12
Meninge	2	8
Osteo-articular	1	4
Cutaneous	1	4
Germs		
<i>Escherichia coli</i>	8	28
<i>Klebsiella oxytoca</i>	5	20
<i>Golden staph</i>	4	16
<i>Klebsiella pneumoniae</i>	3	12
<i>Pseudomonas aeruginosa</i>	3	12
<i>Serratia marcescens</i>	2	8
<i>Enterobacter Cloacae</i>	1	4

Table 2: Site of infection and germs involved.

Therapeutic aspects

The average time to the introduction of fluoroquinolones was 15 days ± 7 days with extremes ranging from 5 to 36 days. They were administered in 2nd and 3rd intention in 12.6% and 87.4% of cases respectively. Ciprofloxacin was used in 68% (n = 17) of cases and ofloxacin in 32% (n = 8) of cases. They were combined with another antibiotic in 36% (n = 9/25) of cases including, amikacin (3/9, or 33.3%), gentamycin (3/9, or 33.3%), meropenem (2/9, or 22.3%), metronidazole (1/9, 11.1%).

Treatment tolerance

Immediate tolerance

During the 10 days of treatment, hypoglycaemia was the most common side effect in 28% (n = 7) of cases, followed by skin rash 16% (n = 4), cholestatic jaundice 12% (n = 3), hepatic cytolysis 8% (n = 2) and very liquid stool 8% (n = 2). All patients on ofloxacin experienced at least one side effect.

At the renal level, the mean uremia on Day₀ of treatment initiation was 2.8 ± 0.7 mmol/l (Extreme 1.51 - 4.04 mmol/l), at Day₁₀ post treatment, it was 3.3 ± 1 mmol/l (Extreme 2.1 - 6.1 mmol/l) with a statistical difference between these two means (p = 0.0013). The mean serum creatinine on Day₀ of treatment initiation was 58 ± 16 mmol/l (Extreme 39.8 - 99.0 mmol/l), at Day₁₀ post-treatment it was 70 ± 20 mmol/l (Extreme 45.9 - 111.7 mmol/l) with a statistical difference between these two means (p = 0.006). At one-month post-treatment, the mean uremia was 2.92 ± 0.55 mmol/l (Extreme 1.7 - 4.1 mmol/l) and the mean creatinine was 62.72 ± 13.47 mmol/l (Extreme 43.65 - 96.40 mmol/l).

Evolution of anthropometric parameters

Analysis of anthropometric parameters did not show a difference in growth at 1, 6 and 12 months between the group treated and the group not treated with fluoroquinolone, except at the cranial perimeter (Table 3).

Anthropometric parameters	1 month			6 months			12 months		
	Case	Witnesses	P	Case	Witnesses	P	Case	Witnesses	P
Average weight (g)	1495 ± 247	1574 ± 201	NS	5806 ± 1006	5969 ± 869	NS	8737 ± 1229	8448 ± 1740	NS
Medium size (cm)	40.8 ± 2.2	41.4 ± 2.2	NS	57.4 ± 4.5	56 ± 4.6	NS	70.4 ± 4.5	70.4 ± 4.2	NS
Medium PC (cm)	30.9 ± 2	31.6 ± 2.2	NS	40.1 ± 2.7	41 ± 1.8	NS	46.5 ± 2.3	48.1 ± 1.6	0,01

Table 3: Evolution of anthropometric parameters.

Motor development at 12 months

At 12 months of corrected age life, the sitting position was observed in 2 (8%) patients, 9 (36%) crawled on all fours, 6 (25%) stood up without support and 8 (32%) had acquired walking, including 2 without support. There was no significant difference with the control group (Table 4).

	Patients n (%)	Controls n (%)	p
Sitting	2 (8%)	3 (12%)	NS
Four-legged walking	6 (25%)	4 (16%)	NS
Standing with or without support	9 (36%)	10 (40%)	NS
Walking with or without support	8 (32%)	8 (32%)	NS
Total	25 (100%)	25 (100%)	

Table 4: Motor development at 12 months.

Discussion

Prevalence of nosocomial infection

Nosocomial neonatal infection (NNI) is a scourge and is one of the leading causes of neonatal mortality in neonatal wards worldwide. In our study, the prevalence is 26.7%, in line with most prevalences in the sub-region which varies from 34 to 52% or even 73% [6,7]. In our context, this high prevalence is due to poor hygiene and working conditions (means of control and surveillance) and a lack of qualified personnel. The proportion of newborns under 1500 g that we observed is not negligible (32.2%) and may be justified by the fact that prematurity and low birth weight are among the risk factors for the occurrence of NNI [8-10].

Sepsis is the most observed form of expression, and the most identified germs are gram-negative bacilli (GNB) in this study. This observation had already been made in our country [5] and by several studies in the literature, which also note that most of these GNBs are multi-resistant [11-13]. Thus, a little more than half of our newborns under 1500g (50.7%) have been infected with germs resistant to conventional ATB and present in our territory such as beta-lactamines and aminoglycosides (Gentamicin in particular), responding only to ATBs not available in our context (Tazobactam, Piperacillin, Fosfomycin, Vancomycin... etc.) with the exception of fluoroquinolones present in our pharmacies. This rate is very high, but it is well known that 40% of NNI germs in developing countries are resistant to these conventional ATBs [14]. At the AUHC in 2017, quinolones were the only sensitive molecules in 14.5% of NNI cases [5]. In the study by Dutta, *et al.* the rate of ciprofloxacin use in very low-weight newborns was about 25 - 30% in 2006 [15].

The infection was said to be secondary in 100% of the cases in our study, so necessarily nosocomial, but with a possibility that the germ is of primary transmission, achieving rather a primitive infection with resistant germ. Indeed, a study carried out in 2017 at the AUHC showed that multi-resistant bacteria were already present in the 1st stool of the newborn with a proportion of 7.84% on a population of 51 newborns [16]. This justifies the use of fluoroquinolones in this category of the population, with sometimes, this relatively early time of introduction as observed in our study (5th day of life) while there is no MA in the newborn in general and in the premature or hypotrophic newborn specifically. This relatively short time is also observed in the studies of Caudhari, *et al.* [17] and Masoumi, *et al* [18].

Quinolone in pediatrics

Quinolones are a class of antimicrobials that function as direct inhibitors of bacterial DNA synthesis. In the paediatric population, quinolones have been widely used on children aged more than 3 months without restriction, then drastically restricted, following observations of joint damage after their administration in young animals of different species, this restriction also included pregnant women and when breastfeeding [19-21]. But being the only antimicrobials effective in the treatment of certain severe infections or resistant germs, several children have received them, with certain effectiveness and without the observation of serious side effects such as arthropathies or bone damage. Their use is therefore accepted in children in children, especially in those aged 1 to 17 years in the last line, when the benefits are greater than the risks of side effects, especially in multi-resistant infections when there are no effective ATBs that can be used

[18,21-23]. The WHO has also included on the list of essential medicines in children a fluoroquinolone (ciprofloxacin) despite the absence of marketing authorisation in this segment of the population [24].

In neonatology, its use is also recommended in case of infections with multi-resistant germs (but sensitive to ciprofloxacin) involving the vital prognosis [22,25,26]. It is this anti-infectious treatment regimen that is adopted in our services, in all newborns regardless of gestational age and weight. Thus, quinolones, essentially fluoroquinolones, are used in the 2nd or 3rd intention when we observe a lack of clinical-biological improvement after a well-conducted probabilistic antibiotic therapy and/or as soon as an antibiogram imposes it on us in front of the degree of resistance of the identified germ. This pattern in the newborn is also adopted by several authors in the literature [26-28]. Maria Pacifici, *et al.* assure that this antibiotic is effective and safe in the newborn and would reduce the length of hospitalization and the incidence of Gram-negative bacteremia [25].

The most widely used molecule in pediatrics is ciprofloxacin, due to its higher safety profile compared to other fluoroquinolones [18,24]. The intermittent availability of ciprofloxacin on the market justifies the use of ofloxacin in some of our patients. The dose used is still poorly defined in neonatology, most often determined according to the teams and according to the condition of the child. There is great variability in the literature in the dosage used and duration of treatment in paediatrics, but in the majority of studies, the dose used ranges from 10 to 30 mg/kg/day in two doses per day during 10 to 14 days [25,26,29]. In preterm infants, the dose of 10 mg/kg/12 hours was the most widely used in the literature with an average duration of treatment of 13 days [15,27,28]. Aggarwal, *et al.* concluded that this dose is effective and safe in low-weight newborns [30]. Y. Aujard, suggest a dose of 10 mg/kg/12h in newborns of less than 1500g, less than 32 SA and less than 7 days and a dose of 10 mg/kg/8h as soon as they are more than 7 days old and in 1500g and more than 32 SA [31]. However, Zhao, *et al.* defined the appropriate dose in the population of newborns and young infants < 3 months by showing that 90% of newborns with GA < 34 weeks treated with 7.5 mg/kg twice daily and 84% of newborns with GA ≥ 34 weeks and young infants receiving 12.5 mg/kg twice daily, reach efficacy thresholds with minimal risk of overdose (< 8%) [26]. Despite the available evidence of the safety of fluoroquinolones on children in general and newborns in particular, fear of risk remains very high in the minds of pediatricians. We have chosen in our different departments to use the dosage of 8 to 10 mg/kg every 12 hours in slow intravenous of 30 min for 10 days, 8 mg for < 1000g and 10 mg for anyone over ≥ 1000g whether born prematurely or at term. Despite this variability in doses observed in the literature, the meta-analysis of Adefurin, *et al.* does not appear to find a dose- or duration-dependent risk of toxicity [29].

Tolerance of fluoroquinolones

During treatment, hypoglycaemia was the most observed side effect, followed by skin rash, cholestatic jaundice and hepatic cytolysis. The renal records remained generally normal. However, we observed a significant difference in the mean of uremia and serum creatinine between the start and end of treatment. These disorders did not lead to the abandonment of treatment, and they were totally and spontaneously resolved at the end of treatment. In 2013, similar side effects were observed by Oulmaati, *et al.* in newborns of mean gestational age of 37 SA comprising 38% of preterm infants, treated with ciprofloxacin (thrombocytopenia, cholestatic jaundice, skin rash, functional renal failure and hepatic cytolysis), as well as in the meta-analysis of Kaguelidou, *et al.* in 2011, all resolved at the discontinuation of day treatment [27,28]. These various minor side effects are not specific to the newborn, they are described in the package leaflet [19,20].

In the medium and long term, we did not observe any abnormality on the musculoskeletal level, the anthropometric parameters and psychomotor development of our patients were comparable to that of the control group. The small sample size of our study may not allow for differences. However, Kaguelidou, *et al.* in the meta-analysis of 32 articles on the use of ciprofloxacin in neonatology, found no serious adverse events and the short- and long-term impact of ciprofloxacin on cartilage damage and growth was not significantly different from children who did not receive this molecule [28], as well as in Wang, *et al.* [22]. In the Dutta and Chaudhari studies, ciprofloxacin did not affect linear growth at 12 and 6 months respectively [15,17]. However, the presence of musculoskeletal side effects when using fluoroquinolone remains controversial in the pediatric population [20,29] and where they exist, they are modulated by many factors such as

age, underlying pathology, associated treatment. Thus, they are more observed in older children compared to infants and newborns, then, its association with an aminoglycoside [18,20,32] and the type of molecule used [22] are some of these factors.

Conclusion

Our study highlights minor and fully reversible side effects when using fluoroquinolones in low-birth-weight newborns and joins the findings of several other studies in the literature. This has allowed us to continue to use this molecule with more serenity in our various departments, especially on our patients of low birth weight even if the apprehension of the occurrence of a serious effect remains our main fear. However, it is imperative to make every effort to limit the use of this molecule only when necessary. Because the growing emergence of bacterial resistance to fluoroquinolones due to excessive use, sometimes unjustified, could constitute a greater risk than side effects in neonatal medicine.

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