

CEFDINIR AND IRON: CLINICAL AND BIOCHEMICAL RELATIONSHIP

Haila Alshelawi¹ and Saud Saad H Almotairy^{2*}

¹Consultant Pediatric Endocrinologist, Armed Forces Hospital, Qassim, Saudi Arabia.

²Pediatric Department, Armed Forced Hospital, Qassim , Saudi Arabia

Corresponding Author: Saud Saad H Almotairy

Email: dr.saudalmotairy@gmail.com

ABSTRACT

Cefdinir is an oral third generation cephalosporin commonly used to treat paediatric infectious diseases. It causes bloody discoloration of the stool if co administered with iron ion. Iron reduces cefdinir bioavailability by preventing its absorption. In our case, 9 months old boy brought to ER by his parents complain of bloody stool two days after initiation of cefdinir therapy. Few cases with similar presentation have been reported.

1.0 Introduction

Cephalosporin is a group of beta lactam containing antibiotics , other are penicillin , monobactam, carbapenems and beta lactamase inhibitors. They are so named beta lactam because there unique four-membered lactam ring. In figure-1 shown the basic unit of the cephalosporine group, and aminocephalosporinic acid nucleus. Substitution of the molecule at R1 and R2 produce different cephalosporine.

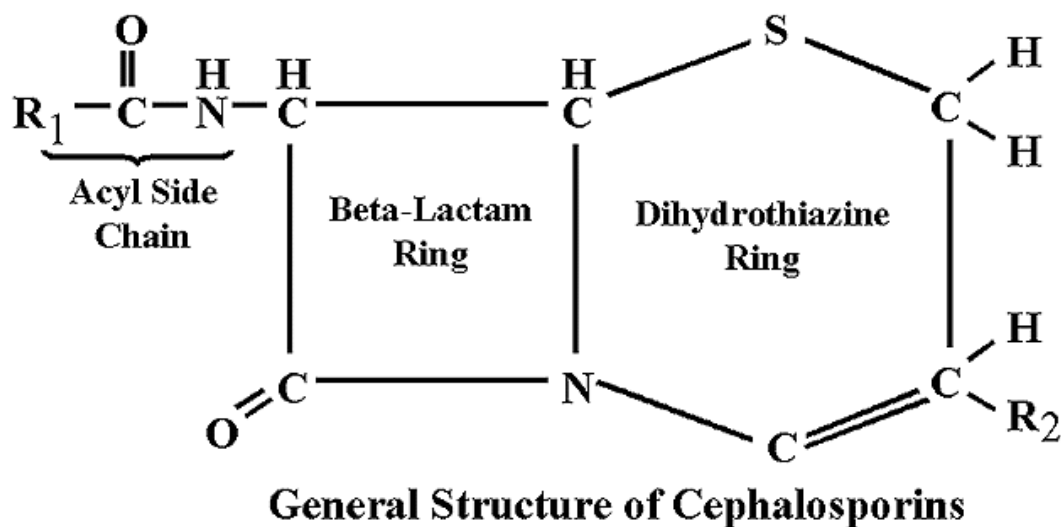


Figure1: Basic of cephalosporine group

There are four groups or generation of cephalosporine see table1. It is mainly classified so depend on the spectrum of antimicrobial activity.

Table1: classification of cephalosporin

| | | |
|--------------------------|----|--|
| First generation | PO | Cefadroxil , cephalexin , cephradine |
| | IV | cefazolin |
| Second generation | PO | Cefaclor , cefuroxime ,cefprozil , |
| | IV | Cefoxitin , cefotetan , cefuroxime |
| Third generation | PO | Cefdinir , cefixime , cefpodoxime , |
| | IV | Ceftriaxone , ceftazidime , cefotaxime |
| Fourth generation | PO | |
| | IV | cefepime |

Legends: PO : per oral , IV: intra venous

The cephalosporin medication have a broad spectrum of antibacterial activity which explain there extended clinical use. In table 2 , summarized the spectrum of antibacterial activity of cephalosporin based on there generation classification.

Table 2: overview of the spectrum of cephalosporine

| GENERATION | GRAM POSITIVE | GRAM NEGATIVE | ANAEROBIC | ATYPICAL | NOTICE |
|---------------|---------------|-----------------------------|-------------|----------|-------------------------------|
| FIRST | Very active | Ecoli, proteus , klebsiella | peptococcus | X | MRSA is not sensitive |
| SECOND | active | Extened | cefotetan | X | First spectrum G. is included |
| THIRD | active | Very active | X | X | Ceftazidime antipseuomons |
| FOURTH | Very active | Very active | X | X | Pseudomons activity |

Cefdinir appear to be rapidly absorbed from gastrointestinal tract in pediatric patient with time to peak plasma concentration (Tmax) of ~ 2 hours. The bioavailability of the suspension formulation is 20% greater than that of capsule formulation. It is mainly eliminated by renal route as unchanged. Cefdinir has bactericidal activity against gram positive aerobic bacteria including staphylococci (except MRA) and streptococci (group A, B, C and G). It has an excellent activity against neisseriaceae, haemophilus and maraococi. Unlike cefixime, cefdinir appears to exert little effect on normal human faecal flora therefore it has low risk of antibiotic-associated diarrhoea.

Bloody stool discoloration associated with cefdinir treatment is one of the complaints which make the parent and the family worry about the general health of the patient although it is

benign side effect. Our aim of presenting a case report with cefdinir associated bloody stool is to clarify the mechanism of the phenomena through a comprehensive literature review.

2.0 Case report

9 months old Saudi boy brought to ER by his parents complain of bloody stool since few hours. Three days ago, the patient complains of cough. On the next day, he developed fever. At this moment, he visited PHC physician which diagnose him as acute tonsillitis and treat him by cefdinir (14 mg / kg / OD). Until now, the patient received two doses of cefdinir. There is no diarrhoea, vomiting, SOB, abdominal pain, abnormal movement or convulsion. Stool was red in colour tomato paste-like. Past history was unremarkable. He was breast feed up to 4 months of age then bottle feeding started. At sixth months, solid food initiated gradually. During examination, the patient was playful, pink, well hydrated and perfused. The vital signs were within normal limit. Abdomen examination was unremarkable. PR examination show no fissure or blood. Upon laboratory workup, stool occult test was negative. CBC, RFT, LFT, stool culture and abdominal ultrasound were all normal. Stool also showed clostridium difficile antigen positive. The patient admitted to Paediatric ward for observation, the cefdinir treatment discontinued and supportive therapy provided. 24 hours later, stool colour was back to its normal colour then the patient discharge home.

2.1 Literature review

Red stool discoloration caused by coadministration of cefdinir and iron are described in package insert but few cases have been reported in literature. A search of PubMed using the term “ cefdinir iron “ reveal 5 published case report (Table-1). All the cases were on cefdinir therapy and the complaint resolved after discontinuation of the drug. A google scholar and Europe PMC search done using the term “cefdinir iron” which show the previous 5 cases report (Table-1), a paper describing cefdinir-iron interaction and many unrelated papers based on the title.

2.2 Summary

We are presenting a 9 months old boy complain of red stool after initiation of cefdinir therapy. There is few documented cases with similar presentation.

2.3 Discussion

The interaction between cefdinir and iron is mentioned in the package insert of the drug. As observed in the table (Table-3), the onset of the red discoloration of the stool due to co-administration of cefdinir and iron is within 48 hours and resolved often within 24 hours of stopping cefdinir treatment without complication.

A study done at 1993 to assess the absorption of cefdinir if administer with iron. The study divided the volunteers into 3 groups. First group will receive cefdinir alone, second group will receive cefdinir and iron at the same time and the third group will receive iron 3 hours after administration of cefdinir. There is marked reduction in cefdinir absorption in the second group where cefdinir and iron co administered at the same time, but first and third group there absorption were the same. (Figure 1)

Table 3: Show the summary of all published case report with cefdinir associated red stool

| AGE | GENDE R OF THE PATIE NT | DIAGNO SIS FOR WHAT CEFDIR WAS USED IN THE CASE | YEAR OF PUBLICATI ON OF THE CASE | ONSET OF RED STOOL AFTER INITIATI ON OF CEFDIR | RESOLVE D WITHIN (HOURS) AFTER CEFDIR R WITH HOLD | GUAIA C TESTE | CEFDIR DOSE | SOURCE OF IRON |
|-----------------------|-------------------------------------|--|---|--|--|----------------------|----------------------|--------------------------|
| 6 YRS ² | male | Pulmona ry infection | 2000 | 24 hours | 24 hours | -ve | Not mention ed | Feeding formula |
| 5 MON ² | male | AOM | 2000 | 48 hours | After D/C cefdinir | -ve | Not mention ed | Feeding formula |
| 9MO N ³ | male | AOM | 2008 | 5 TH DAY | 48 hours | -ve | 15 mg/kg/d ay | Feeding formula |
| 7 MON ⁴ | male | AOM | 2008 | 6 th day | Not mention ed | -ve | 100mg/d ay | Ferrous gluconat e |
| 5 MON ⁵ | male | AOM | 2011 | 48 hours | Not mention ed | Not mention ed | Not mention ed | Not mention ed |

Legends: mon = months

Figurer 2 below shows time courses of cefdinir plasma concentrations for the three study arms.

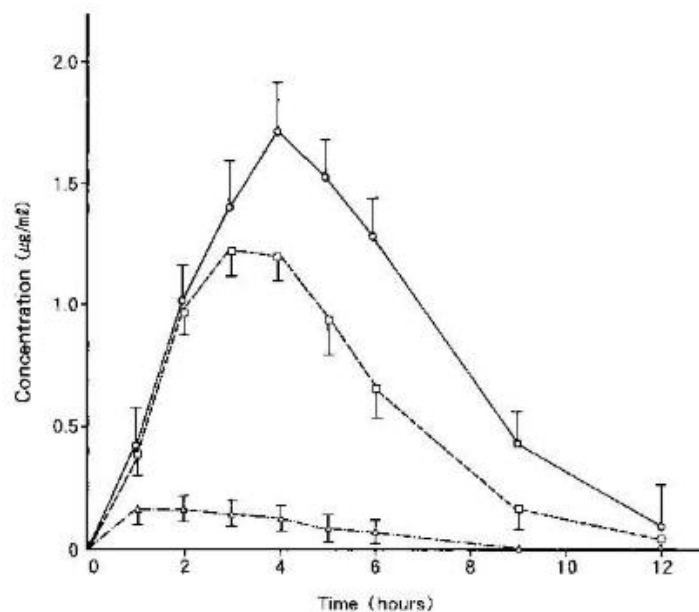


Fig. 1. Mean \pm SD absorption time course of cefdinir plasma concentrations for the three study arms. After fasting overnight, subjects received a single oral dose of 200 mg cefdinir with 100 ml water. *Circles*, Cefdinir alone (study 1); *triangles*, cefdinir and 210 mg iron ion preparation (study 2); *squares*, 210 mg iron ion preparation 3 hours after cefdinir administration (study 3).

Another study done at 1994 to assess the bioavailability of cefdinir if co-administrated with irons. The two structurally related antibiotics, cefdinir and cefixime, have been used in the study. The difference between cefdnir and cefixime is that cefdinir has oxymini side chain and cefixime has carboxyomethoxymini group (Figure 3).

The study concludes to that cefdinir form stable complexes with iron via oxymine side chain where cefixime did not.

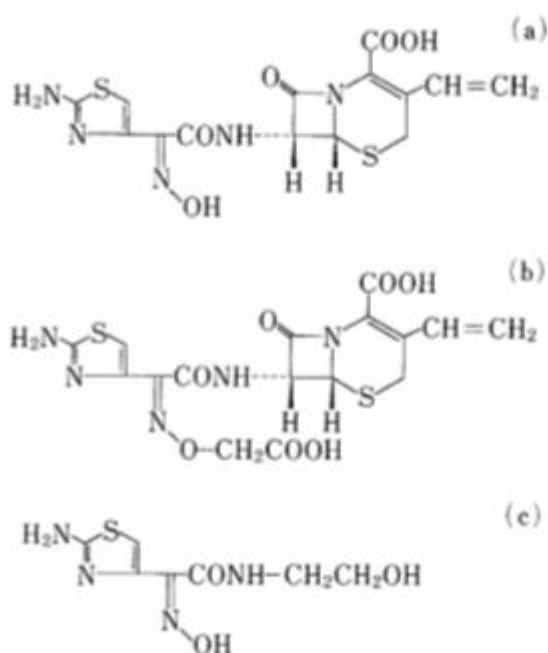


Fig. 3: Show the structure of CFDN (a), CFIX (b) and Compound I (c) , cefdinir has oxymini side chain and cefixime has carboxyomethoxymini group

3.0 Conclusion

Cefdinir absorption is impaired by iron through formation of chelating complex in gastrointestinal tract if co administered. The doctor should ask about any source of iron if the patient will receive cefdinir. Awareness of cefdinir-iron interaction will prevent unnecessary hospitalization. Guaiac test and clinical presentation will provide enough data to exclude serious differential diagnosis.

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