Cefazolin Induced Liver Injury and Hypoprothrombinemia

Dear Sir, We encountered an uncommon adverse effect with cefazolin, a first generation cephalosporin in a young male with medulloblastoma. Cefazolin is a commonly used antibiotic for surgical prophylaxis.

A 6-year-old male presented with one week of blindness, difficulty walking and vomiting. He had complained of headache and vomiting for 6 months, which worsened over one week. Examination showed normal power in all limbs, presence of cerebellar signs, slurred speech and bilateral optic atrophy with papilledema. Brain imaging confirmed medulloblastoma with hydrocephalus and spinal metastases.

He received cefazolin injection, 500 mg twice daily, intravenously for seven doses, in peri-operative period for ventriculo-peritoneal shunt, following which he developed derangement in liver function tests (LFT) and prothrombin time, infection with hepatotropic viruses was excluded, other potential hepatotoxic drugs including those used during anesthesia, were also ruled out. Trend of LFT and prothrombin time is summarized in Table 1. His LFT improved after few days of follow up and international normalized ratio (INR) reversed with vitamin K injection. There was no eosinophilia. There was no evidence of bleeding from any sites during this event.

Following improvement in parameters, he underwent midline sub-occipital craniotomy for subtotal resection of the tumor. Stage IV medulloblastoma was diagnosed and he was advised for chemotherapy and radiation.

Our patient developed prolonged prothrombin time and drug induced liver injury (DILI), following the use of cefazolin. The temporal association of the adverse event with the use of this antibiotic and the improvement following its discontinuation pointed toward the association. A re-challenge with the drug would have confirmed it, but it was considered unethical. Using RUCAM scale,¹ this adverse reaction was rated as probable result of cefazolin use.

Cefazolin induced symptomatic coagulopathy was first described in 1974, when a patient with renal failure, on hemodialysis got this antibiotic and the adverse reaction was confirmed by an inadvertent challenge with the same drug again.² In an elegant study by Netelson et al., normal subjects were administered three different first generation cephalosporins, no coagulopathy developed with cefazolin use while abnormalities were detected in few subjects who received cephalothin, authors concluded that coagulopathy due to cephalosporins may be clinically relevant in patients with renal dysfunction and those with concomitant use of other drugs with similar effects.³

Table 1 Trend of Investigations with Respect to Day of Exposure to Cefazolin.

Day of cefazolin exposure	PT (control)	INR	Bilirubin (mg/dl)	Direct (mg/dl)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	GGT (IU/L)
0	13.4 (13.2)	1.02	0.32	0.1	35	23	–	–
4 ^a	100 (13.2)	10.3	–	–	–	–	–	–
5	67.9 (13.2)	6.6	3.11	1.84	6170	4360	264	109
6	43.5 (13.2)	3.95	–	–	–	–	–	–
7	22.4 (13.2)	1.84	1.84	0.8	1595	3040	204	228
8			1.22	0.49	273	1908	328	195
9	16 (13.2)	1.25	1.15	0.5	102	1420	490	185
10	15.4 (13.2)	1.2	0.88	0.2	65	1015	502	175
11	17.1 (13.2)	1.35	0.92	0.3	38	414	258	99
12	14.6 (13.2)	1.12	–	–	–	–	–	–
13	13.9 (13.2)	1.07	1.15	0.4	32	332	119	–

^aCefazolin was stopped on day 4.

PT: prothrombin time; AST: aspartate aminotransferase; ALT; alanine aminotransferase; ALP: alkaline phosphatase; GGT: gamma glutamyl transferase.

Cephalosporin induced coagulation defects have been most often noted with presence of N-methylthiotetrazole (NMTT) side chain examples of which include cefamandole and cefoperazone. Methylthiadiazolethiol (MTDT) side chain, which is present in cefazolin, has been found to inhibit vitamin K-epoxide reductase. Other potential mechanism is, inhibition of vitamin K producing bacteria. These defects have been most commonly noted in patients who are malnourished and have dietary deficiency of vitamin K, they respond well to vitamin K supplementation.⁴

Among the drugs causing DILI, cefazolin was placed in category B (with 12–45 cases reported),⁵ however DILIN group has identified it as underappreciated and, sixth most independent cause of DILI, with a self-limiting, favorable clinical course.⁶

To conclude, since cephalosporin are commonly used group of antibiotics, their adverse effect on coagulation should be remembered, specially in patients receiving anticoagulation and those with liver and renal diseases, which themselves increase bleeding tendency. It is also important to know that cefazolin is not an uncommon cause of DILI, to avoid unnecessary investigations.

CONFLICTS OF INTEREST

The authors have none to declare.

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