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## Cefuroxime-induced thrombocytopenia?

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### Summary

**We present the case of a 77-year-old man who became thrombocytopenic whilst treated parenterally with cefuroxime in the absence of proven infection and recovered when the cefuroxime was discontinued.**

**Keywords:** cefuroxime, thrombocytopenia

Since 1966 there have been a number of case reports suggesting a link between cephalosporin therapy and blood dyscrasias, especially thrombocytopenia.<sup>1</sup> In each case the causal link remains unproven because of the presence of confounding variables and the ethical position that precludes re-exposure of the sensitive individual to confirm the cause and effect. An immunological mechanism has been described in cefotetan-induced thrombocytopenia where potent IgG-cefotetan-dependent antiplatelet antibodies were detected in the patient's serum.<sup>2</sup> An animal model in the dog has also been described.<sup>3</sup>

### Case report

A 77-year-old man known to suffer from mild Alzheimer's disease and recurrent depressive disorder was admitted with a 10-day history of increasing anxiety and agitation and worsening depression. Examination revealed marked psychomotor agitation, perseverations and verbal stereotypies. His cognitive functioning had deteriorated. He appeared physically ill with a fluctuating conscious level, tachycardia, tachypnoea and profuse sweating. He remained apyrexial.

We diagnosed acute confusional state (delirium ICD 10) superimposed on mild dementia precipitating a relapse of his depressive disorder. We started haloperidol 5 mg bid on

admission. Investigations included full blood count, erythrocyte sedimentation rate, mid-stream urine and urinary electrolytes, liver function tests, calcium, glucose, thyroid function tests, VDRL/TPA, three sets of blood cultures, malarial parasites, a chest X-ray and an electrocardiogram.

The significant preliminary result was growth of a *Staphylococcus* species (unspecified) in one blood culture bottle. We commenced cefuroxime 750 mg tid parenterally. We repeated the full blood count on days one and three of cefuroxime therapy and noted the platelet count to have fallen to  $92 \times 10^9/l$ . We considered this to be due to presumed infection or a side-effect of medication. On day five of cefuroxime therapy we received the final microbiological report on the blood culture identifying the organism as *Staphylococcus epidermidis*, a contaminant skin commensal. We stopped cefuroxime and repeated the full blood count days later, finding that the platelet count had risen to  $164 \times 10^9/l$ . Nine days later it was  $325 \times 10^9/l$ . The diagnosis was now a severe depressive episode. A course of electroconvulsive therapy was started on the day after

### Side-effects of cefuroxime

- hypersensitivity reactions
- overgrowth of susceptible organisms
- gastrointestinal disturbance
- pseudomembranous colitis
- haematological parameters altered, including decreased haemoglobin concentration, leucopenia, neutropenia
- positive Coombs test
- transient rise in liver function tests
- pain at injection site
- very rare reports of thrombocytopenia

Box 1

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### Drugs implicated in immune thrombocytopenia<sup>5</sup>

*Drug-dependent platelet-activating IgG (Fc receptor dependent)*

Unfractionated heparin, low molecular weight heparin, pentosan polysulphate, chondroitin sulphate.

*Drug-dependent increase in platelet-associated IgG (Fab-dependent, Fc-independent, binding to glycoproteins IIb/IIIa or Ib/IX or both)*

Quinine, quinidine, vancomycin.

*Drug-dependent increase in platelet-associated IgG (glycoprotein localisation unknown)*

Ampicillin, cephamandole, chlorpheniramine, cimetidine, diazepam, digoxin, gold, hydrochlorothiazide, mianserin, 'sulfa' antibiotics, penicillin, ranitidine, rifampicin.

*Probable drug-induced thrombocytopenia (established by drug rechallenge or drug-dependent phase 1 assay)*

Acetaminophen, acetazolamide, actinomycin, allyl-isopropyl-acetylcarbamide, alprenolol, aminoglutethimide, amiodarone, antazoline, aspirin, carbamazepine, cephalexin, cephalothin, chlorthalidone, chlorthiazide, danazol, desferrioxamine, desipramine, difluoromethylornithine, digitoxin, diflunisal, diphenylhydantoin, ethchlorvynol, furosemide, gentamycin, imipramine, iopanoic acid, levamisole, alpha-interferon, beta-interferon, lidocaine, mepabromate, methicillin, minoxidil, morphine, methyl dopa, nomifensine, novobiocin, paraaminosalicylic acid, phenyl butazone, oxprenolol, naladixic acid, pirenzepine, procainamide, spironolactone, stibophen.

*Possible drug-induced thrombocytopenia (no rechallenge or in vitro testing)*

Apalcillin, butobarbitone, captopril, chlordiazepoxide/clidinium bromide, chlorpropamide, clinoril, clonazepam, diatrizoate, diazoxide, etretinate, fenoprofen, glibenclamide, heroin, indomethacin, isoniazid, levodopa, lincomycin, nitroprusside, oxyphenbutazone, oxytetracycline, pentamidine, piroxicam, primidone, sulindac, ticlopidine, tobramycin, tolbutamide, tolmetin, toluene.

*Drugs with high incidence of mild thrombocytopenia and positive direct platelet-associated IgG*  
Valproic acid, amrinone.

*Drug-induced lupus anticoagulant syndrome and thromboembolism*  
Procainamide.

*Drug-induced haemolytic-uraemic syndrome*  
Quinine, proguanil, penicillin, ampicillin.

*Drug-induced immune haemolytic anaemia with thrombocytopenia*  
Diclofenac, doxepin, glafenine, nomifensine.

### Box 2

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### Learning points

- severe depressive episode can be difficult to differentiate from organic pathology, especially in the elderly
- many drugs are implicated in immune thrombocytopenia, including many commonly prescribed antibiotics
- cefuroxime appears capable of producing a moderately severe thrombocytopenia

### Box 3

stopping cefuroxime. He received four treatments over two weeks; the haloperidol was then reduced and stopped. He made a complete recovery.

### Discussion

Early investigative results suggested a staphylococcal infection which was treated blind with cefuroxime 750 mg tid parenterally for five days. When the platelet count was noted to be falling, other causes of thrombocytopenia were considered. After the final microbiology report, an infective aetiology was less likely. Throughout treatment with cefuroxime the clinical state remained unchanged, as did the neutrophilia. This made it less likely that the patient had an undiagnosed infection that responded to cefuroxime. The only concomitant drug therapy was haloperidol 5 mg bid, not known to cause thrombocytopenia. In the absence of a proven microbiological cause and with resolution on stopping the cefuroxime we believe that the thrombocytopenia can only have been due to the cephalosporin. We considered it unethical to submit him to rechallenge.

Review of the literature reports cephalosporin and penicillin antibiotics to be implicated in immune thrombocytopenia by a drug-dependent increase in platelet-associated IgG. We believe this case to be the first to implicate cefuroxime directly.

4 ABPI Data Sheet Compendium: Cefuroxime, 1995-6, p 656.

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