Fusidic acid (FA) was first introduced in the early 1960s as an active agent against a wide variety of Gram-positive bacteria, especially Staphylococci, Streptococci and Corynebacteria.\(^1\) FA has been used clinically in some Western countries for more than 30 years and recently has been increasingly used to treat methicillin-resistant Staphylococcus aureus (MRSA) infection.\(^2\) The most common adverse effects are mild gastrointestinal discomfort and diarrhea.\(^1,3\) Rarely-reported hematological side effects such as granulocytopenia and thrombocytopenia have been rarely reported in Western populations, but have not been documented in Asian populations. Between January and April 2001, we identified 2 cases of fusidic acid-induced leukopenia and thrombocytopenia after 2 weeks of fusidic acid treatment. In both cases, hematological abnormalities resolved in 3 to 6 days after discontinuation of fusidic acid. The published literature regarding hematological adverse effects caused by fusidic acid is reviewed in this report, and an immune-mediated mechanism is speculated. We recommend periodic complete blood count check in patients receiving long-term fusidic acid treatment to avoid serious hematological adverse effects.

**CASE REPORTS**

### Case 1

An 82-year-old man with a history of penicillin allergy presented with right ankle pain for one day. On examination, his right lower leg was erythematous and swollen, with local heat and pustules. Gram-positive cocci were identified in the pustule aspirate. His hemogram initially showed white blood cell (WBC) count of 11,400/\(\mu\)L, hemoglobin of 15.3 g/dL, and platelet count of 220,000/\(\mu\)L. Under the impression of cellulitis, he received intravenous vancomycin for 16 days. Subsequently, vancomycin was replaced by oral FA. Fourteen days after beginning FA therapy, he developed petechiae in both legs. Complete blood cell count showed leukopenia (WBC count of 1500/\(\mu\)L) and thrombocytopenia (platelet count of less than 10,000/\(\mu\)L). These hematological abnormalities resolved 3 days after discontinuation of FA.
Through out the pe riod of vancomycin and FA treat ment, the pa tient did not take any other med i ca tion. The se rial data of WBC and platelet counts are shown in Fig. 1A.

Case 2

A 62-year-old woman sus tained a left fem o ral shaft frac ture ow ing to a traf fic ac ci dent in 1999 and had re ceived open re duc tion and in ter nal fix a tion op er a tion. Sub se quently, she was found to have osteomyelitis of the left fem o ral shaft, and re ceived a full course of an ti bi otic treat ment. Osteomyelitis re curred in March 2001. The cul tures of bone ex am i na tion from left fem o ral shaft yielded coagulase-negative Staphylococci, which were sen si tive to vancomycin and FA. At that time, her hemogram was within nor mal lim its. She was started on oral FA ther apy. Two weeks after start ing FA, she de vel oped petechiae in both legs. Her hemogram at that time revealed WBC count of 2,730/µL, with 27.7% neu tro phils and 47.9% lym pho cytes, he mo glo bin of 11.6 g/dL and platelet count of 6,160/µL. She was re ferred to our hos pi tal and re ceived trans fu sion of ran dom-donor platelet con cen trates, but thrombocytopenia did not im prove. Bone mar row as pi ra tion showed myeloid and megakaryocytic hyperplasia, sug gest ing periph eral de struc tion (Fig. 2). The other drugs she took concurrently were oral hypoglycemic agents, glipi zide and metformin, which she had been tak ing for many years prior to this ad mis sion. Af ter bone mar row as pi ra tion, FA was re placed by in tra ve nous vancomycin with out dis con tinu a tion of oral hypoglycemic agent. Neutropenia and thrombocytopenia re solved 6 days af ter dis con tinu a tion of FA (Fig. 1B).

DISCUSSION

The he ma to log i cal ad verse ef fects caused by FA are rare. There are 10 pub lished cases of FA-in duced blood dyscrasias.4-8 These in clude 8 iso lated neutropenia, 1 iso lated thrombocytopenia and 1 neutropenia plus thrombo cytopenia. In all the cases, blood dyscrasias de vel oped 4 to 42 days af ter start ing FA ther apy, and re solved 2 to 7 days af ter dis con tinu a tion of FA (Table 1).

Revell et al. and Ev ans re por ted 3 cases of neutropenia during FA and flucloxacilll combination therapy for
osteomyelitis or septic arthritis. The patients’ neutrophil counts dropped after 4, 17 and 42 days of FA and flucloxacillin combination therapy, respectively. All these 3 patients recovered rapidly on cessation of both drugs. A decrease in patient neutrophil count recurred on reinstitution of the FA in the case reported by Revell et al. However, in one case reported by Evans, the neutrophil count dropped 42 days after FA and flucloxacillin treatment, but the neutrophil count remained stable after the reinstitution of FA. It is likely that flucloxacillin instead of FA was the culprit behind neutropenia in this particular case, given the much longer onset time (42 days) than the rest of the reported cases.

Vial et al. reported 5 cases of neutropenia in the course of FA treatment. Neutropenia occurred after a mean of 21 days of FA treatment. Complete recovery occurred in all cases 5 to 9 days after cessation of FA. Bone marrow aspiration were performed in 4 cases, showing normocellularity, hypercellularity (in 2 cases) and moderate myeloid hypoplasia. They were unable to exclude other drugs as a likely cause of neutropenia in all cases, although in 4 cases FA was considered most likely to be responsible.

El-Kassar et al. reported that severe thrombocytopenia (10,000/µL) was noted after 10 days of FA and vancomycin combination treatment for MRSA infection. The platelet count normalized 7 days after cessation of both drugs. Reinstitution of single intravenous infusions of FA and vancomycin resulted in a rapid decrease in platelet count to 4,000/µL within 10 h, but eventually platelet count normalized, 6 days later. In this study, transfusion of random-donor platelet concentrates failed to correct the platelet count in both episodes of thrombocytopenia. An IgG antibody specifically recognizing platelet glycoprotein IIb/IIIa only in the presence of FA but not vancomycin was identified in their patient’s serum, which suggests that thrombocytopenia caused by FA is drug-induced immune thrombocytopenia.

Leibowitz et al. documented a case of neutropenia and thrombocytopenia (22,000/µL) in a patient receiving FA monotherapy for two weeks. Both neutropenia and thrombocytopenia resolved promptly upon discontinuation of FA. In our report, 2 cases of FA-induced neutropenia/leukopenia and thrombocytopenia developed after 2 weeks of oral FA treatment, and hematological abnormality resolved in 3 to 6 days after discontinuation of FA. In Case 2, thrombocytopenia did not improve after transfusion of random-donor platelet concentrates. Peripheral destruction was indicated by bone marrow examination showing megakaryocyte and myeloid hypoplasia, and cytopenias resolved 6 days after re-implanting FA with intravenous vancomycin. Given the prompt recovery of cytopenias after discontinuation of FA in both our and previously published cases, it is very likely that FA-induced hematological adverse effects are immune-mediated.

In Taiwan, FA has been approved for clinical use for approximately 6 years. In our institute, we have frequently used oral FA to replace intravenous vancomycin for the treatment of MRSA infection since January 2000. Among 90 patients treated with FA, one patient (Case 1) who developed leukopenia and thrombocytopenia. To our best knowledge, our report is the first documenting FA-induced hematological adverse effects in the Chinese population. With the increased use

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NA = not available.

* The duration of recovery is 2 days in one case, and not available in another case.

Table 1. Comparisons of duration of onset and recovery of fusidic acid (FA)-induced blood dyscrasia in reported cases

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of FA in the treatment of MRSA, though the risk of hematological adverse effect is rather rare, it should not be overlooked. We recommend weekly complete blood count check after starting FA therapy to avoid severe hematological adverse effects.

REFERENCES


