American Journal of Hematology 15:375–379 (1983)

Aplastic Anemia Associated With Intravenous Chloramphenicol

Jane B. Alavi

Hematology-Oncology Section, Department of Medicine, University of Pennsylvania, Philadelphia

A patient is presented who developed aplastic anemia 3 months after exposure to intravenous chloramphenicol. She died of this disease 4 years later. Other cases of marrow aplasia due to parenteral chloramphenicol are reviewed, in order to emphasize that this complication, although rare, is not restricted to the use of oral chloramphenicol.

Key words: aplastic anemia, chloramphenicol

INTRODUCTION

Chloramphenicol is frequently implicated as a cause of bone marrow aplasia. Because of this hazard, the indications for the use of this compound have been narrowed over the years [1]. Nevertheless, it is still used inappropriately, perhaps in part because there is a common belief that the parenteral form has not been associated with aplastic anemia [2]. A patient encountered recently will be discussed here, to emphasize that parenteral chloramphenicol may indeed cause delayed and fatal marrow aplasia.

CASE REPORT

The patient was a 27-year-old woman who underwent exploratory laparotomy in April 1975 for a mesenteric cyst. The cyst was drained, and a pancreatoduodenostomy was performed. There was no intraabdominal infection or abscess. The postoperative course was uneventful, but the patient was given 12 days of intravenous chloramphenicol in a total dose of 30 g as a prophylactic measure. Extensive search of the hospital and pharmacy records reveals that oral chloramphenicol was never dispensed to this patient.

Laboratory studies obtained in March 1975 included hemoglobin of 13.2 g/dl, hematocrit 37%, leukocyte count 7,100/mm^3 with a normal differential count. In

Received for publication January 25, 1983; accepted April 21, 1983.

Address reprint requests to Dr. Jane B. Alavi, Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104.

April there was mild anemia, but the leukocyte count was again normal, and no unusual bleeding occurred after her surgery. Between March and July 1975, the patient was treated with numerous additional drugs, including erythromycin, tetracycline, nitrofurantoin, gentamicin, prochloperazine, diphenhydramine, folic acid, chlordiazepoxide, oxycodone, iron sulfate, conjugated estrogens, analgesics, and expectorants. She never received phenylbutazone, and there was no history of exposure to industrial toxins or benzene.

In June 1975, ecchymoses and petechiae appeared on the lower extremities. In mid-July she was hospitalized again because of fever and cellulitis of the right ear and face. Laboratory studies revealed hemoglobin 9.7 g/dl, leukocyte count 2,800/mm^3 with 31% neutrophils, and platelet count 40,000/mm^3. When she was referred to the Hospital of the University of Pennsylvania 1 month later, the hemoglobin was 8.5 g/dl, with a reticulocyte count of less than 1%, leukocyte count 3,500/mm^3 with a normal differential, and platelets 34,000/mm^3. A bone marrow biopsy revealed moderate marrow hypoplasia, particularly in the red cell and megakaryocytic series. Over the next month the platelet count dropped to a level of approximately 20,000/mm^3. However, the blood counts then remained relatively stable and she required only intermittent red cell transfusions and had no documented infections until June 1976. At that time the platelet count had fallen to 9,000/mm^3, the leukocyte count to 2,600/mm^3 (37% neutrophils), and she developed more profuse mucosal hemorrhages and began to require platelet and red cell transfusions on a regular basis. She did not respond to 3 months of oxymetholone trreatment and by late 1976 she required platelet transfusions every 7–14 days. A bone marrow biopsy was repeated in June 1977 and this showed less than 10% cellularity. She did not improve after a 5-day course of antithymocyte globulin. During 1977 and 1978, she was maintained with frequent platelet transfusions from an HLA compatible sibling. Her granulocyte count gradually fell to less than 500/mm^3, and she began to have frequent bacterial infections. She died of invasive aspergillosis and hemorrhage in April 1979. The autopsy showed 10% cellularity of the bone marrow without megakaryocytes or erythroid elements.

DISCUSSION

This patient developed aplastic anemia after chloramphenicol administration exclusively by the parenteral route. There is no evidence that she received oral chloramphenicol. The appearance of bruising and infection 2½ months after exposure to chloramphenicol is compatible with the usual time course for this complication [3]. Although she received numerous other medications, none of these is associated with a significant risk of bone marrow aplasia. Chlordiazepoxide has been reported to cause aplastic anemia in one patient [4], and nitrofurantoin in another patient [5]. In contrast, chloramphenicol has been the major drug associated with fatal aplastic anemia in most of the recent reviews. In a review of the reported cases of aplastic anemia from 1950 to 1977, Alter et al [6] found that 20–30% were due to chloramphenicol, and that other drugs were infrequently implicated.

It has been recognized for more than 20 years that chloramphenicol is a dangerous drug with profound effects on the bone marrow [7, 8]. The dose-related, acute bone marrow toxicity is almost always reversible if the drug is discontinued. However, fatal marrow aplasia has been almost exclusively reported to occur as a

later complication, weeks to months after the chloramphenicol therapy. Most of the early reports and larger series describing chloramphenicol-induced aplastic anemia did not mention the route of administration [3]. However, subsequent reports indicated that the oral route was the primary one, or that patients who had received parenteral chloramphenicol may also have been given the oral form of the drug during treatment [9, 10]. As a result, there has been some speculation that fatal bone marrow aplasia may be related to the route of administration. In particular, it has been postulated that intestinal bacteria degraded the oral drug into a toxic compound which was the cause of the marrow damage [11]. This hypothesis was supported by very scanty evidence and never confirmed by other investigators. A more current and well-researched hypothesis regarding chloramphenicol toxicity has been proposed by Yunis and colleagues in a series of recent papers. They suggest that the nitro group in chloramphenicol may be reduced in vivo to a nitroso group, resulting in a compound which they showed to be toxic to hematopoietic stem cells [12]. This nitroreduction could take place either in the human liver or in the intestinal lumen since nitroreductases have been demonstrated in both sites [13]. Thus, marrow damage could theoretically result from either intravenous or oral chloramphenicol.

In recent years, a few reports have described patients who appeared to have developed aplastic anemia in relation to parenteral chloramphenicol. In Wallerstein's study [9], one patient (an 11-year-old girl) was exposed to the oral drug 4 and 6 years prior to the aplasia, but received intramuscular chloramphenicol only 9 months before developing anemia. Two patients developed fatal aplastic anemia after intravenous drug, yet both had early marrow suppression, occurring within 7–12 days, which never improved, and one was also given cimetidine [14, 15]. These are more likely to be examples of dose-related rather than idiosyncratic marrow damage. Two other cases have been described in the European literature. The patient reported by Grilliat et al [16] received intravenous chloramphenicol for 22 days and developed aplastic anemia 6 weeks later. She was given numerous other drugs, but none with a high propensity to cause bone marrow suppression. Domart's patient received 1 g per day intramuscularly for 14 days, 3 months before the diagnosis of aplastic anemia [17].

In addition, a few patients developed aplastic anemia after exposure to the drug by other routes. Two took chloramphenicol eye drops for 2 months to 2 years and developed partially reversible marrow hypoplasia [18, 19]. One patient died from aplastic anemia which was diagnosed 3 months after he discontinued use of chloramphenicol–polymyxin B eye ointment [20]. Another patient developed fatal aplastic anemia after using chloramphenicol eye drops and ointment for 1 month [21]. A shepherd in Italy died of aplastic anemia after 2 years of exposure to chloramphenicol-containing spray which he applied to the feet of his sheep [22]. It is possible that these patients absorbed the drug through the gastrointestinal tract, by a route from the nasolacrimal ducts to nasopharynx and thus to the throat, or there may have been direct systemic absorption from the nasal mucosa.

Several factors may help to explain the paucity of reported cases of aplastic anemia due to intravenous chloramphenicol. First, many patients receive both the oral and perenteral forms of the drug during a single illness. Second, as the indications for the use of chloramphenicol have narrowed in recent years, the patients receiving it have been more seriously ill, and either may not have survived the underlying disease or may have been exposed to additional marrow toxic drugs. Third, the intravenous form of chloramphenicol was prescribed infrequently until recently;

whereas in 1974 the fraction of chloramphenicol sold for parenteral use was 14%, this rose to 55% by 1979 [23]. Fourth, aplastic anemia following chloramphenicol is very rare, occurring only once in 24,000–40,000 patients at risk [3]. The number of cases expected in this country can be estimated. About 5 million grams of chloramphenicol is sold yearly; if half is given by the intravenous route, and the average total dose per course of treatment is 15 g [24], then about 167,000 patients are at risk. Thus, only 4–7 cases of aplastic anemia would be expected in a year.

Since there is no substantial evidence to the contrary, it seems prudent to assume that intravenous chloramphenicol is as likely as oral chloramphenicol to cause irreversible marrow aplasia. Physicians should continue to examine the medical indications for this drug [24–26] and avoid its use in trivial or inappropriate clinical settings.

ACKNOWLEDGMENTS

The author is grateful for the secretarial assistance of Ms. Felicia Shore.

REFERENCES

1. Kucers A: Current position of chloramphenicol chemotherapy. J Antimicrob Chemother 6:1–4, 1980.
2. Glickman RA: Warning—Chloramphenicol may be good for your health. Arch Intern Med 135:1125–1126, 1975.
3. Best WR: Chloramphenicol-associated blood depression. JAMA 201:99–106, 1967.
4. Menon GN: Hypoplastic anemia—An unusual complication of chlordiazepoxide hydrochloride therapy. Postgrad Med J 41:282–283, 1965.
5. Dimant J, Washington AW, Alter AA, Groh D: Side effects after treatment with nitrofurantoin (letter). Arch Intern Med 137:811–812, 1977.
6. Alter BP, Porter NU, Li FP: Classification and etiology of the aplastic anemias. Clin Haematol 7:431–465, 1978.
7. Hodgkinson R: Blood dyscrasias associated with chloramphenicol. An investigation into the cases in the British Isles. Lancet 1:285–287, 1954.
8. Wilson LE, Harris MS, Heustell HH, Witherbee OO, Kahn J: Aplastic anemia following prolonged administration of chloramphenicol. JAMA 149:231–234, 1952.
9. Wallerstein RO, Condit PK, Kasper CK, Brown JW, Morrison RF: Statewide study of chloramphenicol therapy and fatal aplastic anemia. JAMA 208:2045–2050, 1969.
10. Plaut ME, Best WR: Aplastic anemia after parenteral chloramphenicol. Warning renewed (letter). N Engl J Med 306:1486, 1982.
11. Holt R: The bacterial degradation of chloramphenicol. Lancet 1:1259–1260, 1967.
12. Yunis AA, Miller AM, Salem Z, et al: Nitroso-chloramphenicol: Possible mediator in chloramphenicol-induced aplastic anemia. J Lab Clin Med 96:36, 1980.
13. Salem Z, Murray T, Yunis AA: The nitroreduction of chloramphenicol by human liver tissue. J Lab Clin Med 97:881–886, 1981.
14. Daum RS, Cohen DL, Smith AL: Fatal aplastic anemia following apparent "dose-related" chloramphenicol toxicity. J Pediatr 94:403–406, 1979.
15. Farber BF, Brody JP: Rapid development of aplastic anemia after intravenous chloramphenicol and cimetidine therapy. South Med J 74:1257–1258, 1981.
16. Grilliat JP, Streiff F, Hua G: Cytopenie mortelle apres therapeutique par hemisuccinate de chloramphenicol. Ann Med Nancy 5:754–762, 1966.
17. Domart A, Hazard J, Husson R: Aplasie medulaire mortelle apres administration de chloramphenicol par voie intra-musculaire chez deux adults. Sem Hop Paris 37:2256–2258, 1961.
18. Rosenthal RI, Blackman A: Bone marrow hypoplasia following use of chloramphenicol eye drops. JAMA 191:136–137, 1965.
19. Carpenter G: Chloramphenicol eye-drops and marrow aplasia. Lancet 2:326–327, 1975.

20. Abrams SM, Degnan TJ, Vinciguerra V: Marrow aplasia following topical application of chloramphenicol eye ointment. Arch Intern Med 140:576–577, 1980.
21. Fraunfelder FT, Bagby GC, Kelly DJ: Fatal aplastic anemia following topical administration of ophthalmic chloramphenicol. Am J Ophthalmol 93:356–360, 1982.
22. Del Giacco GS, Petrini MT, Janelli S, Carcossi U: Fatal bone marrow hypoplasia in a shepherd using chloramphenicol spray (letter). Lancet 1:954, 1981.
23. Data supplied by Food and Drug Administration to U.S. Senate, in connection with the antibiotic certification program, 1978 and 1980.
24. Fink TJ, Gump DW: Chloramphenicol: An inpatient study of use and abuse. J Infect Dis 138:690–694, 1978.
25. Feder HM, Osier C, Maderazo EG: An audit of chloramphenicol use in a large community hospital. Arch Intern Med 141:597–598, 1981.
26. Roy WA, Federspiel CF, Schaffner W: Prescribing of chloramphenicol in ambulatory practice: An epidemiologic study among Tennessee Medicaid recipients. Ann Intern Med 84:266–270, 1976.