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BONE MARROW DEPRESSION INDUCED BY CHLORAMPHENICOL OR PHENYLBUTAZONE

LEUKEMIA AND OTHER SEQUELAE

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With two registries for adverse drug reactions, a follow-up survey was made of 151 cases reported of bone marrow depression following use of chloramphenicol (124 patients), phenylbutazone (24), or both drugs (3). Leukemia subsequently developed in three patients with bone marrow depression attributed to use of chloramphenicol, but only one had characteristics suggesting a cause-and-effect relationship between drug exposure and leukemia. A review of clinical and epidemiologic information provides inadequate evidence that either drug is leukemogenic. Among other sequelae in the survey were four cases of hemolytic anemia; these four cases included two with paroxysmal nocturnal hemoglobinuria. Several problems arise in evaluating a causal association between drug exposure and diseases such as leukemia.

The etiology of human leukemia is generally considered to be obscure. Epidemiologic studies, however, have demonstrated that sufficient doses of ionizing radiation can induce chronic myelocytic leukemia or acute leukemia.¹⁻⁴ Furthermore, clinical observation suggest strongly that these forms of leukemia are causally related to prolonged exposure to benzene.⁵ Since ionizing radiation and benzene are bone marrow depressants, one may suspect leukemogenic potential in other agents that cause marrow hypoplasia. The possibility is consistent with observations that aplastic anemia occasionally precedes the diagnosis of chronic myelocytic leukemia and acute leukemia.⁶ This "preleukemic" period, which may last many years, has been noted following exposure to radiation or benzene.⁷

A number of drugs with the capacity to depress bone marrow function have been suspected in the etiology of certain cases of leukemia, usually on the basis of case studies or uncontrolled surveys of leukemia patients. Among these drugs have been chloramphenicol,⁸⁻¹⁰ sulfonamides,¹¹ aminopyrine,¹² and amphetamine sulfate.¹³ Recently, interest has focused on phenylbutazone, for since 1960 a total of 29 cases of leukemia have been reported following its use.¹⁴⁻²⁷ Since there has been no information on the populations treated with this drug, it is unknown whether or not the leukemia cases were chance occurrences.

This paper presents the findings of a follow-up survey of cases previously reported to two drug-reaction registries because of bone marrow depression attributed to chloramphenicol or phenylbutazone, the drugs most commonly reported to cause aplastic anemia.²⁸ The study was undertaken to determine the frequency of leukemia following marrow depression and to evaluate evidence that either of the drugs may be leukemogenic.

MATERIALS AND METHODS

The patients with drug-induced bone marrow depression were ascertained from the Registry on Adverse Reactions of the American Medical Association (AMA) and the Adverse Reactions Branch of the Food and Drug Administration (FDA). Officials at each registry prepared a roster of physicians (total, 180) who had reported one or more cases (total, 234) of marrow depression attributed to phenylbutazone or chloramphenicol between 1954 and 1965. The marrow depression consisted of erythroid hypoplasia, leukopenia, thrombocytopenia, or pancytopenia, and was presumed to be exclusive or recognized leukemia, or other diseases or agents that might induce blood dyscrasias. Each physician was notified of the intended survey by a letter from registry officials, and was asked if we might contact him for follow-up information. The AMA and FDA then sent us a listing of 126 physicians who replied to the letter and were willing to participate in the survey, along with the number of cases reported by each physician. Because of confidentiality of the data, neither registry divulged any information on individual patients prior to the survey.