The present studies suggest the following modus operandi for chloramphenicol therapy: (1) for trivial infections avoid the use of the drug altogether; the risk of chloramphenicol treatment may be greater than that of the disease itself; (2) obtain serial reticulocyte counts on all patients receiving chloramphenicol; and (3) if the reticulocyte counte drops abruptly or falls below 0.5%, obtain a bone marrow aspirate for study. Stop therapy with the drug if vacuoles are seen in the primitive rubriblasts or if there is a marked reduction in the erythropoietic activity of the marrow. Although in this series leukopenia and thrombopenia were always accompanied by erythropoietic abnormalities, the possibility of selective depression of these elements can not yet be completely discarded.

At the present time lack of knowledge regarding the mechanism of toxicity makes it difficult to predict which patients will develop irreversible marrow depression as a result of chloramphenicol treatment. On the one hand, the morphologic changes in the marrow and their frequency along with evidence of dose-dependency in some patients suggests a direct chemical effect.[1, 3a] On the other hand reports of bone marrow hypoplasia after token doses of chloramphenicol are compatible with a hypersensitivity phenomenon.[8] Both direct toxic poisons and hypersensitivity reactions[9] may cause vacuolization of cells. The fact that in vitro studies done outside the humoral environment within the host have failed to demonstrate metabolic abnormalities induced by therapeutic levels of the drug[10, 11] is consistent with but does not prove a hypersensitivity mechanism for toxicity. The sensitivity of erythropoiesis to chloramphenicol noted in this study may be a result of the more ready diffusion of free chloramphenicol into red cell precursors than into the other cells of the marrow.[12] Despite common belief, the toxicity is probably not related to the nitrobenzene ring of chloramphenicol, since an analogue without this structure proved to be considerably more toxic.[13]

This and other studies indicate that most patients developing chloramphenicol toxicity seem to pass through 2 phases of marrow depression, an initial reversible period of variable duration followed by an often serious period of damage which does not remit until the drug is stopped and may not remit, no matter what is done. Early in the reversible stage rapid recovery follows cessation of treatment. Later in the reversible stage, cessation of therapy is followed by a slower return of the marrow to normal. These same principles which apply to the erythropoietic system also apply to depession of thrombopoiesis and leukopoiesis by chloramphenicol. In a few patients, the reversible stage may be quite short. This may be because of prior therapy, high doses, or of hypersensitivity. One or all of these factors may be enhanced by high drug levels caused by high doses or abnormalities in drug metabolism as in liver disease. Our present state of knowledge does not permit more than a speculative explanation for the underlying mechanism for the toxic effects of chloramphenicol reported in this study.

SUMMARY AND CONCLUSIONS

Fifteen patients with bone marrow depression associated with chloramphenicol treatment are presented. Erythropoiesis was most often affected, followed in order by suppression of thrombopoiesis and leukopoiesis. Monitoring erythropoiesis by serial reticulocyte counts during chloramphenicol therapy has been found to be of value in detecting early evidence of drug toxicity.

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