the drug with the patients in a fasting state. This tended to minimize fluctuation in serum iron due to diurnal variation and changes in chloramphenicol blood levels due to difference in rate of absorption from the gastrointestinal tract.

The reason for the correlation of erythropoietic depression with high free chloramphenicol levels is not known. Studies on the mechanism of chloramphenicol toxicity in vitro have, in general, revealed no effect on immature erythrocytes or bone marrow function unless levels far exceed those found in the blood when therapeutic doses of the drug are employed.[9,10] The amount of chloramphenicol required to produce in vitro depression far exceeds the levels observed in this study. Although protein synthesis by bacterial ribosomes in cell-free systems is readily inhibited by chloramphenicol, mammalian ribosomes are not affected by remarkably high concentrations of chloramphenicol.[11,12] This biological difference makes it possible to use chloramphenicol advantageously in the treatment of bacterial infections. However, chloramphenicol probably does have some effect on hemoglobin synthesis since the drug blocks the reticulocyte response in patients with pernicious anemia receiving cyanocobalamin (vitamin B_{12}) and also prevents the reticulocyte response to iron in patients with iron deficiency anemia.[13] Since patients with liver disease and renal disease are known to have a shortened erythrocyte life-span and an inadequate marrow compensatory activity, chloramphenicol might be expected to induce anemia with greater frequency in these patients. However, bone marrow function as reflected by peripheral blood values did not appear to be a factor in the development of toxic effects.

The manner in which chloramphenicol affects hemoglobin synthesis in immature cells is not known. Preliminary experiments indicate that chloramphenicol may interfere with the deposition of messenger ribonucleoprotein on the ribosomes of mammalian reticulocytes.[14] Whether these observations are related to the profound changes that occur in iron metabolism is still speculative. Nevertheless, the serum iron is a sensitive index of early toxic effects and often begins to rise three-four days after beginning treatment. Similarly when the drug is stopped, the serum iron promptly returns to pretreatment levels. These changes in serum iron and per cent saturation of IBG are consistent and may represent a specific biochemical lesion produced by the drug. The majority of the patients who did not develop toxic effects did show slight elevation in serum iron during treatment, but these were not sufficient to be interpreted as being significant of toxicity. In addition, other bone marrow depressants such as radiation, alkylating agents, and antimetabolites do not produce a consistent elevation of serum iron and per cent saturation of IBG.

The relationship of erythropoietic depression to aplastic or hypoplastic states associated with chloramphenicol remains unknown. However, it is reasonable to assume that the erythropoietic depression observed in this study represents a reversible stage in the development of aplastic anemia that is usually irreversible. Therefore, in severe renal or liver disease chloramphenicol should be used with caution and followed carefully with frequent serum iron and reticulocyte counts. If possible, determination of free chloramphenicol in the serum would be an additional safeguard. In liver disease the presence of both ascites and jaundice or other evidence of severe parenchymal damage constitutes a contraindication to the use of this drug.

SUMMARY

In 16 patients with liver disease treated with chloramphenicol eight developed erythropoietic depression. In this group with liver disease, the frequency of toxic effects was markedly increased in the presence of both ascites and jaundice. In 19 patients with moderately severe renal disease six showed signs of toxic effects. A group of 16 patients without renal or liver disease showed no evidence of bone marrow toxic effects.

An elevated level of serum free chloramphenicol was found in all instances of erythropoietic depression. There was no correlation between the metaoblic products of chloramphenicol and toxicity. Drug hypersensitivity did not appear to a factor in the development of erythropoietic depression.

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