PROCEEDINGS OF THE

# BRITISH PHARMACOLOGICAL SOCIETY

28th and 29th MARCH, 1972

UNIVERSITY OF BIRMINGHAM

## COMMUNICATIONS

In communications with more than one author, an asterisk (*) denotes the one who presented the work.

### Multiple emulsions, a suitable vehicle to provide sustained release of cancer chemotherapeutic agents

CHRISTINE J. BENOY*, L. A. ELSON and R. SCHNEIDER

*Department of Clinical Pharmacology, Medical School, Birmingham and Institute of Cancer Research, Surrey*

Multiple emulsions had first been suggested as a method of producing prolonged antibody response instead of Freund's adjuvant, because of their notable advantage of low viscosity and consequent ease of injection (Herbert, 1965). The use of a number of drugs in the form of a multiple emulsion has been developed at Birmingham.

A multiple emulsion consists of an internal primary aqueous phase dispersed in an oily phase which is further dispersed in an external secondary continuous aqueous phase. Cancer chemotherapeutic agents may be incorporated into the primary aqueous phase, the rate of release of which may be controlled by varying the three basic parameters of the water-in-oil emulsion, the internal phase volume, the concentration of primary detergent, and the osmolarity of the disperse phase.

Some preliminary work on methotrexate sodium containing multiple emulsions showed an enhanced therapeutic activity against the $L_{1210}$ leukaemia compared with treatment with the drug in aqueous solution (Elson *et al.*, 1970).

Further work carried out on multiple emulsions containing cancer chemotherapeutic agents have produced most encouraging results. A single dose of the optimum methotrexate sodium containing multiple emulsion formulation tested in mice implanted with the R1 lymphoma was found to be more effective in preventing the death of mice, not only than a single injection of methotrexate sodium in aqueous solution, but also of five daily aqueous injections of the drug at the same dose level.

A similar result was obtained when the effect of multiple emulsions containing methotrexate was investigated on the haematological response of rats. A single large dose of aqueous methotrexate sodium (10 mg/kg) was similarly effective as the multiple emulsion (2 mg/kg) in lowering the numbers of white cells, but was

more toxic, causing diarrhoea and severe weight loss. The multiple emulsion caused no weight loss and only slight diarrhoea in some cases. If folinic acid was administered three days after treatment with methotrexate sodium containing multiple emulsion, the reduction in the white cell count was unaffected but recovery was rapid, and a large secondary neutrophilia resulted. Earlier administration of folinic acid, however, prevented so profound a reduction in the white cell count, and promoted an earlier recovery from the effect of the emulsion with only a small secondary neutrophilia.

A single injection of cytosine arabinoside in a multiple emulsion was as effective as five daily doses of the drug in aqueous solution at the same dose level.

Vinblastine sulphate as a single aqueous injection caused a gradual increase in the number of bone marrow cells arrested in metaphase for up to four hours after administration. When the drug was administered in a multiple emulsion, the increase in the number of arrested metaphases was still continuing after 48 hours.

REFERENCES

ELSON, L. A., MITCHLEY, B. C. V., COLLINGS, A. J. & SCHNEIDER, R. (1970). Chemotherapeutic effect of water–oil–water emulsion of methotrexate on the mouse $L_{1210}$ leukaemia. *Europ. J. Clin. & Biochem. Res.*, **15**, 87.

HERBERT, W. J. (1965). Multiple emulsions; a new form of mineral–oil antigen adjuvant. *Lancet*, **ii**, 771.

## The role of iron in the metabolism of tissue ascorbic acid

A. ODUMOSU* and C. W. M. WILSON

*Department of Pharmacology, University of Dublin, Trinity College, Dublin 2, Ireland*

Lipschitz *et al* (1971) studied the effect of altered ascorbic acid (AA) tissue stores on iron metabolism in scorbutic male guinea-pigs. They showed that the hepatic iron concentration is decreased and that the release of iron from different body stores is affected by AA tissue levels. A corresponding study has been carried out on female guinea-pigs in which the effect of alteration of tissue iron stores has been investigated on AA metabolism. Three groups of guinea-pigs (Fe, FeD and Sc) were placed on a scorbutic diet supplemented with AA 20 mg orally daily (Odumosu & Wilson, 1970) during which each animal in Group Fe received a total dose of 100 mg active iron as ferrous sulphate by stomach tube. Group FeD received the same dose of iron, but between days 15–20, the animals each received 1·0 g desferrioxamine. Group Sc received only the diet and AA supplement. Administration of the supplement was stopped on the twentieth day (Day 0). Plasma and liver concentrations of AA and iron were measured on Day 0, Day 24, and Day 36 of the scorbutogenic diet (Table 1). On Day 0, plasma AA concentrations were highest in the Fe group which also had the highest value for plasma iron. On Day 24, plasma AA was significantly lower in the Sc group than in the other two groups, which had received iron. It can be concluded that tissue iron overload is associated with raised plasma AA levels. On Day 0, hepatic AA concentrations were similar in all the groups even though hepatic iron concentrations were highest in the Fe group and lowest in the Sc group. It can be concluded that hepatic iron does not affect liver AA concentrations in the presence of tissue AA saturation. On Day 24 hepatic AA was highest in the Sc group and lowest in the Fe group.