PRELIMINARY COMMUNICATIONS

Methodichlorophen as Anti-tumour Drug

L. A. PRICE, J. H. GOLDIE, BRIDGET T. HILL

British Medical Journal, 1975, 2, 20-21

Summary

Methodichlorophen was given to 26 patients with terminal malignant disease. Eight patients received adequate doses, and five of them showed objective evidence of tumour regression while three failed to respond. Those who responded included four out of five patients with lung cancer (three with squamous-cell carcinoma and one with oat-cell carcinoma) and a patient with hypernephroma. Two patients with testicular teratomas and one with acute myeloid leukaemia failed to respond. The drug may be given safely by mouth to outpatients if certain precautions are taken.

Introduction

Diaminopyrimidines possess antitumour activity in tissue culture, animals,² and man.^{3,4} Our interest in methodichlorophen* (2, 4-diamino-5-(3', 5'-dichlorophenyl)-6-methylpyrimidine; B.W.50197) was stimulated by the observation that it inhibited the growth of a methotrexate-resistant animal tumour⁵ and was the most effective antitumour diaminopyrimidine in other experimental systems.¹ Using a simple tissue-culture technique we confirmed its effectiveness against methotrexate-resistant cells and predicted that (a) the drug would be most effective if given in the highest possible dose for the longest possible time⁶ and (b) it might be possible to protect methotrexate-sensitive cells (found in human bone marrow) but still retain a lethal concentration of the drug in the methotrexate-resistant cells (found in various tumours) by giving folinic acid at the same time.⁷ We report here the preliminary results of the application of these principles in clinical practice.

Patients and Methods

All the patients studied were considered to have terminal disease because either no treatment existed for their tumour or, more usually, that the condition was inoperable and resistant to radiotherapy and a variety of antitumour drugs. Methodichlorophen was given in doses varying from 1.5 to 4 mg/kg. The average dose was 2.2 mg/kg once a

*The name methodichlorophen is under review by the Wellcome Foundation and may be changed.

Institute of Cancer Research, Royal Marsden Hospital, London SW3 6JJ

L. A. PRICE, M.R.C.P., Senior Lecturer in Medicine and Honorary Consultant Physician

St. Michael's Hospital, Toronto, Canada

J. H. GOLDIE, M.D., F.R.C.P., Consultant Physician

Department of Cellular Pathology, Imperial Cancer Research Fund Laboratories, London

BRIDGET T. HILL, PH.D., Senior Scientist

week by mouth. Calcium folinate (Leucovorin, Lederle) was given at the same time by mouth, intravenously, or intramuscularly in an average dose of 45 mg. A routine peripheral blood count was taken just before treatment every week. If there was moderate depression of the platelet count no methodichlorophen was given, but the usual dose of calcium folinate was always given. If severe depression of platelets occurred the principle of folinic acid "rescue" was applied—that is, methodichlorophen was omitted and 15 mg of calcium folinate given every six hours for four days or until the marrow recovered. Baseline clinical or radiographic measurements of tumour size were recorded before the first treatment and again after six weeks' treatment. Response was defined as a 50% reduction in tumour size.

Results

Twenty-six patients received the drug, but 13 died before receiving adequate doses of methodichlorophen—that is, at least six doses of at least 2 mg/kg at weekly intervals. Of the remaining 13 five patients were clinically unchanged and were continuing on the drug at the time of writing, five responded, and three did not respond. The three failures were two patients with testicular teratomas and one with acute myeloid leukaemia. Of the five who were clinically unchanged three had carcinomas of the prostate, one had squamous head and neck cancer, and one had carcinoma of the lung. The five who responded included four with lung cancer (three with squamous-cell and one with oat-cell carcinoma) and one with hypernephroma.

CLINICAL DETAILS OF RESPONDERS

Case 1.—A 62-year-old man with squamous-cell carcinoma of lung and brain metastases had had radiation treatment and three courses of combination chemotherapy using adriamycin, methotrexate, cyclophosphamide, and vincristine. His response to methodichlorophen stopped after two and a half months of treatment.

Case 2.—This 54-year-old man had a disseminated hypernephroma with large deposits on chest wall, brain, left clavicle, and lungs. He had been treated with radiation to painful areas, medroxyprogesterone acetate, and dexamethasone. His response to methodichlorophen continued after one year's treatment.

Case 3.—Squamous-cell carcinoma of lung with liver metastases was shown on scanning and confirmed by liver biopsy in this 65-year-old man. He had had no treatment. His response to methodichlorophen continued after three months of treatment.

Case 4.—A 55-year-old man with squamous-cell carcinoma of lung had been previously treated with radiation. Response to methodichlorophen continued after three months' treatment.

Case 5.—Oat-cell carcinoma of lung was confirmed histologically in this 66-year-old man. He had had six courses of combined therapy consisting of adriamycin, methotrexate, cyclophosphamide, and vincristine. His response to methodichlorophen continued after three months' treatment.

SIDE EFFECTS

Three patients developed marrow depression despite folinic-acid protection, but this was always reversible by folinic-acid rescue. Four patients felt hazy and one developed a severe frontal headache. Both these symptoms are particularly likely to occur on doses over 3 mg/kg and can be prevented by reducing the dose. A blotchy erythematous rash mainly on the trunk occurred in three patients, but if it was essential to continue with methodichlorophen the rash could be blocked by corticosteroids. Two patients mentioned looseness of the bowels not amounting to diarrhoea, which was easily treated with codeine phosphate. All patients said that these side effects were minor compared with those of their previous drug therapy.

Discussion

Though we studied few patients, we are encouraged by the response in patients with lung cancer, especially since three had the squamous-cell type, which is notoriously resistant to standard antitumour drugs. Methodichlorophen is lipophilic and so reaches high concentrations in the lung, brain, adrenals,

Case 3. Chest x-ray pictures (a) immediately before treatment and (b) after six weeks on methodichlorophen.

kidney, and pancreas.⁸ Since tumours in these sites respond poorly to present antitumour agents we propose to extend the trial to include more tumours in these organs in the hope of identifying a subgroup which might respond well to the drug. If activity against lung tumours is confirmed we plan to set up a study in which methodichlorophen would be given as adjuvant therapy for bronchial carcinoma immediately after primary treatment with surgery or radiation in "bad risk" groups.

Methodichlorophen has a half life of about eight days,⁹ which ensures a prolonged concentration in the sites mentioned above.

The simultaneous administration of folinic acid, however, protects the bone marrow from the antifolate depressant effects of the drug while lethal concentrations of the agent remain in the tumour. The mechanism of this "selective folinic-acid protection" is not clear, but there are at least two possible explanations. In tissue culture folinic acid blocks the uptake of methodichlorophen into methotrexate-sensitive cells but does not affect its uptake into methotrexate-resistant cells.⁷ Therefore an exploitable transport difference may exist between bone marrow and methotrexate-resistant tumour cells. Alternatively the lipophilic nature of methodichlorophen might cause relatively more of it to be retained in the tumour compared with folinic acid. Whatever the explanation selective folinic-acid protection can be used clinically to protect the marrow to a very large extent without apparently reducing the antitumour effect. Hence, treatment can be given in the outpatient department if the patient is well enough. Moderate marrow depression can usually be corrected by omitting the drug and giving a dose of calcium-folate of about 60 mg, though we do not know why one dose of calcium folinate should reverse the depression. If severe marrow depression occurs the patient should be admitted to hospital and given a standard folinic-acid rescue. Methodichlorophen can then be restarted with a higher concurrent dose of calcium folinate—for example, 75 mg.

Since the mechanism of most antitumour drugs is unknown it is inadequate to assess "antifolates" simply in terms of their ability to inhibit the enzyme dihydrofolate reductase (DHFR). Methodichlorophen is a much weaker inhibitor of DHFR than methotrexate,⁶ but it is greatly superior for killing the methotrexate-resistant cells which are often encountered clinically. Potentially valuable antitumour drugs may thus be excluded on the criterion of DHFR inhibition, and the use of resistant tumour cells in tissue culture may be a far more relevant model for approaching clinical problems than the traditional enzymatic approach. Before methodichlorophen's value in clinical cancer chemotherapy can be accurately defined further clinical trials must be performed.

We thank the Wellcome Foundation for supplies of methodichlorophen and acknowledge our many helpful discussions with Dr. C. A. Nichol and Dr. A. D. H. Griffith. We also thank Professor P. K. Bondy for helpful comments during the preparation of the manuscript. L.A.P. is grateful to colleagues at the Royal Marsden Hospital who referred the patients to this trial.

Requests for reprints should be sent to Dr. L. A. Price, Royal Marsden Hospital, Fulham Road, London SW3 6JJ.

References

- ¹ Clarke, D. A., *et al.*, *Cancer Research*, 1952, 12, 255.
- ² Sugiura, K., *Cancer Research*, 1953, 13, 431.
- ³ Murphy, L. M., *et al.*, *Journal of Clinical Investigation*, 1954, 33, 1388.
- ⁴ Geils, G. F., *et al.*, *Blood*, 1971, 38, 131.
- ⁵ Nichol, C. A., *Advances in Enzyme Regulation*, 1968, 6, 316.
- ⁶ Hill, B. T., Goldie, J. H., and Price, L. A., *British Journal of Cancer*, 1973, 28, 263.
- ⁷ Hill, B. T., Price, L. A., and Goldie, J. H., *Biochemical Pharmacology*, 1975, 24, 535.
- ⁸ Stickney, D. R., *et al.*, *Proceedings of the American Association of Cancer Research*, 1973, 14, 52.
- ⁹ Nichol, C. A., personal communication, 1973.