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Letters to the Editor

RENAL FUNCTION AND ELECTROLYTE DISTURBANCES IN NORMOCALCAEMIC AND HYPERCALCAEMIC PATIENTS TREATED WITH MITHRAMYCIN

Several authors have drawn attention to the side-effects arising after intravenous infusion of Mithramycin. Gastrointestinal complaints are the most frequent. Several workers (Baum, 1968; Brown and Kennedy, 1965; Kennedy, 1970; Ream *et al.*, 1968) have also noted the possibility of renal intolerance. To our knowledge no precise study of renal function has been carried out in the course of the administration of Mithramycin.

Seven men and 10 women suffering from malignant disease, 8 of them having hypercalcaemia, were treated with an intravenous perfusion of Mithramycin. A study of the renal function was carried out. A loading dose of Inulin and P.A.H. was given at time t_0. The serum concentrations of Inulin and P.A.H. were kept constant by maintenance infusion at a constant rate of 2 ml/min. This infusion continued throughout the 270 min of the investigation. In the first period or control period, two specimens of urine were collected (u_1 and u_2) corresponding to successive 10 min periods and two samples of blood (b_1 and b_2) were taken at the middle of each urine collection period. The Mithramycin infusion diluted in 5% dextrose solution was then started at a rate of 25 μg/kg over 3 hours. Three specimens of urine were taken, each corresponding to a period of 1 hour (u_3, u_4 and u_5). Three blood samples were also taken (b_3, b_4 and b_5). After stopping the Mithramycin infusion, two specimens of urine (u_6 and u_7) were taken, after two successive intervals of 20 min and two blood samples were also taken (b_6 and b_7).

The following results were recorded:

1. The intravenous infusion of 25 μg/kg of Mithramycin at a constant rate over 3 hours is well tolerated. The only abnormal manifestation was the development in one patient of a moderate degree of oedema of the eyelids 30 min after the beginning of the infusion, but this did not necessitate arrest of the treatment.

2. Our results demonstrate the absence of any change in glomerular filtration or P.A.H. clearance following a short infusion of Mithramycin.

3. We observed no plasma concentration variations of sodium, chloride, magnesium and phosphorus throughout the infusion of Mithramycin but plasma potassium was reduced in our 17 patients ($4{\cdot}08 \pm 0{\cdot}42$ before and $3{\cdot}53 \pm 0{\cdot}27$ after Mithramycin). This variation in plasma levels was not accompanied by an increase of the urinary output of potassium. Hypokalaemia was also reported by Baum (1968) and by Ryan, Schwartz and Northrop (1970) but no systematic study of the variations in plasma potassium had been undertaken in their patients.

4. The serum calcium level falls constantly during the intravenous infusion of Mithramycin. The fall in serum calcium varies in degree, is transient and often insufficient to rectify any marked hypercalcaemia. The maximal change seen in our hypercalcaemic patients was 2·0 mg% and in patients with normal serum calcium the maximal change was 0·6 mg%. This fall in serum calcium is never associated with an increase of the urinary calcium excretion. An increase of the urinary phosphate excretion was noted at the end of the perfusion. A secondary secretion of parathormone could explain the increased phosphaturia and the limited action of the Mithramycin.

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METASTATIC KIDNEY CANCER TREATED WITH MULTIPLE DRUG THERAPY AT THE ROTTERDAM RADIOTHERAPY INSTITUTE

Sir,—Price and Goldie (1971) reported promising preliminary results of multiple drug therapy in the treatment of metastatic solid cancer. Based on these data it was decided to assess the possibilities of a slightly modified form of treatment in patients with metastatic kidney cancer.

Between 1971 and 1973 18 patients were submitted to multiple drug chemotherapy (Table). All patients had proven adenocarcinoma of the kidney. The histological diagnosis was made either on the nephrectomy

TABLE.—*Rotterdam Radiotherapy Institute Multiple Drug Therapy*

At 0 h	
Cyclophosphamide	700 mg/m², max. 1 g i.v.
5-fluorouracil	500 mg/m², max. 1 g i.v.
Vincristine	1 mg/m², max. 2 mg i.v.
Methotrexate infusion	25 mg/m², in a 6 hours infusion, 4 times. Total max. 200 mg.
At 24 h	
120 mg folinic acid i.v.	
At 30 h	
15 mg folinic acid i.m., 5 times, at 6 h intervals	
Repeated every 4 weeks.	

specimen or on a biopsy taken from a metastasis. All patients had multiple skeletal—and/or lymph node—and/or soft tissue—and/or visceral metastases. All patients had measurable signs of progressive growth of their malignancy.

Pulmonary metastases were not considered to be reliable for assessing progress of metastases as in a previous study it became evident that these metastases have a tendency towards unpredictable spontaneous fluctuation and regression (Werf-Messing and Gilse, 1971).

Painful or "dangerous" lesions, for instance metastases with risk of fracture, cord compression, inferior vena cava obstruction, etc, were treated by radiotherapy.

Eighteen patients (4 females and 14 males) selected according to the above mentioned criteria, received multiple drug therapy. The majority of patients had previously been treated unsuccessfully with megestrol acetate, 60 mg daily. The average age of the patients was 61 years.

Because of serious complications, progressive metastases or death in spite of chemotherapy, only one course was given in 2 cases. For the same reasons treatment was not repeated after two courses in 5 cases; 11 patients received three or more courses of multiple drug therapy.

In no case could objective response to chemotherapy be detected. Slight subjective improvement was observed in one patient. In another case it was doubtful whether subjective improvement was real or just the improvement after recovery from side-effects of chemotherapy.

As a rule the complications of this treatment were not severe: severe nausea (6 cases), severe thrombopenia (1 case), loss of hair (2 cases, of which one in combination with severe nausea), cardiac failure (1 case), ulceration of buccal mucosa (3 cases), sepsis (1 case), candida infection (1 case).

Though the report of Price and Goldie was encouraging, kidney cancer patients at the Rotterdam Radiotherapy Institute had no demonstrable objective benefit by multiple drug therapy. The complication rate would have been acceptable had the