PROPHYLAXIA OF CYSTINE CALCULOSIS BY α-MERCAPTOPROPIONYL-GLYCINE ADMINISTERED CONTINUOUSLY OR EVERY OTHER DAY

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INTRODUCTION

Cystinuria is a complex autosomal recessive inherited disorder found in approximately one out of 7000 births (1). The disease affects the renal tubular reabsorption of certain filtered amino acids, i.e., cystine, lysine, arginine and ornithine. Owing to the defective intestinal transport of these amino acids, three types of cystinuria may occur (2). The disease occurs equally in both sexes, but males are severely affected and have a higher mortality rate.

The main clinical manifestation of the disease is cystine nephrolithiasis. Cystine calculi precipitation and formation take place when cystine urine concentration exceeds the limit of solubility (1.580 μmol/l at a temperature of 37°C and pH = 7). α-mercaptopropionyl-glycine (α-MPG) reacts with cystine in a disulphide-exchange reaction, leading to the production of a mixed disulphide (which is significantly more soluble than cystine) and cysteine. Therefore a α-MPG can be useful in the therapy and prevention of urine calculosis.

The prophylaxis requires the drug to be administered orally on a long-term basis (3,4). Remien et al. (5) and Hautmann et al. (6) stated that α-MPG supply must be permanent; hyperlipidaemia secondary to this therapy may occur (7). Therefore it is important to define the amount and modalities of drug administration for the prevention of cystine calculosis (8).

The aim of this paper is to demonstrate that cystine calculosis can be prevented by administering a low dose of α-MPG to the patient either continuously or every other day.

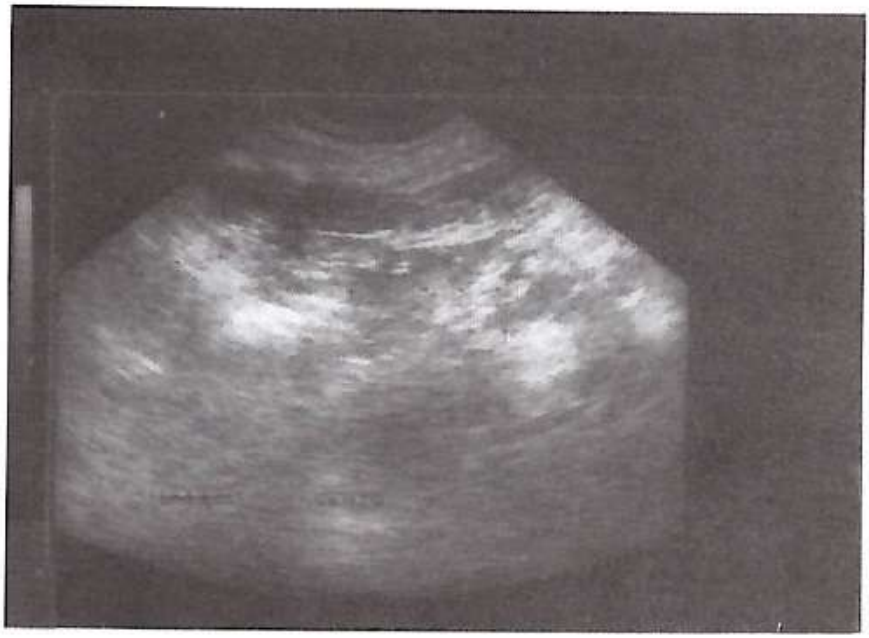
MATERIALS AND METHODS

M. Vincenzo, a 29-year-old male, presented left kidney hypoplasia and a typical homozygous cystinuria type I which was diagnosed at 13 years. Calculosis of the bladder had been surgically removed two years previously. The treatment given to the patient was aimed at preventing the formation of new calculi. Further lithiasis was prevented by means of α-MPG (Santen Pharmaceutical Co. Ltd., Osaka, Japan) continuously administered in two divided doses. The boy was given 14 mg kg^{-1} day^{-1} of the drug for 3 years, followed by 1.5 mg kg^{-1} day^{-1} for 6 months. The dosage was prudently raised to 2.5 mg kg^{-1} day^{-1} for 6 months, then decreased to 2 mg kg^{-1} day^{-1} for 3 years, set at 4 mg kg^{-1} day^{-1} for the remaining 7 years and 6 months, and eventually at 4 mg kg^{-1} day^{-1} every other day for 1 year without either calculosis or side effects being observed (fig. 1).

Repeated measurements of creatininaemia, azotaemia, glycaemia, cholesterolaemia, red and white blood cells and urine analysis gave normal results.

M. Giovanni, a brother of Vincenzo, aged 24, presented left renal hypoplasia (glomerular filtration rate = 5 ml/m') and a typical homozygous cystinuria type I, with bilateral calculosis (fig. 2) first diagnosed at 5 years. Calculi were dissolved by means of α-MPG and, in absence of calculi, prophylaxis of calculosis was performed with the same drug. α-MPG was continuously administered in two divided doses of 10-4 mg kg^{-1} day^{-1} for 4 years and then, in accordance with the previous case, of 4 mg kg^{-1} day^{-1} for 5 years.

Since neither calculosis nor any side-effects were observed, the patient was administered 4 mg kg^{-1} day^{-1} of α-MPG in one dose every second day for 2 years. The kidney ultrasound scanning (fig. 3) and abdomen X-ray showed no calculosis. Repeated measurements of creatininaemia, azotaemia, glycaemia and red and white blood cell count were normal. At the age of 22 the patient arbitrarily discontinued the treatment with α-MPG. After 6 months, the subject complained of abdominal pain and vomiting, and presented hyperazotaemia and hypercreatininaemia.



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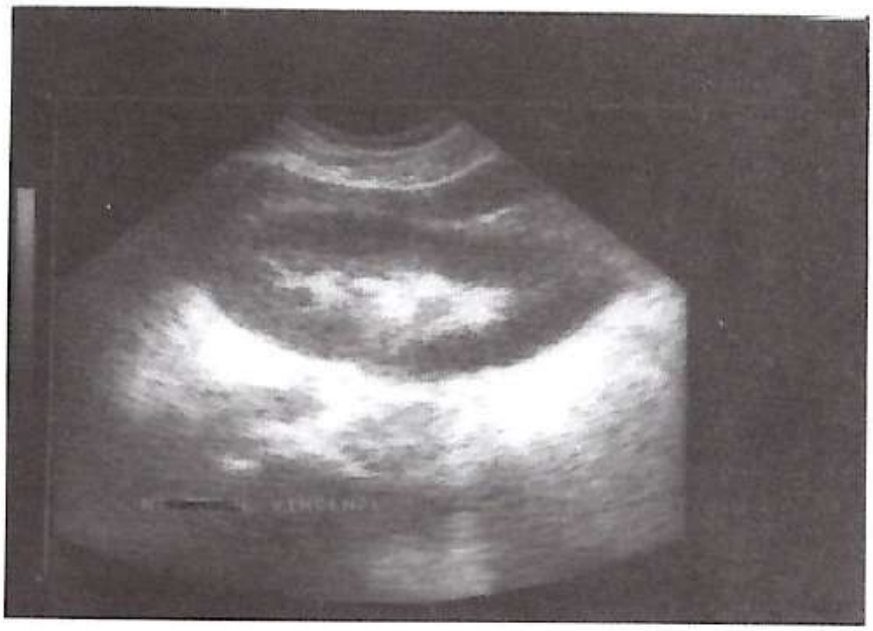

B

Fig. 1 - M. Vincenzo, aged 29; Ultrasound scanning:
A) Left kidney hypoplasia;
B) Right kidney showing lack of calculosis after prophylaxis with α-mercaptopropionyl-glycine.

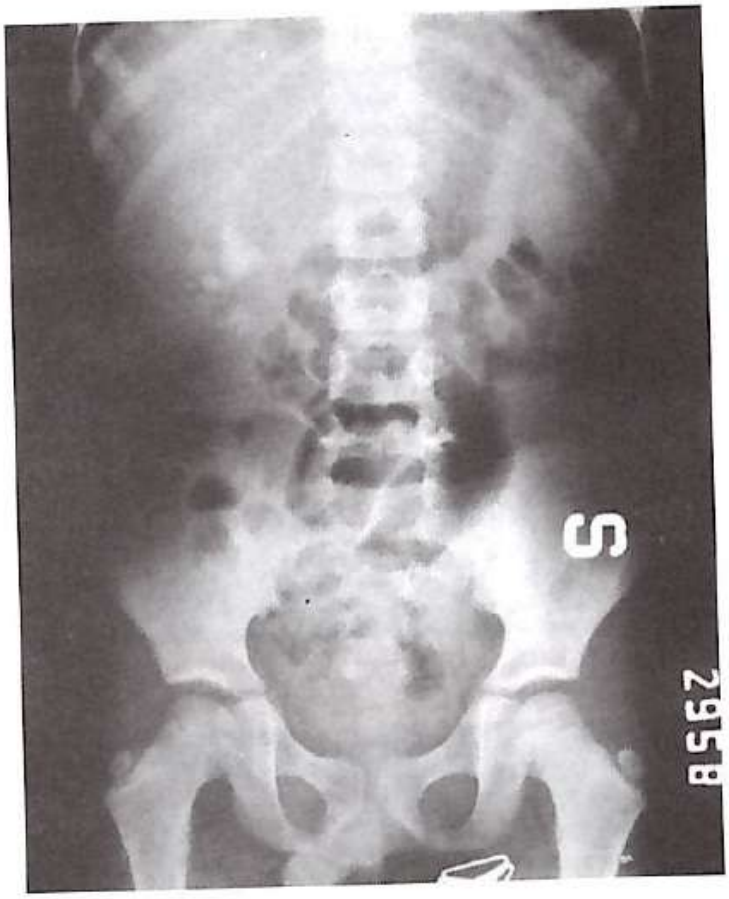

Fig. 2 - M. Giovanni; aged 5: Abdominal X-rays demonstrating bilateral calculosis.

A right ureteral calculus was demonstrated by ultrasound scanning and abdominal X-ray.

The patient had dialysis for 20 days; as a result the calculus spontaneously migrated, the renal insufficiency disappeared and the renal function returned normal. The dialysis was interrupted and, after azotaemia and creatininemia normalised, the preventive treatment with α-MPG (4 mg kg^{-1} day^{-1} every other day) was started. After one year, no calculosis could be observed by ultrasound scanning and x-ray. Repeated measurements of creatininaemia, azotaemia, glycaemia, cholesterolaemia, lipemia, red and white blood cells and urine analysis were normal.

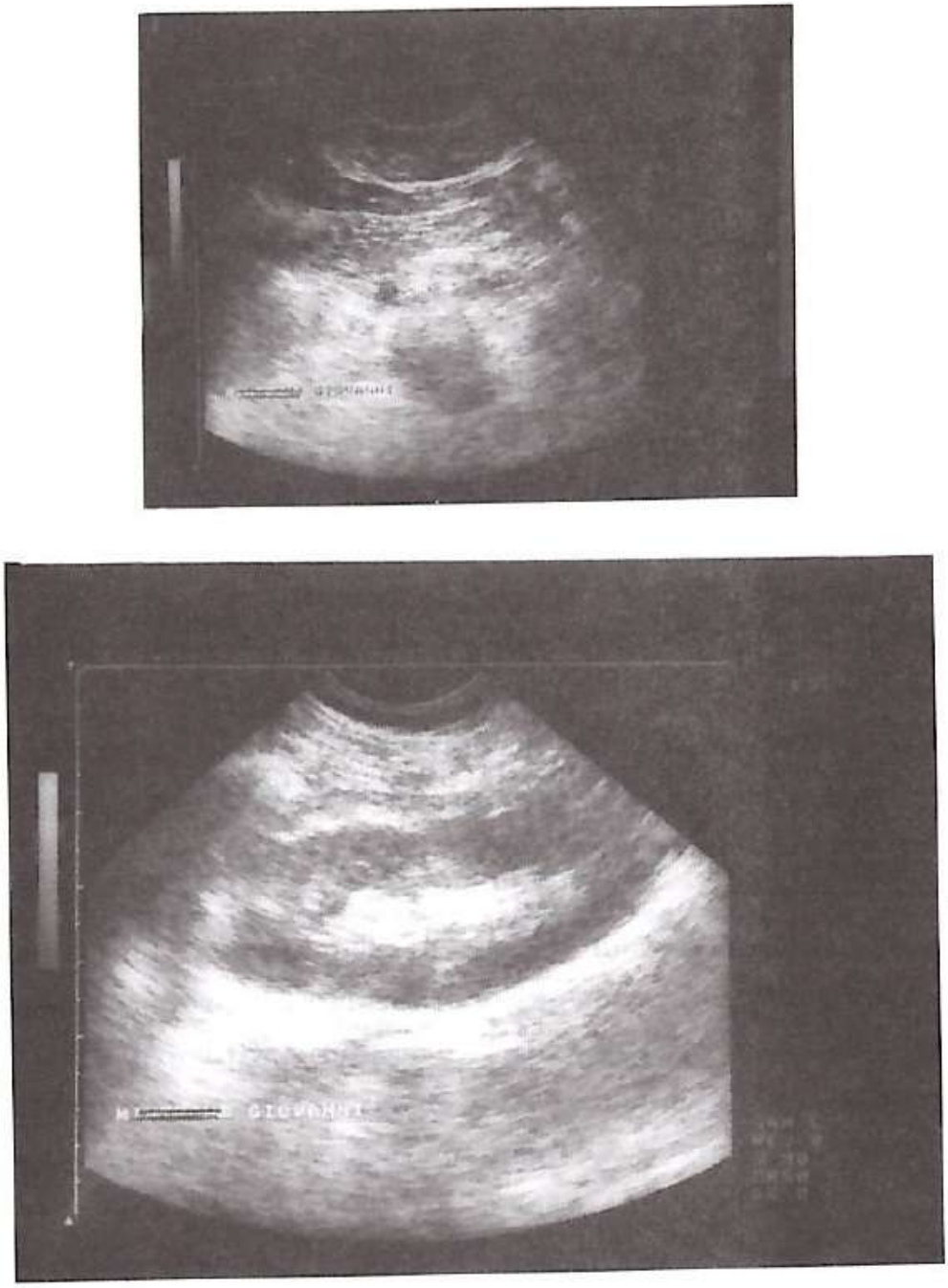

Fig. 3 - M. Giovanni, aged 24; Ultrasound scanning:
A) Left kidney hypoplasia;
B) Right kidney: absence of calculosis after α-mercaptopropionyl-glycine prophylaxis.

RESULTS

In our homozygous cystinuric patients with renal unilateral hypoplasia a 1.5-4 mg kg^{-1} day^{-1} dosage of α-MPG supplied continuously was effective

for the prophylaxis of cystine calculosis.

Similar results were observed in five adults with cystinuria who had been given preventive treatment with α-MPG for 5 years.

Prophylaxis with α-MPG in a low dosage every other day (4 mg kg^{-1} day^{-1} every other day) for 1 and 1-2 years respectively was useful also in these subjects.

DISCUSSION

α-MPG is very effective in dissolving cystine calculi. In our opinion in homozygous cystinuric patients with renal unilateral hypoplasia a low dosage of this drug (1.5-4 mg kg^{-1} day^{-1}) supplied continuously is effective in the prophylaxis of cystine calculi.

In these subjects 4 mg kg^{-1} day^{-1} supplied every other day can be effective for a short time in prophylaxis of cystine calculosis.

In order to better define the amounts of drug and the modalities of administration in the prevention of nephrolithiasis in cystinuric patients further research is necessary.

We determined the efficacy of α-mercaptopropionyl-glycine administered in a low dosage continuously or every other day for prophylaxis of cystine calculosis. Two homozygous cystinuric patients with previous calculosis and renal unilateral hypoplasia had been given preventive treatment with α-mercaptopropionyl-glycine continuously administered in a low dosage (1.5-4 mg Kg^{-1} day^{-1} for $14\frac{1}{2}$ years and 10^{-4} mg Kg^{-1} day^{-1} for 9 years respectively). Neither calculosis, nor side effects were observed. Subsequently, the patients were given 4 mg Kg^{-1} of the drug every second day for 1 and 1-2 years respectively without calculosis or side effect being observed. A low dosage of α-mercaptopropionyl-glycine(1.5-4 mg Kg^{-1} day^{-1}) supplied continuously or, for a short time, 4 mg Kg^{-1} day^{-1} supplied every other day can be effective in the prophylaxis of cystine nephrolithiasis in some homozygous patients with renal unilateral hypoplasia, with lower risk of side effects.

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1) LEVY H.L., Genetic screening, p. 1 in: "Advances in Human Genetics", Harris-Hirschhorn Eds., Plenum Press, New York, 1973.
2) ROSENBERG L.E., Science, 1966, 154, 1341-1343.
3) SEGAL S., THIER S.O., Cystinuria, p. 2479 in: "The Metabolic Basis of Inherited Disease", Scriver-Beaudet-Sly-Valle Eds, McGraw-Hill, New York, 6th edition, 1989.
4) BERIO A., IRCS Med. Sci., 1980, 8, 659.
5) REMIEN A., KALLISTRATOS G., BURCHARDT P., Eur. Urol., 1975, 1, 227-228.
6) HAUTMANN R., TERHORST B., STUHLSATZ H.W., LUTZEYER W., J. Urol., 1977, 117, 628-632.
7) SISKIND M.L., POPOVTZER M., Amer. J. Kidney Disease, 1992, 19, 179-180.
8) CHOW G., STREET S.B., J. Urol., 1996, 156, 1576-1578.

KEY WORDS: prophylaxis, cystine, calculosis, α-mercaptopropionyl-glycine.

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