Captopril is not clinically useful in reducing the cystine load in cystinuria or cystinosis

Sirs,

Following the report that captopril in a dose of 1 mg/kg per day produced a significant fall in urinary cystine excretion in children with cystinuria, which was predicted to be of therapeutic value [1], we treated five children aged 3–15 years for a month. Blood pressure recording was performed twice daily by the parents and was stable throughout. Three 24-h urine samples were obtained before treatment, and three collections were made after 1 month on captopril, to measure cystine excretion. Analyses were performed using automated ion-exchange chromatography with ninhydrin detection. It has been postulated [1] that captopril in the urine of a patient with cystinuria forms a new complex, presumably a captopril-cysteine dimer, which is much more soluble than cystine. We confirmed that when sufficient captopril was added in-vitro to the urine of patients with cystinuria, there was a reduction in the size of the cystine peak. However, when the urine from our patients undergoing captopril treatment was examined, there was no new peak corresponding to a captopril-cysteine dimer detectable on the chromatogram, and the fall in mean (SD) ratio of cystine to creatinine from 330 (132) to 319 (178) μmol/mmol was minimal, and not statistically significant.

Theoretical calculations suggest that only a small reduction in the excretion of cystine would be expected. A captopril dose of 1 mg/kg per day is equivalent to 4.6 μmol/kg per day; if the total dose was absorbed and excreted in the urine in the form of a captopril-cysteine dimer it would result in a reduction in the daily urinary free cystine excretion of 2.3 μmol/kg. Our patients excreted between 31 and 76 μmol/kg per day cystine, so we would expect that dose of captopril to produce reductions of between 3% and 7.5%. Unfortunately, these quantities would be insufficient to be of clinical benefit, and it seems unreasonable to consider giving much higher doses of captopril.

We wondered whether captopril would form soluble complexes with intracellular cystine in patients suffering from cystinosis thereby providing a useful clinical agent to replace cysteamine or phosphocysteamine which are highly unpalatable and frequently produce nausea [2]. We are not aware of this having been tried before; episodes of repeated renal failure previously reported in a cystinotic patient treated with captopril were due to allergic interstitial nephritis occurring in the transplanted kidney [3]. A 6-year-old girl with nephropathic cystinosis, who had well-preserved renal function and white cell cystine concentrations maintained in the heterozygote range by cysteamine (160 mg/day), was given captopril 1 mg/kg per day for 8 weeks. Her blood pressure remained normal. During the first 4 weeks on captopril she also continued to take her full dose of cysteamine, but during the second 4 weeks she received only half her usual dose, and the white cell cystine concentration rose to twice the upper limit seen in heterozygotes; it returned to its previous levels after the captopril was discontinued and the cysteamine was increased back to its normal dose.

We conclude that captopril has no clinical role in rendering cystine more soluble either in cystinuria or cystinosis. Both conditions present difficult management problems. In cystinuria high levels of motivation and compliance are necessary to drink large volumes of fluid spread evenly throughout the day, every day for life, and penicillamine has a high incidence of side effects. In cystinosis the taste and smell of the medication present an enormous problem. There is a clear need to continue the search for alternative preparations that are more palatable and have fewer side effects.

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