Inhibition of angiotensin converting enzyme with enalapril maleate in infants with congestive heart failure

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We studied the inhibition of angiotensin converting enzyme (ACE) in eight infants with congestive heart failure (CHF) poorly controlled with digoxin and diuretics, treated orally with 0.25 mg kg⁻¹ enalapril maleate once a day. Baseline ACE activities were compared between these infants and control children without CHF or ACE inhibitor. Except for one infant who vomited, inhibition of ACE activity was 75.5 ± 12.2%, 75.5 ± 10.5% and 51.7 ± 12.2%, at 4, 12 and 24 h after drug intake respectively. There was no correlation between postnatal age and inhibition of ACE activity. In infants with CHF, mean baseline ACE activity was significantly higher than in control infants (36.4 ± 7.2 µU ml⁻¹ vs 26.9 ± 6.9 µU ml⁻¹, *P* < 0.05). These results were very similar to those seen in adults.

Keywords angiotensin converting enzyme enalapril infants congestive heart failure

Introduction

Medical therapy for congestive heart failure (CHF) in infants usually associates digoxin and diuretics (Kaplan, 1990). If this treatment is inadequate, vasodilators, and especially angiotensin converting enzyme (ACE) inhibitors, are currently suggested (Artman & Graham, 1986); Initial dose recommendations of oral enalapril, one of the ACE inhibitors were 0.08 mg kg⁻¹. However, its use in pediatrics has been poorly evaluated for this indication (Eronen *et al.*, 1991; Frenneaux *et al.*, 1989; Lloyd *et al.*, 1989; Rheuban *et al.*, 1990).

Enalapril is a monoester monoacid prodrug, that has to be converted *in vivo* into enalaprilat, its active form. After single oral administration of 10 mg enalapril in healthy adult volunteers, a typical picture of polyphasic decline in serum concentration was observed with an apparent half-life from 11 to 35 h; maximal plasma concentration was observed during the fourth hour (Ulm *et al.*, 1982). In infants, measured half-life seemed to be shorter (5.7 to 9.7 h) (Lloyd *et al.*, 1989) but the period for which sampling continues was inadequate.

Both optimal dose and administration rhythm of enalapril have been poorly studied in infants with CHF. Assessment of the pharmacodynamic properties of enalapril in these circumstances by a biochemically-based method as measurement of ACE inhibition seemed to be a necessary step to evaluate drug impregnation. To our knowledge, the kinetics of inhibition of ACE activity, particularly by enalapril when used in children, was un-

known. The main objective of this study was to measure the inhibition of ACE activity by enalapril in infants with CHF and to compare the baseline ACE activity between these infants and children without CHF.

Methods

Patients

Eight infants (four boys, four girls) with CHF secondary to a left-right shunt were included. Parental consent was obtained in all cases. The children were aged from 3 weeks to 6 months (mean ± 1 s.d. = 2.9 ± 1.9 months) and weighed between 3.3 to 6.5 kg (mean ± s.d. = 4.4 ± 1.1 kg). Enalapril was prescribed because the CHF was poorly controlled, despite digoxin and diuretics. Poor control was defined as difficulty in feeding, low weight gain and the persistence of CHF signs. During the study, systolic and diastolic blood pressure (sBP) and heart rate (HR) were measured every 4 h.

Ten control children (eight boys, two girls), without CHF or ACE inhibitor treatment, were selected. During blood sampling for other reasons, 1.5 ml was drawn to assay baseline ACE activity (Ao). None of these children had abnormal arterial tension.

Methodology

In infants with CHF, a dose of 0.2 to 0.3 mg kg⁻¹ enalapril was orally administered. The dose was prepared from the adult 5 mg tablet. For the eight infants with CHF, four blood samples of 1.5 ml were taken just before (*t*0) and then 4 (*t*4), 12 (*t*12) and 24 (*t*24) h after drug administration. In control children, one blood sample was drawn. Blood was immediately centrifuged and plasma was frozen at -18° C until assay. ACE activity was measured by the spectrophotometric method, using hippurylhistidine-leucine as substrate (Cushman & Cheung, 1971). Inhibition of ACE activity was calculated as previously reported (Biollaz *et al.*, 1982).

Baseline ACE activities were compared between infants and control children by a Mann-Whitney test. Results were presented as mean ± standard deviation (mean ± s.d.).

Results

The drug was well tolerated during the study except in one child who vomited after 4 h. The sBP was not significantly decreased at *t*4, then returned to normal. This initial fall in sBP was not associated with an increase in HR; mean value at *t*0 was 150.6 ± 15.9 beats min⁻¹ and 146.0 ± 13.1 beats min⁻¹ at *t*4.

In control children, Ao was 26.9 ± 6.9 mu ml⁻¹ (range from 15.8 to 35.1); in infants with CHF, mean baseline ACE activity was significantly (*P* < 0.05) increased at 36.4 ± 7.2 mu ml⁻¹ (range from 28.2 to 50.7) (Figure

Figure 1 Comparison of baseline ACE activity between infants with CHF and control infants (Chi-square = 5.34, *P* = 0.03).

1). After administration of enalapril, mean ACE activity was 9.6 ± 9.1, 10.2 ± 5.3 and 19.4 ± 6.9 mu ml⁻¹ at *t*4, *t*12 and *t*24, respectively. For the child who vomited, inhibition of ACE activity was 78.8, 44.6 and 6.1% at *t*4, *t*12 and *t*24, respectively. For the seven remaining infants, the mean values were 75.5 ± 12.2% (range = 90.9–40.8), 75.5 ± 10.5% (range = 83.3–54.2) and 51.7 ± 12.2% (range = 64.5–30.6), respectively.

ACE activity and inhibition of ACE activity were not significantly correlated with age in infants with CHF.

Discussion

Baseline ACE activity was higher in infants with CHF than in control children, suggesting an increased activity of the renin-angiotensin-aldosterone system during heart failure. Other reports have already observed this difference, with higher values of plasma renin activity (Scammell & Diver, 1987) and of plasma aldosterone in infants with CHF (Baylen *et al.*, 1980). Our results are consistent with early maturity of ACE activity because we did not find any correlation between postnatal age and baseline ACE activity or inhibition of ACE activity. Others have failed to demonstrate a correlation between gestational age and baseline ACE activity in neonates without CHF (Maury *et al.*, 1984).

If we exclude the infant who vomited, inhibition of ACE in our study measured at *t*4 was 75.5 ± 18.2%; 24 h after drug intake, it was only 51.7 ± 12.2%. These values were consistent with those observed in adults. In healthy volunteers, administration of a single 10 mg dose of enalapril resulted in a maximum inhibition of approximately 95% at *t*4 and between 70–80% at *t*24 and this inhibition was below 20% 3 days later (Biollaz *et al.*, 1982). The pharmacodynamic half-life as assessed by ACE inhibition in our study is very similar to that seen in adults.

Pediatric evaluation of enalapril could be difficult for many reasons. Indeed, for heart failure in childhood, there is no universally agreed measurement of severity and quality of life as the NYHA classification used in adults. Secondly, there is no good evidence that an exact percent inhibition of ACE is required for efficacy in the treatment of heart failure.

After a single dose of 0.25 mg kg⁻¹ enalapril in infants, inhibition of ACE activity was 75.5 ± 12.2%, 75.5 ± 10.5% and 51.7 ± 12.2% at *t*4, *t*12 and *t*24, respectively. The extent of ACE inhibition and the duration of biochemical action which occurs in infants were close to those observed in adults.

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