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THE KINETICS OF ORAL CIMETIDINE IN CHILDREN WITH CYSTIC FIBROSIS

Cimetidine has been recommended as supplementary treatment for patients with exocrine pancreatic insufficiency to prevent acid-peptic inactivation of enzyme replacements (Cox *et al.*, 1979). In a study of various types of pancreatic enzyme replacement therapy in cystic fibrosis cimetidine was included in the programme. As no details of cimetidine kinetics in childhood were available, a small study of cimetidine kinetics was included in the protocol. The study was approved by the Brisbane Royal Children's Hospital Ethical Committee. A daily dose of 20 mg/kg was chosen based on the adult dose of 1000–1600 mg daily, and the fact that in the weight range of subjects studied an adjustment in drug dosage for increased surface area has been recommended (Shirkey, 1969).

Eleven children with cystic fibrosis, aged between 73 and 163 months were given a 2 week course of oral cimetidine. The daily dose of 20 mg/kg was given in three divided doses at 07.00 h, 12.00 h and 17.30 h, each immediately followed by a main meal. All children were on oral vitamin supplements, inhalations of salbutamol or orciprenaline and inhalations of gentamicin. One child was taking co-trimoxazole and two were taking flucloxacillin (Table 1). Drug therapy did not change during the trial period. No child had clinical or biochemical evidence of renal impairment.

Blood samples were taken at the end of the course of cimetidine for measurement of creatinine and liver function tests, and a questionnaire including questions relating to possible side effects was completed by the subjects and their parents before and at the end of the course of cimetidine. On the last day of this 2-week period they attended the hospital for measurement of cimetidine levels. The morning dose of cimetidine was taken at 07.00 h and at 12.30 h an indwelling intravenous cannula was inserted and a blood sample taken for a pre-dose level: the child's usual oral dose of cimetidine was then taken, and 5 ml blood samples removed at 30, 60, 120, 180 min after the administration of cimetidine.

The samples of whole blood were stored at −20°C and assayed in a single batch by the high pressure liquid chromatography method of Randolph *et al.*, (1977). Results show a mean whole blood pre-dose

Table 1 Details of individual patients

Subject	*Age (months)*	*Drugs*	*Weight (kg)*	*Pre-dose (μg/ml)*	*Peak (μg/ml)*	*AsT (iu/l)*	*Creatinine (mmol/l)*
1	132	C	25.8	2.93	4.27	41	0.04
2	153		29.2	3.46	3.87	34	0.06
3	106		31.0	3.34	3.77	26	0.06
4	126		25.6	3.21	4.77	29	0.05
5	113	F	34.8	3.05	4.15	29	0.07
6	73		19.2	2.76	3.36	42	0.05
7	140		27.0	3.54	4.55	28	0.05
8	112		14.8	2.87	4.07	42	0.04
9	122		26.4	5.97	8.08	28	0.05
10	77		20.8	4.19	4.84	24	0.05
11	163	F	41.8	4.81	4.81	18	0.08
Mean	120		26.9	3.65	4.59	31	0.05

C = co-trimoxazole, F = flucloxacillin, AsT = normal range 9–40 iu/l

Table 2 Whole blood cimetidine levels (μg/ml)

Time (min)	*Mean ± s.d. (μg/l)*	*Range (μg/ml)*	*Significance relative to 0 h time*
0	3.65 ± 0.98	2.76 – 5.97	
30	4.24 ± 1.37	3.11 – 8.08	$P < 0.02$
60	4.25 ± 1.24	2.62 – 7.54	$P < 0.05$
120	3.93 ± 1.37	2.44 – 7.67	NS
180	3.48 ± 1.36	2.03 – 7.03	NS

level of 3.65 ± 0.98 μg/ml, and a mean whole blood peak level of 4.59 ± 1.25 μg/ml. The pre-dose level cannot be interpreted as a true trough level since the dosing intervals are unequal. Table 2 shows values for each sampling time. The rise between 0 and 30 min is significant ($P < 0.02$, paired *t*-test). No estimate of the half-life of cimetidine has been made from these figures, but the peak and pre-dose levels are higher than those in adults given a similar dose studied by Cohen *et al.* (1980) who found in adults given 300 mg cimetidine i.v. every 6 h that peak levels were 3.85 μg/ml plasma, and trough levels 1.52 μg/ml plasma. The only study of patients with cystic fibrosis to have reported cimetidine levels was in a group of children and adults, at 90 to 120 min after various oral doses (Cox *et al.*, 1979), but the results were means for each dosage group; levels were lower on 150 or 200 mg doses (mean 1.26 ± 0.17 μg/ml) but an exact comparison cannot be made since Cox *et al.* (1979) used doses which were not related to weight. In adults a blood level of 2 μg/ml of whole blood would be expected to produce approximately 90% inhibition of gastric acid output and the effects are similar in several species of experimental animals (Brimblecombe & Duncan, 1977), so these levels in children probably exceed the therapeutic requirement. Cohen *et al.* (1980) measured intragastric pH levels in the study referred to above, and report mean pH of 6.23 at peak cimetidine level (3.85 μg/ml plasma) and mean pH of 5.26 at trough cimetidine level (1.52 μg/ml plasma); if these results can be extrapolated to children with cystic fibrosis then the whole blood levels of cimetidine achieved in this study would have effectively raised intragastric pH. Liver function tests and creatinine levels were normal at the end of the 2 week period (Table 1) and no side effects were reported.

It is concluded that cimetidine levels produced by a daily oral dose of 20 mg/kg in children with cystic fibrosis are higher than reported figures for maximal suppression of gastric acid output in adults, however no apparent untoward effects are seen at this dose in the short term. Further definitive studies of the pharmacokinetics of cimetidine in children are required.

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