Exhibit P

S.2.9. Study No: HVT/80/27

TO INVESTIGATE THE URINARY RECOVERY OF CEFUROXIME AFTER A SINGLE ORAL DOSE OF 250mg CEFUROXIME AS E47 ESTER IN FOUR DIFFERENT ISOMER RATIOS

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The method of preparation of pure amorphous material outlined in HVT/80/18 led to a slight imbalance in the proportions of A and B isomers : the yields from crystallization were not identical. Although a 50:50 mix was tested in HVT/80/18, the proportions could be as different as 60:40. Since isomers A and B were absorbed to differing extents (HVT/77/14), the effect of variation in ratio was tested. Ratios of A:B of 60:40, 50:50, 40:60 and 30:70 were given in aqueous suspension at doses of 250mg cefuroxime as ester to 12 volunteers in a double-blind, cross-over study. The 30:70 mix was included to see if better absorption could be obtained using a higher proportion of the more soluble isomer.

The respective 12h urinary recoveries of cefuroxime averaged 35.8%, 40.6%, 39.6% and 41.5%. Two-way analysis of variance showed that there was no significant difference between these values. No volunteer suffered diarrhoea in this study.

To: Dr. R.D. Foord (2)

From: Miss A.M. Paton
Dr. S.M. Harding

Date: 13th October, 1980

Trial No: HVT/80/27

Human Volunteer Trial to Investigate the Urinary Recovery of Cefuroxime After Single Oral Doses of 250mg Cefuroxime as E.47 ester in Four Different Isomer Ratios.

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Summary

The currently preferred method of obtaining cefuroxime as E.47 ester of sufficient purity for development involves the separation of the two isomers A and B. When this procedure is followed, the yield is not precisely 50:50. This study was to investigate whether this variation in yield was of importance in the absorption of the ester and also to see whether a mixture incorporating a higher ratio of the more soluble isomer B had better absorption than a 50:50 ratio.

Twelve volunteers received A:B in ratios of 60:40, 50:50, 40:60 and 30:70 in a double-blind cross-over study on four consecutive days. The dose on each occasion was equivalent to 250mg cefuroxime, the ester being given in aqueous suspension as in previous experiments. The 50:50 mixture gave 40.6% urinary recovery over 12h whereas the 60:40 (A:B) gave 35.8% which was significantly lower ($p<0.01$). Higher proportions of B did not improve the urinary recovery (40:60, 30:70 / A:B :- 39.6%, 41.5%).

It therefore appears that a 50:50 ratio is better absorbed than a 60:40 (A:B) ratio and therefore attempts should be made to achieve a ratio close to unity during production. The inclusion of higher amounts of the more soluble isomer does not improve the absorption and is of no advantage.

Addendum:

After this report was written, the validity of the use of the Student's 't' test was questioned at the Oral Cefuroxime Project Committee meeting. If the question is asked: "is the 60:40 mix less well absorbed than the 50:50 mix?" the answer is "yes", whether one uses a t test, a chi-squared sign test or a Wilcoxon Sum Ranks test. However, there is always a scatter of results to be found with urinary recovery experiments such as this and a two way analysis of variance between all groups shows no significant difference. Whatever the finer points of the statistical method used it is the investigator's opinion that it would be preferable to chose a ratio approximating to unity.

1. Investigator

Dr. S.M. Harding

2. Design of Study

12 healthy volunteers to be given single oral doses of 250mg cefuroxime as E.47 ester in four different isomer ratios.

To be a 4-part double-blind cross-over study.

For full details see protocol HVT/80/27.

3. Control agents

None

4. Drug Codes

250mg cefuroxime as E.47 ester in following isomer ratios

1: Isomer A:Isomer B in ratio 60:40
2: A:B in 50:50 ratio
3: A:B in 40:60 ratio
4: A:B in 30:70 ratio

The aqueous suspensions were made up in a volume of 10ml containing pluronic F.68 (a wetting agent), castor sugar and buttermint flavouring. They were made up on the morning of dosing in the Pharmacy Division.

Volunteers were dosed as below:-

Volunteer Number	8th Sept. 1980 Ratio No.	9th Sept. 1980 Ratio No.	10th Sept. 1980 Ratio No.	11th Sept. 1980 Ratio No.
1	1	2	3	4
2	2	3	4	1
3	3	4	1	2
4	4	1	2	3
5	4	1	3	2
6	3	2	4	1
7	2	3	1	4
8	1	4	2	3
9	1	4	3	2
10	2	3	4	1
11	3	2	1	4
12	4	1	2	3

5. Selection of volunteers

Volunteers were selected from Glaxo Staff on the basis of willingness to participate and absence of concurrent illness or medication. Volunteers were not approached if they had participated in a phase I clinical study within the previous month.

6. Anthropometry

As below:

Volunteer Number	Age (yr)	Weight (kg)	Height (cm)
1	30	69	174
2	25	76	174
3	37	90	185
4	30	72	178
5	21	77	185
6	39	70	167
7	24	71	180
8	31	72	180
9	30	65	175
10	36	75	184
11	29	64	170
12	32	66	177
Average	30	72	177
Range	21-39	64-90	170-185

7. Aims

To assess the 12h urinary recoveries of cefuroxime after single oral doses of cefuroxime as E.47 ester in four different isomer ratios.

8. Timing of samples

Volunteers were dosed at 9.30 a.m.

Timed urine collections were made 0-6h and 6-12h after dosing. Volumes were measured and a 20ml aliquot sent for antibiotic assay.

9. Assays

Microbiological assay (MBA) was performed by Mr. J. Thornton, Chemotherapy, using a large plate agar dilution assay method and Staph. aureus 864 as assay organism.

10. Adverse reactions

The severity of adverse reactions, was coded in the following way:-

0 no intestinal disturbance
+ wind/loose stool
++ 2-4 loose stools/day
+++ more than 4 loose stools/day

The latter two were regarded as definite drug effects. Volunteer 7 had diarrhoea ++ symptoms.

Volunteer 6 had headaches with dose 2 and 4, the former being quite severe.

11. Results (See Table I and Fig. 1)

The average 12h urinary recovery of cefuroxime for all four doses in all 12 volunteers was 39.4%. Urinary recoveries for doses 2, 3 and 4 were similar, being 40.6% (S.E.$\pm$2.7), 39.6% (S.E.$\pm$1.5) and 41.5% (S.E.$\pm$2.4) respectively. Dose 1 (A:B isomer ratio of 60:40) had a lower 12h urinary recovery of 35.8% (S.E.$\pm$3.0).

The difference in absorption of dose 1 compared with doses 2 and 4 was significantly different using the student's 't' test ($p<0.01$). The results for volunteer 12 were excluded from the analysis due to the incomplete collection for dose 1. Figure 1 shows the mean values $\pm$1 S.E.

12. Conclusions

Cefuroxime as the E.47 ester in an A:B isomer ratio of 60:40 is significantly less absorbed than the 50:50 isomer ratio. Higher amounts of isomer B did not improve the absorption of the ester.

Alexandra M Paton.

Miss Alexandra M. Paton

Stuart Harding

Dr. Stuart M. Harding

amp/jeb
13.10.80

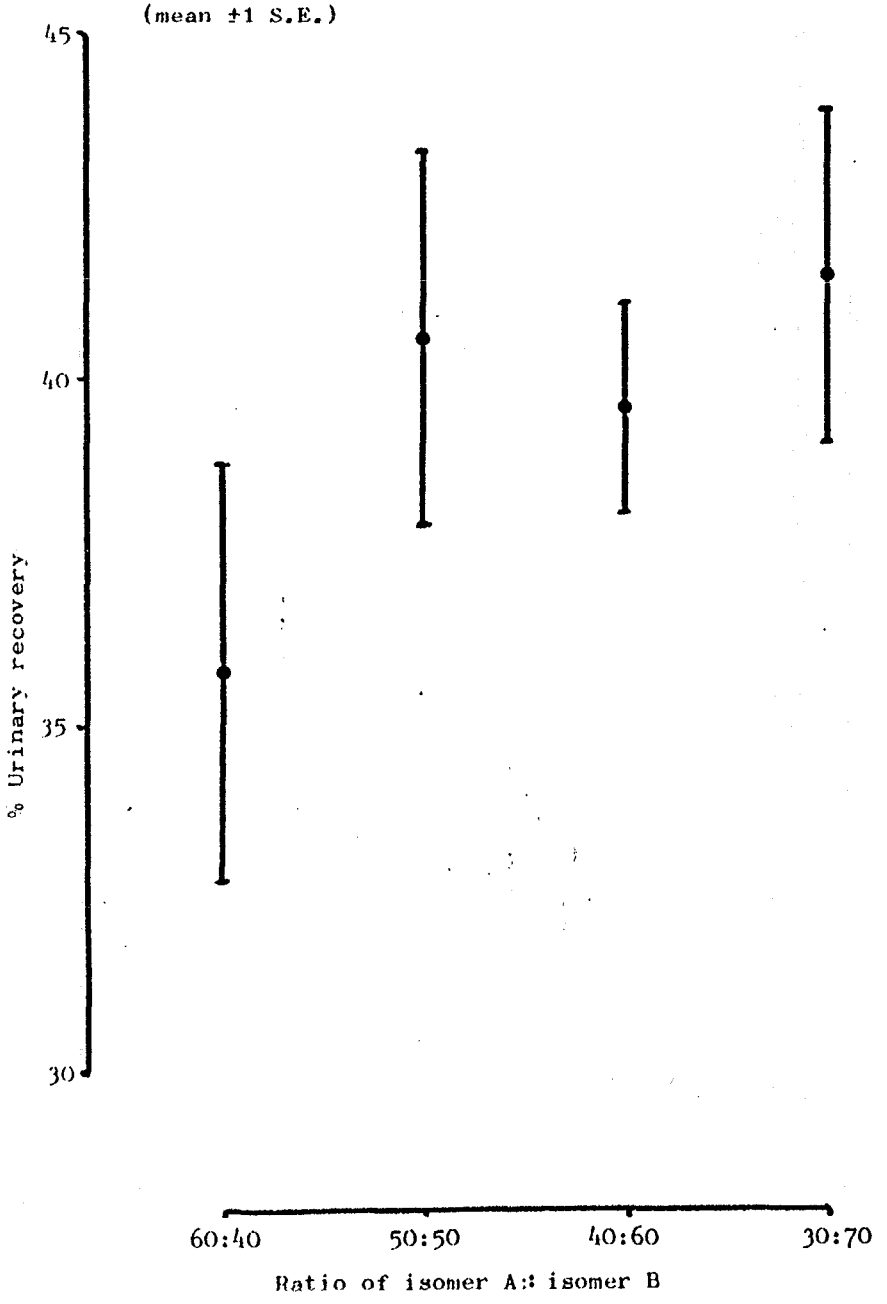
Table I

Percentage urinary recovery of cefuroxime in 12 hours after single doses of 250mg cefuroxime as E.47 ester in four different isomer ratios, in 12 healthy male volunteers.

Volunteer Number	Dose 1 60:40	Dose 2 50:50	Dose 3 40:60	Dose 4 30:70	Average for Volunteers
1	44.4	44.4	44.1	41.8	43.7
2	30.7	46.9	47.0	35.2	40.0
3	48.9	46.1	37.6	44.6	44.3
4	29.7	38.7	40.0	30.7	34.8
5	25.4	25.4	33.8	37.3	30.5
6	33.5	39.6	43.1	40.3	39.1
7	52.1	53.9	43.5	58.4	52.0
8	42.0	49.3	38.6	46.7	44.2
9	23.7	42.3	39.8	37.0	35.7
10	29.9	37.7	31.6	36.4	33.9
11	34.0	39.7	32.6	53.3	39.9
12	NR	23.5	43.6	36.6	34.6
Average	35.8	40.6	39.6	41.5	39.4
Standard Error	3.0	2.7	1.5	2.4	1.8

NR = No Result Ratio = A:B

Figure 1 Urinary recovery of cefuroxime from E.47 ester



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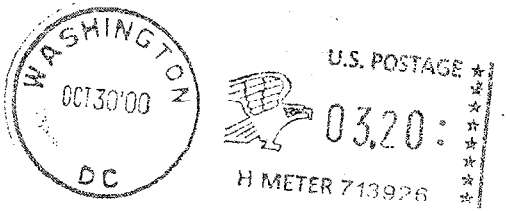

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