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BIOEQUIVALENCE STUDY OF TWO LIQUID FORMULATIONS OF BENZYDAMINE

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ABSTRACT

A bioequivalence study of two liquid formulations containing benzydamine hydrochloride was carried out to evaluate the influence of a change of the excipients and the addition of a flavouring agent, ICEBERG AR 84/05/15, on the absorption of benzydamine.

No statistically significant differences were observed suggesting that the two formulations are bioequivalent.

KEY WORDS Benzydamine Bioequivalence ICEBERG AR 84/05/15

INTRODUCTION

Benzydamine is a non-steroidal anti-inflammatory drug, which selectively inhibits the localized inflammatory process without interfering with the humoral factors often conditioning the inflammatory response.[1-4]

The analgesic and anti-inflammatory effects of benzydamine have been shown to be present in man after both systemic and topical administration.[5-14]

This paper reports a bioequivalence study of two liquid formulations of benzydamine to evaluate the influence of a change of the excipients and the addition of a flavouring agent, ICEBERG AR 84/05/15, on the absorption of benzydamine.

EXPERIMENTAL

Materials

Product A:

Benzydamine hydrochloride	3·000 g
Nipagin	0·180 g
Nipasol	0·020 g
Saccharin sodium	0·333 g
Anti-foam C silicone	0·004 g
Demineralized water q.s. to	100·000 ml

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Product B:

Benzydamine hydrochloride	3·000 g
Citric acid monohydrate	1·820 g
Flavour ICEBERG AR 84/05/15	0·100 g
Glycerol	5·000 g
Nipagin	0·180 g
Nipasol	0·020 g
Saccharin sodium	0·660 g
Tartrazine dye	0·500 g
Demineralized water q.s. to	100·000 ml

Methods

The two products were administered to eight healthy male subjects aged 19–31 years, bodyweight 65–80 kg, according to Table 1.

The trials were separated by a 1-week wash-out period. The subjects fasting overnight were treated orally with 50 mg of benzydamine hydrochloride (1·66 ml of benzydamine hydrochloride 3 per cent solution) diluted with 50 ml of water.

Blood samples were drawn at 0, 0·25, 0·5, 1, 2, 4, 6, 8, 24, 48, and 72 h and collected in heparinized tubes. After the first 4 h the subjects were allowed to eat.

Subjects were submitted to clinical laboratory tests before the start and after the end of the study to verify drug tolerance.

The analytical procedure to determine the plasma concentrations of benzydamine was the same as that already described[15] with the following modifications: a column LC18 (250 × 4·6 mm 5 micron) and a precolumn LC18 Supelco Inc. were used; the mobile phase consisted of acetonitrile :

Table 1. Experimental design

Subjects				Products' sequence	
No.	Initials	Age	Bodyweight	First trial	Second trial
1	GF	20	76	A	B
2	BL	19	79	B	A
3	TP	32	83	A	B
4	TA	27	75	B	A
5	MM	26	80	A	B
6	MR	27	67	B	A
7	SU	31	80	A	B
8	BS	24	65	B	A

methanol : water : dodecilammine at the ratio of 420 ml : 300 ml : 280 ml : 0·1 per cent and was used at the flow of 2 ml/min.

The statistical analysis was performed using the Student's *t*-test.

RESULTS

Figure 1 shows the time course of the mean plasma concentrations of benzydamine (expressed in ng ml^{-1}) after administration of the two products. Table 2 reports the individual data.

No differences were observed between the plasma concentrations obtained with the two products either in the absorption, distribution or elimination phase. The trend of the mean plasma concentrations with both formulations may be fitted by the following triexponential equation.

$$Y = Le^{-at} + Me^{bt} - Ne^{-Kat}$$

The estimated coefficients and exponents are reported in table 3. Table 4 shows the pharmacokinetic parameters obtained with the two formulations. No significant differences were observed among all parameters examined.

As far as the clinical laboratory tests are concerned, the two products did not produce any significant change thus suggesting that they are well tolerated.

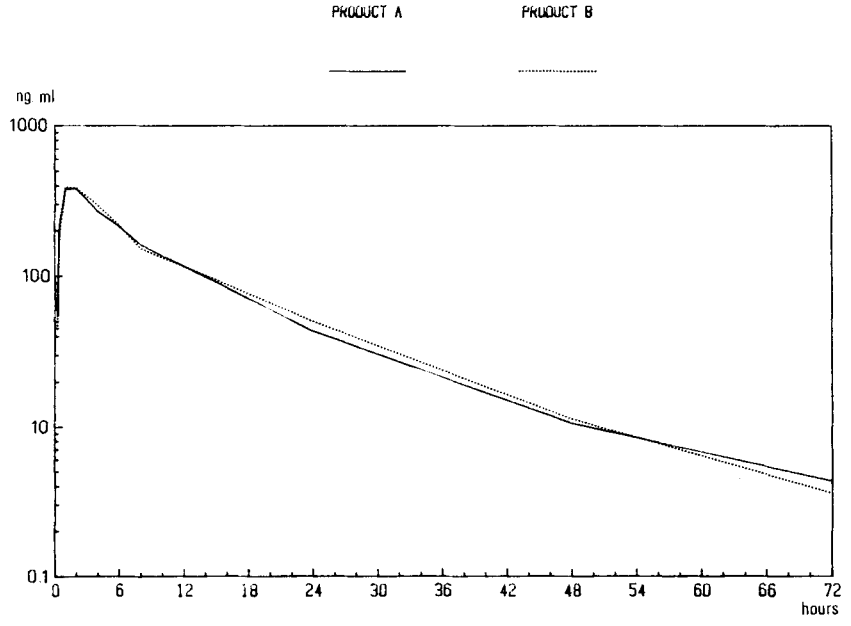

Figure 1. Time course of the mean plasma concentrations of benzydamine (expressed as benzydamine hydrochloride ng ml^{-1}) after oral administration of the product A or B

Table 2. Individual plasma levels of benzydamine (ng ml^{-1}) after administration of the two formulations

Subject	Time (h) 0·25	0·5	1	2	4	6	8	24	48	72
Product A										
1	79·13	304·86	363·24	411·89	255·85	243·24	129·73	29·19	6·49	3·89
2	166·53	453·88	558·37	424·49	293·88	223·67	169·79	22·20	1·42	1·31
3	47·66	154·89	406·81	343·83	277·45	209·36	200·85	84·43	16·17	5·79
4	38·12	169·41	388·23	405·88	303·53	239·99	211·76	42·70	29·99	9·88
5	15·29	220·12	388·28	391·33	314·90	239·99	154·39	39·74	5·50	2·44
6	7·48	46·75	221·29	352·20	249·34	199·47	158·96	46·75	7·48	2·80
7	9·63	177·55	379·18	409·28	276·86	215·17	144·45	57·78	12·04	3·91
8	71·99	265·45	356·36	319·99	196·36	152·72	119·99	22·18	5·45	4·36
Mean	54·48	224·11	382·72	382·36	271·02	215·45	161·24	43·12	10·57	4·30
± SE	18·68	42·77	32.36	13·56	13·27	10·58	11·36	7·34	3·20	0·93
Product B										
1	21·22	189·39	636·73	581·22	424·49	293·88	222·04	47·35	6·53	1·31
2	22·33	184·99	312·58	376·37	250·38	159·48	121·20	54·86	7·66	4·78
3	8·61	76·14	347·58	327·72	235·03	162·20	135·72	55·28	14·23	1·99
4	58·20	303·00	450·00	412·50	343·50	300·00	222·00	76·50	29·10	10·20
5	72·89	302·21	451·84	405·92	305·18	234·07	93·33	38·52	7·11	1·18
6	16·82	160·97	378·49	339·33	294·38	246·52	166·77	44·66	8·99	2·90
7	1·97	42·74	276·16	401·09	325·47	210·41	n.s.	63·78	14·14	5·26
8	153·60	270·00	301·50	262·50	195·00	151·50	105·00	19·20	2·70	0·90
Mean	44·46	191·18	394·36	388·33	296·68	219·76	152·29	50·02	11·31	3·57
± SE	17·83	34·66	41·59	32·82	25·26	20·94	20·05	6·06	2·89	1·11

n.s. = no sample

Table 3. Estimated coefficients and exponents of the triexponential equation obtained for the two formulations

Parameters	Product A	Product B
L	423·5816	493·9082
a	·5218	·2729
M	306·3989	157·3642
b	·0808	·0508
N	980·3137	904·3473
Ka	1·8358	1·7746

Table 4. Pharmacokinetic parameters

Subject	Product A				Product B			
	C_{max} ng ml^{-1}	T_{max} h	$t_{1/2}$ h	AUC ng ml^{-1} h^{-1}	C_{max} ng ml^{-1}	T_{max} h	$t_{1/2}$ h	AUC ng ml^{-1} h^{-1}
1	411·89	2	17·3	3976·4	636·73	1	9·9	5980·2
2	558·37	1	11·6	4324·4	376·37	2	13·9	4122·9
3	406·81	1	11·6	5818·3	347·58	1	9·9	4262·9
4	405·88	2	23·1	5658·2	450·00	1	17·3	6720·2
5	391·33	2	11·6	4419·9	451·84	1	9·9	3953·0
6	352·20	2	11·6	4190·0	378·49	1	11·6	4583·9
7	409·28	2	11·6	4742·9	401·09	2	13·9	5322·2
8	356·36	1	23·1	3269·6	301·50	1	11·6	2857·1
Mean	411·52	1·6	15·2	4549·9	417·9	1·2	12·2	4726·2
± SE	22·60	0·18	1·86	299·99	35·89	0·16	0·93	434·87

CONCLUSIONS

The results obtained indicate that the plasma concentrations obtained with the two products have a similar trend. Both products show similar peak concentrations (411–417 ng ml^{-1}) between 1–2 h and an elimination phase with a half-life of 12–15 h. Since the two formulations do not show any significant difference in all pharmacokinetic parameters studied, it can be concluded that the two formulations of benzydamine are bioequivalent. Moreover, no changes in the clinical laboratory tests after treatment indicate that the two formulations are well tolerated.

REFERENCES

1. B. Silvestrini, in *Non-steroidal Anti-inflammatory Drugs*, S. Garattini and M. N. G. Dukes (Eds), Excerpta Medica Foundation, Amsterdam, 1965, p. 180.
2. B. Silvestrini, *Panminerva Med.*, **9**, 135 (1967).
3. B. Silvestrini, in *Inflammation*, B. Silvestrini, S. Tura and W. G. Spector (Eds), Excerpta Medica Foundation, Amsterdam, 1968, p. 26.
4. B. Silvestrini, *Panminerva Med.*, **11**, 587 (1969).
5. M. De Gregorio, in *Non-steroidal Anti-inflammatory Drugs*, S. Garattini and M. N. G. Dukes (Eds), Excerpta Medica Foundation, Amsterdam, 1965, p. 422.
6. V. Gagliardi, *Parodontol. Stomatol.*, **1**, 40 (1968).
7. H. Kopera, in *Inflammation*, B. Silvestrini, S. Tura and W. G. Spector (Eds), Excerpta Medica Foundation, Amsterdam, 1968, p. 100.
8. G. Schlag, H. Kopera, S. M. Stulemeijer and W. L. C. Veer, *Arzneim. Forsch.*, **20**, 1725 (1970).
9. G. Benfatto and N. Marotta, *Clin. Ginecol.*, **9**, 627 (1967).
10. C. Marchiori, *Valsalva*, **48**, 195 (1972).
11. V. Pinelli, *Atti LIV Congr. Soc. Ital. Laring. Otol. Rinol.*, Napoli **2**, 255 (1966).
12. M. Mega, *Clin. Europ.*, **17**, 23 (1978).
13. P. Pierfederici, G. Gandolfi-Colleoni and R. Secli, *Clin. Europ.*, **17**, 35 (1978).
14. V. Facchini, *Clin. Europ.*, **17**, 43 (1978).
15. B. Catanese, A. Lagana, A. Marino, R. Picollo and M. Rotatori, *Pharmacol. Res. Commun.*, **18**, 385 (1986).