International Journal of Pharmaceutics, 16 (1983) 241–251
Elsevier

Influence of tiemonium on the gastrointestinal absorption of aspirin

J.-M. Aiache [1], S. Pradat [1], S. Aiache [1], J.-P. Kantelip [2], J.-F. Pognat [3] and Luu Si Nang [3]

[1] *Laboratoire de Biopharmacie, Faculté de Pharmacie, Université de Clermont-Ferrand, 63001 Clermont-Ferrand;* [2] *Laboratoire de Pharmacologie, Faculté de Médecine, Unité INSERM U195, 28 place Henri Dunant - B.P. 38, 63001 Clermont-Ferrand Cedex; and* [3] *C.E.R.M. de Riom, 63200 Riom (France)*

(Received January 13th, 1982)
(Modified version received February 18th, 1983)
(Accepted March 9th, 1983)

Summary

The present study illustrates the importance of bioavailability testing whenever two active ingredients are combined in the same formulation in order to be administered simultaneously. The negative influence of the major spasmolytic drug, tiemonium, on the absorption of aspirin was demonstrated in the dog. This activity is so important that it was logical to suppose that this effect would be the same in man. In order to remove this effect, a special formulation was designed in which the two ingredients were released one after the other. Even so, an initial experiment in man gave unexpected results which were shown in an in vitro study to be due to extraneous factors connected with the preparation of the tablets. The importance of such in vitro investigations in avoiding hasty interpretation of in vivo findings is thus once again demonstrated.

Introduction

Little work has been done on the influence of drugs on gastrointestinal absorption of aspirin. Nevertheless, it is known that antacids (Morgan and Truitt, 1964; Koch Weser, 1974) and stomach liners (Robert et al., 1980) regulate absorption of aspirin, while metoclopramide (Wainscoot et al., 1976) reduce it.

The aim of this work was to determine the influence of a spamolytic drug, tiemonium methylsulfate, on the absorption of acetylsalicyclic acid. Two separate studies were done, the first in the dog and the second in man. The results of the first

study provided data which led to the elaboration of a special formulation used in the second study.

I. Experiments on the Dog

The influence of tiemonium on the absorption of aspirin was investigated in the dog. Two routes of administration were compared: intravenous and oral.

(1) Intravenous administration

Procedure

Five thoroughbred beagle dogs weighing from 7 to 10 kg were used. This group was composed of 3 males and 2 females in order to show a possible sex difference in results. Dosages were as follows: Formulation A, 100 mg/kg of lysine acetylsalicylate mixed with 1 mg/kg of tiemonium methylsulfate; and Formulation B, 100 mg/kg of lysine acetylsalicylate alone.

Each dog received the two formulations one week apart in the following random order.

Dogs	M1 *	M2 *	M3 *	F4 **	F5 **
Weight (kg) ***	8.4	9.2	9.5	7.3	8.6
1st administration	A	B	B	A	B
Weight (kg) ***	8.5	9.2	9.4	6.9	8.3
2nd administration	B	A	A	B	A

* Male.
** Female.
*** Weight of dogs just before administration (first or second).

Blood samples (3.5 ml) were taken for salicylate assay at the following times after administration: 0.50; 1; 1.50; 2; 3; 4; 6; 8 and 12 h.

Salicylate assay

The method used was that of Cid et al. (1971) and consists of precipitation of total blood proteins with Hg^{++} and simultaneous formation of a colored Fe^{+++} salicylate complex which is directly assayed spectrophotometrically at 549 nm.

Results

Mean blood salicylate concentrations found in the 5 dogs after i.v. administration are given in Table 1.

Conclusion

Analysis of variance performed on blood salicylate values and on elimination

TABLE I

MEAN BLOOD SALICYLATE LEVELS IN DOGS AFTER i.v. INJECTION

	Mean blood salicylate levels (μg/ml)								
	Time								
	0.50 h	1 h	1.50 h	2 h	3 h	4 h	6 h	8 h	12 h
A (mean)	130	127	117.5	112	104	95.5	71.5	49.5	30
A (standard deviation)	13.46	12.55	10.31	12.55	17.19	16.62	20.66	20.57	22.64
B (mean)	124	118	115	108.5	101	91	69.5	53	26.5
B (standard deviation)	17.55	15.95	12.37	8.40	14.43	16.83	21.68	30.54	30.5

A = aspirin + tiemonium; B = aspirin alone.

constants obtained after smoothing with a data processor showed no statistically significant difference between aspirin administered alone and aspirin plus tiemonium. Furthermore, there is no statistical difference between male and female dogs. The spasmolytic drug does not therefore seem to affect neither the elimination rate of aspirin given intravenously nor the apparent volume of distribution and consequently the clearance of this drug.

(2) Oral administration

Procedure

The same dogs were used as above, each bearing the same number as before. Dosages were as follows: Formulation A contains 200 mg of encapsulated acetyl salicylic acid mixed with 20 mg of tiemonium in hard gelatin capsule; and Formulation B contains 200 mg of encapsulated acetyl salicylic acid in hard gelatin capsule.

The dose administered was adjusted to 200 mg/kg of aspirin and 20 mg/kg of tiemonium.

Each dog received the two formulations one week apart in the following random order.

Dogs	M1 *	M2 *	M3 *	F4 **	F5 **
Weight (kg) ***	9.5	10.2	10	8.5	9.5
1st administration	B	A	A	B	A
Weight (kg) ***	9	9.4	9	7.7	8.5
2nd administration	A	B	B	A	B

* Male.

** Female.

*** Weight of dogs just before administration (first or second).

Blood samples (3.5 ml) were taken for salicylate assay at the following times after administration: 0.50; 1; 1.50; 2; 4; 6; 8; 12 and 24 h.

Salicylate assay

The same method was used as above.

Results

Mean blood salicylate concentrations and AUC found in the 5 dogs after oral administration are given in Table 2.

Conclusion and Discussion

In all cases, the micro-encapsulated aspirin is absorbed very slowly but when it is added with tiemonium the absorption rate is slower. This is checked in peak time (T_{max}) (approximately 5 h of difference) but the maximum concentration (C_{max}) are very close.

TABLE 2

MEAN BLOOD SALICYLATE AND AUC IN DOGS AFTER ORAL ADMINISTRATION

Dogs	Mean blood salicylate levels (μg/ml)									Mean AUC	Standard deviation
	Time										
	0.50 h	1 h	1.50 h	2 h	4 h	6 h	8 h	12 h	24 h		
A (mean)	6.5	21	31	40.5	58.5	94.5	120	147.5	78	2393.4	558.5
A (standard deviation)	6.52	15.47	23.56	27.64	34.49	60.45	53.88	28.17	21.75		
B (mean)	8	30	54	84	140	168	155	131	61	2645.5	568.8
B (standard deviation)	6.94	6.85	19.25	21.98	25	28.53	33.73	38.23	28.15		

A = aspirin + tiemonium; B = aspirin alone.

This is confirmed by the values of the absorption constant (K_a) of aspirin ($K_a = 0.80244$) which is 4.7 times higher than aspirin + tiemonium ($K_a = 0.17849$).

However, the amount of absorbed drug is the same as can be seen with the areas under the curves (analysis of variance, $P = 0.05$). It seems that when tiemonium is administered by oral route, it reduces the absorption rate of aspirin without modified the absorbed amount. Furthermore there is no difference owing to the sex of the animals.

However, the delay observed in aspirin absorption in dogs is so important that it was not possible to discard the hypothesis of an identical delay in man. Therefore, in view of eliminating this effect, a special formulation was designed in which the two active ingredients are released successively. Tiemonium was placed in the core of a tablet and microencapsulated aspirin in the outer layer. The latter drug is thus released immediately on arrival in the stomach while release of tiemonium is delayed. This formulation was tested in man.

II. Experiments in man

(1) First experiment

Procedure

In this first experiment the following formulations were used.

Formulation A	
Core	
Tiemonium	50 mg
Potato starch	45 mg
Polyvidone K 90	2 mg
Talc	2 mg
Glycerol palmito-stearate	1 mg
Outer layer	
Encapsulated acetylsalicylic acid	525 mg
Potato starch	35.5 mg
Avicel PH 101	20 mg
Polyvidone K90	1.5 mg
Talc	8 mg
Glycerol palmito-stearate	10 mg
Formulation B	
Core	
Potato starch	67.9 mg
Polyvidone K90	1.4 mg
Talc	1.4 mg
Glycerol palmito stearate	0.7 mg
Lactose	28.6 mg
Outer layer	
Like formulation A	

From the pharmaceutical point of view, the tablets were made as follows.

Formulation A: the core was made after a wet granulation of the various ingredients by a rotative machine (Manesty MD500); the outer layer was tableted after wet granulation of the different ingredients around the core with the same tableting machine.

Formulation B: the core was made like in formulation A but the outer layer was tableted by direct compression directly around the core.

For the two formulations (A and B), the desintegration time was close to 15 min and hardness to 16 kgp. The dissolution rate of aspirin from the two formulations evaluated by the basket method in distilled water at 100 rpm indicated that 100% of aspirin was released in 90 min.

Subjects

Eight healthy volunteers were used; all had normal kidney functions. Each subject received the two formulations one week apart in the following random order.

Subject	1	2	3	4	5	6	7	8
1st administration	A	B	B	B	A	B	A	A
2nd administration	B	A	A	A	B	A	B	B

Subjects received 3 tablets in the morning without food but they could eat 4 h later.

Blood salicylate was assayed at the following times after administration: 0.50; 1; 2; 3; 3.50; 4; 5; 6; 8; 12 and 24 h.

Salicylate assay

The method used was a scaled-up version of that used above; 1 ml of blood was used instead of 0.2 ml with other reagent quantities being adjusted accordingly.

Results

Mean blood salicylate concentrations and AUC found after oral administration are given in Table 3.

Conclusion and Discussion

Analysis of variance performed on the areas under the curves showed in this experiment a statistically significant difference between the two tablets forms. Thus, C_{max} is quite different, though T_{max} does not differ significantly. This finding is unexpected given that the tiemonium should be released later.

Therefore, a second dissolution test was undertaken in order to show a difference between the two formulations. This dissolution test was performed by the paddle method at 60 rpm using distilled water as dissolution medium at 37°C. The results obtained are presented in Table 4.

TABLE 3

MEAN BLOOD SALICYLATE AND AUC IN MAN AFTER ORAL ADMINISTRATION

	Mean blood salicylate levels (μg/ml)											Mean AUC	Standard deviation
	Time												
	0.50 h	1 h	2 h	3 h	3.50 h	4 h	5 h	6 h	8 h	12 h	24 h		
A (mean)	0	0.78	8.28	13.13	18.47	18.75	24.88	28.94	28.59	21.59	1.41	244.5	154.8
(standard deviation)	0	2.21	10.37	12.78	14.50	15.77	18.84	19.65	15.34	13.61	2.63		
B (mean)	4.69	11.88	27.53	35.63	42.50	43.75	43.13	47.81	30.60	21.91	1.88	371.6	150.9
(standard deviation)	4.71	11.40	16.64	18.70	18.60	19.63	11.90	13.04	18.43	14.30	2.67		

A = aspirin + tiemonium; B = aspirin alone.

TABLE 4

MEAN DISSOLVED ASPIRIN FROM FORMULATIONS A AND B

Tablet	Mean aspirin levels (μg/ml)					
	Time					
	0.25 h	0.50 h	1 h	2 h	3 h	4 h
A (mean)	32.5	43	60.5	92	110.5	130
A (standard deviation)	0.28	1.37	3.26	12.67	5.42	7.71
B (mean)	40.9	98.5	192.5	334.5	403	411.2
B (standard deviation)	8.20	8.94	48.28	41.44	52.25	54.01

Conclusion

By using the paddle method, the results obtained showed that the tablets of batch A released only 24.75% of their aspirin content in 4 h, whereas those of batch B released 78.30% of their aspirin content in the same time. This difference in vitro is likely to occur in vivo.

(2) Second experiment:

Procedure

Formulation. Owing to this difference of the release rate we modified the manufacturing process. The core of the two formulations was always made after a wet granulation but the outer layer of those was tableted by direct compression, after mixing of the different ingredients, around the core. The compression pressure was strictly determined: the disintegration time was close to 15 min, hardness 12 kgp and in vitro release rate evaluated again with the paddle method. The formulation A released 71.2% of its aspirin content in 1.50 h and the formulation B released 71.6% of its aspirin content in the same time. Using these new batches, a second bioavailability study was performed in man.

Subjects. The same subjects and the same experimental conditions were used. Each subject received the two formulations one week apart in random order. Blood salicylate was assayed at the following times after administration: 0.50; 1; 2; 3; 3.50; 4; 5; 6; 8; 12 and 24 h.

Salicylate assay. The method used was the same as above.

Results

Mean blood salicylate concentrations and AUC_0^{12} found in this second experiment are given in Table 5.

Conclusion

The results obtained show that the two formulations A and B are bioequivalent.

TABLE 5

MEAN BLOOD SALICYLATE AND AUC IN MAN AFTER ORAL ADMINISTRATION

Subject	Mean salicylate levels (μg/ml)											Mean AUC	Standard deviation
	Time												
	0.50 h	1 h	2 h	3 h	3.50 h	4 h	5 h	6 h	8 h	12 h	24 h		
A (mean)	5.88	18	29.88	36.38	39.25	40.50	48.75	48.88	43.25	21.63	1.13	420.81	78.33
A (standard deviation	10.13	10.99	17.84	14.92	14.71	12.36	7.27	8.63	7.30	7.93	2.23		
B (mean)	10.63	20.88	35.50	48	52.25	56	56.88	51.75	40.50	25.13	2.75	467.22	102.51
B (standard deviation	6.78	7.64	9.07	7.71	9.87	9.86	13.87	13.02	10.98	10.02	5.20		

A = aspirin + tiemonium; B = aspirin alone.

The two bioavailability parameters, absorbed amount and absorption rate are not different. The absorbed amount, determined from the areas under the curves, were practically the same (no statistically significant difference at $P = 0.05$). Similarly, T_{max} and C_{max} were not different at $P = 0.05$ with the exception of subject 3 who gave abnormal values.

Discussion and Conclusion

Tiemonium administered by peroral route to animals slows down the absorption of aspirin though without reducing the total amount absorbed. This effect is reminiscent of that described for metoclopramide and antispasmodics in general which slows down absorption by inhibiting peristaltic movement without affecting total amount absorbed (Koffel, 1979).

The association of tiemonium with aspirin needs a special formulation to separate the release of the two drugs in the gastrointestinal tract. This formulation is not easy to develop and the results obtained indicate the importance of the tablets': (1) manufacturing process (wet granulation or direct compression); (2) pharmaceutical parameters (hardness); and (3) determination of release rate of the drug (basket or paddle method).

To complete this study, blood levels of tiemonium might have been determined but its very low absorbed amount did not allow accurate assay except in the case of the labelled drug.

References

Cid, E., Delporte, J.-P. et Jaminet, F., Méthode rapide de dosage des salicylates dans le sang. Pharm. Acta. Helv., 46 (1971) 737–741.

Koffel, J.-C., Interférences médicamenteuses. Vol. XXII, Bull. Soc. Pharm. Strasbourg, 1979, p. 91–102.

Morgan, A.M. and Truitt, E.B., Gastrointestinal factor in aspirin absorption. J. Pharm. Sci., 53 (1964) 129–134.

Robert, H., Trublin, F. et Delcambre, B., Etudé de l'influence des conditions d'aministration sur la biodisponibilité de différentes formulations d'acide acetylsalicylique, 2ème Congrès International de Technologie Pharmaceutique, APGI Paris 3–5 juin 1980, p. 151.

Wainscoot, G., Kaspi, I. and Volans, G.N., The influence of thiethylperazine on the absorption of effervescent aspirin in migraine. Br. J. Clin. Pharmacol., 3 (1976) 1015–1021.

Koch-Weser, J., Drug therapy: bioavailability of drugs. N Engl. J. Med., 291 (1974) 233–237.