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The effect of food on the oral absorption of isosorbide-5-mononitrate

While complete gastrointestinal absorption of isosorbide-5-mononitrate (IS-5-MN) has been shown in fasting subjects (Taylor *et al.*, 1981; Abshagen *et al.*, 1981), nothing is known about the influence of concomitant food intake on the pharmacokinetics of this drug. We measured plasma drug concentrations after a single oral dose of IS-5-MN in healthy human subjects, both fasting and after a standard breakfast.

The study was approved by the Ethics Committee of Pfizer International, Brussels. The participants were submitted to physical examination and comprehensive laboratory tests before the study. Six male and three female healthy volunteers, aged 22–41 years received one 40 mg tablet (Mono Mack®, MACK, Illertissen, FRG) after an overnight fast and either 3 h before or together with a standard breakfast consisting of two rolls with 40 g butter, 50 g marmalade and 200 ml of caffeine free tea. The order of administration before or with food was randomly allocated with a wash out time of 14 days.

Venous blood samples were taken at increasing time intervals up to 12 h after administration and IS-5-MN plasma concentrations were analysed by a g.l.c. ECD method with isosorbide-2-mononitrate as internal standard (Laufen *et al.*, 1983). The limit of detection of this method was 5 ng/ml. Linear calibration curves were obtained in the range of 20–2000 ng/ml. The weekly checked difference between found and given concentrations, unknown to the analyst, was random and ranged between 0 and –18.9%

(mean 6.7%). Between-day precision was 4.7%. Ninety-five per cent of IS-5-MN and 94% of the standard were recovered from plasma. The overall reproducibility of duplicate estimations in this trial was $\pm 3.9\%$ (coefficient of variation).

Terminal elimination half-lives were obtained by exponential regression. They were used to correct the trapezoidal AUC to an infinite time. The observed differences between the two modes of administration in peak times, peak heights, AUCs and half-lives were tested by the Student's *t*-test for paired data.

The measured pharmacokinetic parameters are shown in Table 1. IS-5-MN plasma concentrations increased more rapidly when the dose was administered without food than together with food. On average, food postponed the peak concentration by about 40 min and reduced the peak height by about 20%. However, these changes did not reach statistical significance at $P = 0.05$. Terminal plasma half-lives were apparently not influenced by food intake. There was also no significant change in the areas under the curve, which were on average 16.4% higher with food than without food. A posterior estimation of the type II error showed that real differences between the treatments, which are high enough to presume therapeutical implications, such as a 25% difference in AUC, a doubling of the peak time or an increase in peak height of about 40% would have been detected, if present, with a probability of 0.8 at a significance level of $P = 0.05$.

Table 1 Parameters of isosorbide-5-mononitrate plasma pharmacokinetics obtained after oral administration of a single 40 mg tablet in the fasting state (F) and together with a standard breakfast (NF).

Volunteer	Sex	Peak time (h)		Peak height (ng/ml)*		AUC (ng ml ⁻¹ h)		Terminal half-life (h)	
		F	NF	F	NF	F	NF	F	NF
1	M	0.25	0.75	1353	689	4796	4234	4.3	3.4
2	M	0.50	3.00	1049	740	6439	5939	4.1	4.4
3	F	0.50	1.50	1407	714	7010	9815	4.2	9.5
4	F	2.00	1.50	707	744	5654	5921	4.9	4.3
5	M	0.25	1.00	809	966	3484	5479	4.3	4.7
6	M	0.50	2.00	807	819	2593	6036	2.8	3.2
7	F	3.00	3.00	757	757	7219	7430	5.4	5.6
8	M	1.50	1.00	699	521	4762	4002	4.2	3.6
9	M	0.75	1.00	779	786	3793	4415	3.7	4.2
Mean		1.03	1.64	930	749	5083	5919	4.2	4.8
s.d.		0.95	0.86	275	118	1622	1818	0.7	1.9
P		> 0.05		> 0.10		> 0.10		> 0.30	

P level of the type-I error for the difference between F and NF.

*Conversion factor: 1 ng/ml = 5.23 nmol/l.

Food was found to have little influence on the total bioavailability of isosorbide dinitrate (Taylor *et al.*, 1982), but mean peak drug concentrations were significantly reduced. We observed a similar trend for IS-5-MN. The apparent reduction in peak drug concentrations with concomitant food intake may be explained by a slowing of the rate of absorption. An influence of food on the rate of drug absorption without an effect on the total amount absorbed is observed for many drugs, and is probably related to the slowing of gastric emptying (Welling, 1977). Our investigation shows that the high systemic bioavailability of oral IS-5-

MN is maintained when the drug is taken with food. It is inferred that in long time therapy—e.g. two times 40 mg daily—the influence of a light meal on the efficacy and dose-related side-effects of IS-5-MN will be negligible.

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