

Title: EFFECT OF FOOD ON METOCLOPRAMIDE BIOAVAILABILITY

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**Introduction.** The presence or absence of food in the stomach can significantly alter the bioavailability of orally administered drugs, an important consideration in the perioperative period. We conducted a study to evaluate the effect of a high fat meal on the oral relative bioavailability of one immediate release (IR) and two controlled release formulations (CR1 and CR2) of metoclopramide.

**Methods.** We designed a six-way, randomized, single dose, crossover, open, feeding/fasting, bioavailability study with blinded analytical procedures. Twenty-one healthy males, mean age 25.9 (range 18 to 50 yrs) completed the study. In order to determine the comparative bioavailability of the three study formulations, single 20mg doses of each of the three metoclopramide study formulations were administered in both the fed and fasted states to all participants. A seven day washout period between each crossover period was observed. Eighteen plasma metoclopramide levels obtained over 36 hours were analyzed using high performance liquid chromatography (HPLC).

**Results.** ANOVA revealed the following differences in area under the plasma concentration-time curve (AUC), the maximal concentration (Cmax), and the time of concentration (Tmax):

	AUC (ng/mlxhr)		
	IR	CR1	CR2
fasted	785	763	857
fed	725	710	835
p value	.02	.03	NS

IR and CR1 exhibited significant differences in AUC while CR2 showed no difference in AUC between the fed and fasted states. Comparisons between the three formulations showed the CR2 formulation to have a significantly higher AUC than either the IR or CR1 formulations in both the fed and fasted states.

	Cmax (ng/ml)		
	IR	CR1	CR2
fasted	84	57	48
fed	71	58	49
p value	.001	NS	NS

The overall Cmax was significantly different between the three study preparations with CR2 showing the lowest and IR showing the highest Cmax. In the fed/fasted analysis, no significant difference was noted with either of the CR preparations while the IR preparation produced a very significant difference between the fed and fasted states.

	Tmax (hr)		
	IR	CR1	CR2
fasted	1.6	3.4	4.2
fed	2.8	4.1	4.1
p value	.001	.02	NS

Data show that Tmax values were not significantly different for the CR2 administered in the fed or fasted states while there was a significant difference with the IR and CR1 formulations. Additionally, the IR Tmax was significantly lower than either CR preparation.

**Discussion:** Food affected the IR formulation the most, and had no effect on the CR2 formulation. Both CR preparations were comparable in overall bioavailability to IR, but exhibited prolonged Tmax and attenuated Cmax values.

In summary, the IR formulation was more sensitive to a high fat meal than the CR formulations, a factor that is important in post operative patients where reliability of dosing is essential.