A COMPARATIVE STUDY OF THE BIOAVAILABILITY OF BROMAZEPAM, OMEPRAZOLE AND PARACETAMOL FOLLOWING ORAL AND NASOGASTRIC ADMINISTRATION IN HEALTHY VOLUNTEERS

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Introduction

Bromazepam (BMZ), omeprazole (OMZ) and paracetamol (PAC) are frequently administered jointly to hospitalized oncology patients to decrease anxiety, prevent stress ulcer and control pain. In enterally fed patients, these drugs are generally administered via nasogastric (NG) tube. Bioavailability by this route is uncertain since it often implies tablet modifying, and because some gastrointestinal parameters are affected, e.g. volume and pH of the gastric fluid, and gastric emptying time. Furthermore, the evidence in the literature is partial, inconclusive and even contradictory regarding the compared bioavailability of drugs administered by the oral and nasogastric routes.

Objectives of the study

To characterize and compare the pharmacokinetic profiles of the 3 drugs BMZ (Lexotanil® 3mg), OMZ (Antramups® 20mg) and PAC (Dafalgan® 1 g soluble tablets) administered orally and via nasogastric tube to healthy volunteers.

Methods

A prospective, monocentric, crossover and randomized study was carried out in 8 healthy volunteers*. Each volunteer was medicated with a 28-day interval according to two distinct protocols:

Nasogastric

Day 0 : Hospitalization, insertion of nasogastric tube, enteral feeding during 24h at a rate of 30 kcal/kg/24h.

Day 1: Enteral feeding interrupted, medication, enteral feeding during 12h. Discharge.

Oral

Day 0 : Three standard meals without hospitalization.

Day 1 : Oral medication, 3 standard meals, discharge.

In both protocols, 13 blood samples were taken from t_0 to $t48_h$.

Plasma samples were analyzed by HPLC-UV using two methods (one for BMZ and OMZ[1], and the other for PAC) validated according to ISO, ICH and FDA criteria.

The pharmacokinetic parameters were analyzed statistically based on a parametric approach (paired t test on natural log) for C_{max}, $AUC_{0-\infty}$, $t_{1/2}$ and by a non-parametric approach (Wilcoxon) for t_{max}. A bioequivalence analysis was carried out in parallel to assess the clinical impact of the differences observed in C_{max}, $AUC_{0-\infty}$ and t_{max}.[2, 3]

Results

Lexotanil®

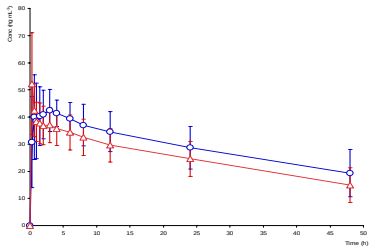

Fig. 1 – Mean concentrations (± SD) after administration of a single dose of bromazepam (3mg) orally (○) and by nasogastric (NG) tube (△).

Parameters		Geometric Means	Variation Coefficient		Ratio of Geometric Means	90% Confidence Limits
C_{max} [ng/ml]	Oral	46	19.7%	p< 0.05	1.20	(1.10-1.30)
	NG	55.1	25.3%			
T_{max} [h]	Oral	1.53	152.0%	p<0.05		
	NG	0.53	160.3%			
$AUC_{0-\infty}$ [ng/ml·h]	Oral	2500	78.0%	p<0.05	0.74	(0.64-0.87)
	NG	1855	56.0%			
$T_{1/2}$ [h]	Oral	39.7	71.9%	p>0.05		
	NG	33.3	40.3%			

Tab.1 - Comparaison of the main pharmacokinetic parameters for Lexotanil®.

Antramups®

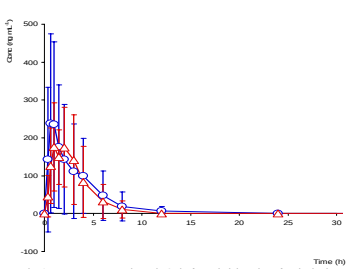

Fig. 2 - Mean concentrations (± SD) after administration of a single dose (20 mg) of omeprazole orally (○) and by nasogastric (NG) tube (△).

Parameters		Geometric Means	Variation Coefficient		Ratio of Geometric Means	90% Confidence Limits
C_{max} [ng/ml]	Oral	189	170.2%	p>0.05	1.24	(0.71-2.16)
	NG	234	57.2%			
T_{max} [h]	Oral	1.33	116.3%	p>0.05		
	NG	1.23	74.0%			
$AUC_{0-\infty}$ [ng/ml·h]	Oral	579	172.1%	p>0.05	1.01	(0.64-1.61)
	NG	587	107.5%			
$T_{1/2}$ [h]	Oral	2.42	172.7%	p<0.05		
	NG	1.16	61.9%			

Tab. 2 - Comparaison of the main pharmacokinetic parameters for l'Antramups®.

Dafalgan® Effervescent

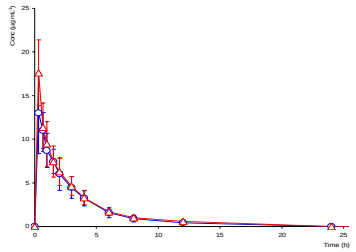

Fig. 3 - Mean concentrations (± SD) after administration of a single dose (1000 mg) of paracetamol orally (○) and by nasogastric (NG) tube (△).

Parameters		Geometric Means	Variation Coefficient		Ratio of Geometric Means	90% Confidence Limits
C_{max} [µg/ml]	Oral	14.1	22.6%	p>0.05	1.26	(1.04-1.53)
	NG	17.7	20.1%			
T_{max} [h]	Oral	0.41	36.8%	p>0.05		
	NG	0.34	35.4%			
$AUC_{0-\infty}$ [µg/ml·h]	Oral	37	25.4%	p>0.05	1.12	(0.98-1.28)
	NG	41.3	20.9%			
$T_{1/2}$ [h]	Oral	2.45	13.6%	p<0.05		
	NG	2.68	14.9%			

Tab. 3 - Comparaison of the main pharmacokinetic parameters for Dafalgan® Effervescent.

Discussion

For bromazepam, a statistically significant difference was observed in the $AUC_{0-\infty}$, with a decrease of ca. 25% in its availability via nasogastric tube. However and taking into account its usual dosage range and half-life (≈ 30h), the clinical impact of this difference appears as minute if not irrelevant.

For omeprazole, its large interindividual variability does not allow one to conclude to a statistically proven bioequivalence of the two modes of administration. A larger group would be necessary to this end.

For paracetamol, the values of the 90% confidence limits suggests a bioequivalence.

**The protocol was approved by the Ethics Committee for Clinical Research of the Faculty of Biology and Medicine of the University of Lausanne, and simultaneously notified to the Federal authorities (Swissmedic).*

Conclusions

This study shows that administration by nasogastric tube does not lead to marked alterations in the bioequivalence of the drugs examined. Hence the clinical consequences of this route of administration can be considered as limited.

Bibliography

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