

The Rate and Extent of Calcium Bioavailability from Two Oral Dosage Forms in Rats

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Abstract. The purpose of the present work was to compare oral bioavailability of calcium from two calcium preparations, Calcium Sandoz forte 500 mg and Calcium Spofa effervescens. The pharmacokinetic study was carried out on rats, and plasma levels of ⁴⁵Ca after administration of labelled calcium solutions were determined. Appropriate equations describing the two-compartment open model and the one-compartment model with first order absorption were fitted to the observed i.v. and oral data, respectively, using weighted nonlinear least-squares regression analysis. The extent and the time profile of the rate of ⁴⁵Ca systemic bioavailability were assessed. Both parameters suggested identical bioavailability of calcium from the two dosage forms compared.

Key words: Calcium — Oral bioavailability — Dosage form

Introduction

Bioavailability of calcium from oral calcium dosage forms may largely differ (Goodman and Gilman 1975). The bioavailability of a drug may be defined in two different ways, namely as the extent of bioavailability, F , and the rate of bioavailability, $B(t)$ (Wagner 1975a).

$$F = \frac{\text{Dose}_{iv} \cdot \int_0^{\infty} C'(t) dt}{\text{Dose}_{po} \cdot \int_0^{\infty} C(t) dt} \quad (1)$$

where $C(t)$ and $C'(t)$ represent the concentration-time curves of the drug following intravenous and oral administration, respectively.

$B(t)$ may be assessed by solving integral equation

$$C'(t) = \frac{\text{Dose}_{po}}{\text{Dose}_{iv}} \cdot \int_0^t B(\tau) \cdot C(t - \tau) d\tau \quad (2)$$

where t and τ represent time.

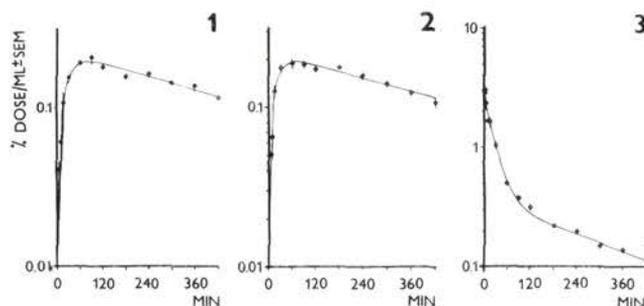


Fig. 1. ^{45}Ca concentration in rat plasma (% dose/ml) following oral administration of ^{45}Ca labelled solution of Calcium Sandoz forte (1), Calcium Spofa effervescens (2), and intravenous administration of $^{45}\text{CaCl}_2$ (3).

Materials and Methods

Calcium Sandoz forte 500 mg (CaSz) contains calcium lacto-gluconate 2.94 g, calcium carbonate 0.3 g, excipients ad 7.0 g, and Calcium Spofa effervescens (CaSp) contains calcium lactate-gluceptate 2.98 g, calcium carbonate 0.3 g, excipients ad 7.0 g. One tablet of each drug contains 500 mg of ionizable calcium.

Male Wistar rats weighing 180–200 g were used. Prior to oral administration, the animals were fasting for 18 h. One tablet per each drug was dissolved in water to a final volume of 180 ml. To 15 ml of the solution 1.3 ml of $^{45}\text{CaCl}_2$ (40 MBq $^{45}\text{Ca} \cdot \text{ml}^{-1}$ or 100 GBq $^{45}\text{Ca} \cdot \text{g}^{-1}$ Ca) was added. The mixtures were administered orally to 3 groups of 6 rats each through a metallic tube (2.79 $\mu\text{l} \cdot \text{g}^{-1}$ body mass) 24 h later. The dose of the calcium administered was 7.22 $\mu\text{g} \cdot \text{g}^{-1}$ body mass. Blood was withdrawn from the retroorbital venous plexus in the first animal group 15; 90; 240; and 420 min, in the second one 10; 60; 180; and 360 min, and in the third one 5; 30; 120; and 300 min, after the administration. $^{45}\text{CaCl}_2$ was administered intravenously to 4 groups of 6 rats each (1 $\mu\text{l} \cdot \text{g}^{-1}$ body mass). The dose of the calcium administered was 1.35 $\mu\text{g} \cdot \text{g}^{-1}$ body mass. Blood was taken in the first animal group 1; 3; and 5 min, in the second one 15; 90; 240; and 420 min, in the third one 10; 60; 180; and 360; and in the fourth one 30; 120; and 300; min, after the administration. To 150 μl of plasma 150 μl of H_2O and 5 ml of Instagel (Packard, Downers Grove, USA) were added. ^{45}Ca was measured by a liquid scintillation spectrometer Packard 300 CD. Exponential equations

$$C'(t) = P(1) \cdot (e^{-P(2)t} - e^{-P(3)t}) \quad (3)$$

$$C(t) = P(1) \cdot e^{-P(2)t} + P(3) \cdot e^{-P(4)t} \quad (4)$$

were fitted to the oral and intravenous ^{45}Ca plasma concentration-time data (Yamaoka et al. 1981), respectively, weighting each data point by 1; $1/C_{\text{obs}}$; or $1/C_{\text{obs}}^2$. $P(i)$ is the optimized computer estimate of the parameter. The equations were optimized using the 1976 version of the NONLIN program (Metzler et al. 1974). The equation with minimum AIC (Yamaoka et al. 1978) was chosen as the best representation for the time course data. Pharmacokinetic parameters were computed according to Wagner (1975b). Appropriate t statistics was used to estimate statistical differences between the pharmacokinetic parameters (Boxenbaum et al. 1974). To obtain the rate of bioavailability $B(t)$, the integral equation (2) was solved by standard means, using Laplace transformations.

Table 1. Parameters $P(i)^a$ of equations (3) and (4)

	Calcium Sandoz forte (oral)		Calcium Spofa effervescens (oral)		$^{45}\text{CaCl}_2$ (intravenous)	
$P(1)$	0.2372	0.0149 ^b	0.2235	0.0101 ^b	2.2076	0.1247
$P(2)$	0.0017	0.0003	0.0016	0.0002	0.0398	0.0036
$P(3)$	0.0409	0.0052	0.0511	0.0054	0.3655	0.0340
$P(4)$					0.0028	0.0003

^a $P(1)$, $P(3)$ for i.v. data and $P(1)$ for oral data are expressed as % dose/ml, and $P(2)$, $P(4)$ for i.v. data and $P(2)$, $P(3)$ for oral data as min^{-1}

^b standard deviation

Table 2. Calcium pharmacokinetic parameters in rats

AUC, area under the curve; $T_{1/2}$, half-life; el, elimination; ab, absorption; c_{max} , maximum plasma concentration; t_{max} , time of c_{max} ; V_{dss} , steady state volume of distribution; F , bioavailability; abs, absolute; rel, relative;

	Calcium Sandoz forte (oral)	Calcium Spofa effervescens (oral)	$^{45}\text{CaCl}_2$ (intravenous)
AUC_0^∞ (% dose. h. ml^{-1})	2.229	2.255	3.100
$T_{1/2\text{el}} \pm \text{SD}$ (h)	6.796 ± 1.199	7.22 ± 0.902	4.125 ± 0.442
$T_{1/2\text{ab}} \pm \text{SD}$ (h)	0.282 ± 0.036	0.226 ± 0.024	
c_{max} (% dose. ml^{-1})	0.207	0.193	
t_{max} (h)	1.352	1.166	
V_{dss} (ml)			138.724
$F_{\text{abs.}}$ (%)	71.903 ^a	72.741 ^a	
$F_{\text{rel.}}$ $F_{\text{abs.}}$ (%)		Sp/Sz = 1.011	
	71.503 ^b	72.350 ^b	

^a by solution of equation (1)

^b by integration ($0 \rightarrow \infty$) of equations (5) and (6)

Results and Discussion

The ^{45}Ca plasma concentration-time dependences after oral administration of ^{45}Ca -labelled CaSz and CaSp, and after intravenous administration of $^{45}\text{CaCl}_2$ are

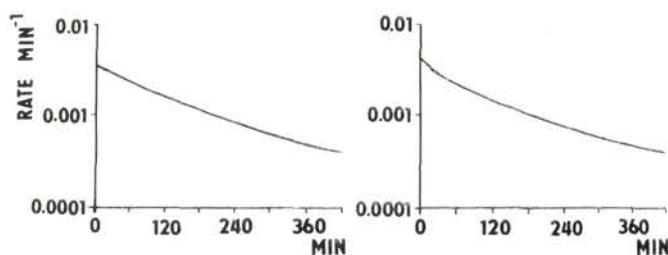


Fig. 2. The initial rate of ^{45}Ca entry into vascular pool $B(t)$ (min^{-1}) vs. time following oral administration of ^{45}Ca labelled solution of Calcium Sandoz forte (1) and Calcium Spofa effervescens (2).

shown in Fig. 1. The parameter estimates of equations fitting optimally to these data are shown in Table 1. Accordingly, a linear open one-compartment model, and a linear open two-compartment model were conferred to the oral and intravenous data, respectively. The derived pharmacokinetic parameters are shown in Table 2. The bioavailabilities of calcium from the preparations compared were identical. Essentially the same figures for bioavailability were obtained by the deconvolution method (solution of equation (2)). Following equations were obtained for the initial entry rates of calcium from CaSz and CaSp, respectively:

$$B(t)_{\text{CaSz}} = 6.036 \cdot 10^{-4} \cdot e^{0.0017t} + 1.177 \cdot 10^{-4} \cdot e^{-0.0409t} + 2.892 \cdot 10^{-3} \cdot e^{-0.0081t} \quad (\text{min}^{-1}) \quad (5)$$

$$B(t)_{\text{CaSp}} = 6.125 \cdot 10^{-4} \cdot e^{-0.0016t} + 1.102 \cdot 10^{-3} \cdot e^{-0.0511t} + 2.584 \cdot 10^{-3} \cdot e^{-0.0081t} \quad (\text{min}^{-1}) \quad (6)$$

The comparative ^{45}Ca initial entry rates for CaSz and CaSp from the intestinal tract into the vascular system are shown in Fig. 2.

In CaSz tablets, calcium is in the form of calcium salts of the lactic, carbonic and gluconic acids, while CaSp contains calcium salts of the lactic, carbonic and D-glucoheptonic acids. Data on the lactate-to-gluconate and lactate-to-glucoheptonate ratios are not available. The dosage form entering the organism represents a solution of calcium salts of three acids with different dissociation constants. The ^{45}Ca tracer, in form of dissociated chloride, increased the calcium concentration in the solution by about 1%. Most works on calcium absorption have stressed the active transport process. Of the total amount in the intestinal lumen, only the ionized fraction is available for the transfer into the vascular pool (Fig. 3) (Wilkinson 1976). The assessment of pharmacokinetic parameters of ^{45}Ca is based on two main assumptions:

1) After complete mixing with calcium, in the solution administered, ^{45}Ca traced well the calcium absorption and elimination pathways.

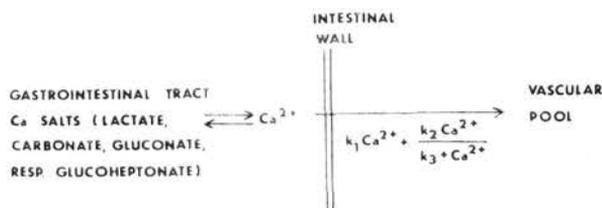


Fig. 3. Diagram of calcium transport from the intestinal lumen to the vascular pool (adapted from Wilkinson 1976). Calcium absorption is a two component process. One component is saturable ($k_2 \cdot \text{Ca}^{2+}/(k_3 + \text{Ca}^{2+})$), and the other one is concentration-dependent and unsaturable ($k_1 \cdot \text{Ca}^{2+}$).

2) The kinetics of ^{45}Ca is dose-independent in the dose range of $1-10 \mu\text{g} \cdot \text{g}^{-1}$.

The initial entry rate at a given time is a reflection of two factors: of the then existing geographical distribution of the unabsorbed dose and of the variable absorption activity along the gastrointestinal tract (Hart and Spencer 1967). The data presented provide information about the rate at which calcium from the two dosage forms is initially absorbed from the gastrointestinal tract after its administration in solution, without specifying the profile of absorption activity along the tract. Our experiment has shown that CaSz and CaSp are completely equivalent with respect to both, the bioavailability of calcium and the rate of calcium bioavailability.

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