Pharmacokinetic Test of Calcium Aspartate Anhydrous

This study tests the metabolic mechanism and the pharmacokinetics on the changes of calcium aspartate anhydrous in animal bodies over time. The results indicate that the absorption metabolism of calcium aspartate anhydrous in rat intestine satisfied the One-Chamber model. The absorption of calcium aspartate anhydrous was relatively slower but more complete than that of other calcium agents tested, including calcium citrate, calcium gluconate and calcium carbonate. This can be explained by the fact that the molecules of calcium aspartate anhydrous are absorbed in the small intestine as opposed to that other calcium compounds are ionized and absorbed in the stomach. The results confirm that calcium aspartate anhydrous stays in serum for a longer time at a higher level. The peak of serum calcium concentration arrived later (t_{max} =0.74hrs), but the half-life was longer ($t_{1/2}$ =4.22hrs) than those of other calcium agents. The area under curve (AUC_{0_t}) is 201.75(μg/ml)·hr (see Fig. 1). The kinetic change of the calcium aspartate anhydrous levels in the serum of household dogs and other dynamic parameters thereof are consistent with those of rats.

1. Agents

(1) Calcium aspartate anhydrous, a white anhydrous powder containing 13% elemental calcium, was formulated with 0.5% CMC to create solutions with calcium concentration of 15mg/ml, 10mg/ml and 5mg/ml respectively.

(2) Calcium citrate, a white powder containing 20.3% of elemental calcium, was formulated with 0.5% CMC into a mixed suspension with calcium concentration of 10mg/ml.

(3) Calcium gluconate, a white crystalline powder containing 8.9% of calcium, was formulated with 0.5% CMC into a mixed suspension with 10mg/ml calcium concentration.

(4) Calcium carbonate, a white powder containing 40.9% of calcium, was formulated with 0.5% CMC into a mixed suspension which has a calcium concentration of 10mg/ml.

2. Animals and apparatus

(1) Animals: Wistar rats of male and female each weighing 150-170 g, 180-220 g respectively, were provided by Department of Laboratory Animals, Shanghai Medical University. Male crossbred domestic dogs each weighing 20.5-26.5kg, were provided by Laboratory Animals, Shanghai Chinese Medical University.

(2) Apparatus: Jarrell-Ash 810 Atomic Absorption Spectrophotometer was produced by Jarrell Ash Corp.,USA; Centrifuge himac CR7 was produced by Hitachi, Japan; DT-100

Single Pan Balance was produced by Beijing Optical Apparatus Factory; VM3 Vortex Mixer was produced by Shanghai Guanghua Scientific Apparatus and Materials Co. Ltd.

3. Dosage and administration

The dosage administered to rats was designed for the following six groups:

(1) Group A: high dosage of calcium aspartate anhydrous in 2.31g/kg body weight (containing 300mg calcium/kg body weight),
(2) Group B: medium dosage of calcium aspartate anhydrous in 1.54g/kg body weight (containing 200mg calcium/kg body weight),
(3) Group C: low dosage of calcium aspartate anhydrous in 0.77g/kg body weight (containing 100mg calcium/kg body weight),
(4) Group D: calcium citrate in a dosage of 0.98g/kg body weight (containing 200mg calcium/kg body weight),
(5) Group E: calcium gluconate in a dosage of 2.25g/kg body weight (containing 200mg calcium/kg body weight), and
(6) Group F: calcium carbonate in a dosage of 0.49g/kg body weight (containing 200mg calcium/kg body weight).

The dosage of calcium aspartate anhydrous for dogs is 1.54g/kg body weight (containing 200mg calcium/kg body weight) in correspondence with that of the medium dosage group of rats.

4. Test

(1) Determination of pharmacokinetic parameters

Sixty lab rats were randomly divided into six groups: the calcium aspartate anhydrous group of high dosage, the calcium aspartate anhydrous group of medium dosage, the calcium aspartate anhydrous group of low dosage, the calcium citrate group, the calcium gluconate group and the calcium carbonate group. Twelve hours after the animals had been fasted, 0.5ml plasma was sampled by excising eyeballs. The plasma was established as the blank group. Then rats were administered agents once in an amount of 20ml/kg body weight by pouring into the stomach. 0.5ml plasma was sampled by taking from eyeballs 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 16 hours later after the administration. The plasma was left for 30 minutes at room temperature and was then centrifuged at 300rpm for 20 minutes. 0.2ml serum was sampled, diluted to 2ml with lanthanum diluents, and homogenized. The concentration of calcium was measured by the Atomic Absorption Spectrophotometer.

(2) Measurement of calcium aspartate anhydrous level in dog serum

Five domestic dogs were administered agents once in an amount of 200ml/kg body weight by pouring into the stomach. 0.5ml blood was sampled respectively from femur vein 0.5, 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours later after the administration. The blood was left for 30 minutes at room temperature and was then centrifuged at 300rpm for 20 minutes. 0.2ml serum was sampled, diluted to 2ml with lanthanum diluents, and homogenized. The solution is stored for measurement.

5. Results

(1) Pharmacokinetic parameters
(i) The enhancement of serum Ca level at various time after the administration of agents was shown in Table I, Fig. 1 and Fig. 2.

Table I. Serum Ca Level Increase vs. Time

	Serum Ca Level Increase (μg/ml, mean/s.d.)										
Group*	**0.25hr**	**0.5hr**	**1.0hr**	**1.5hr**	**2.0hr**	**3.0hr**	**4.0hr**	**6.0hr**	**8.0hr**	**12hr**	**16hr**
A	27.5/3.2	37.8/5.1	38.3/1.6	36.2/2.1	35.3/2.6	27.6/4.4	27.5/6.2	21.3/3.7	13.2/5.4	8.4/2.1	3.6/.3
B	15.5/1.3	30.7/4.3	31.4/5.2	30.6/3.2	30.3/3.2	24.7/2.7	22.3/2.2	13.3/2.4	8.7/4.0	4.9/1.2	2.1/.5
C	9.8/.3	20.5/3.4	27.6/2.4	27.8/2.6	24.4/3.1	18.1/2.9	13.6/2.3	10.3/1.1	2.2/1.2	-	-
D	20.3/3.5	27.8/5.1	27.7/2.6	25.2/3.6	22.1/2.3	16.3/2.8	14.2/2.5	11.8/1.1	-.8/1.1	-	-
E	29.2/5.8	35.7/5.8	25.6/4.5	22.6/4.7	19.6/4.5	21.8/4.4	20.3/5.1	9.6/5.2	3.9/3.4	-	-
F	11.1/5.4	18.6/3.2	18.4/6.5	17.1/5.4	13.2/3.5	10.9/4.3	5.7/4.1	.2/.1	-1.4/1.3	-	-

* Group A: high dosage of calcium aspartate anhydrous
B: medium dosage of calcium aspartate anhydrous
C: low dosage of calcium aspartate anhydrous
D: calcium citrate
E: calcium gluconate
F: calcium carbonate

Fig. 1 Serum Ca Level Increase By Dosage of Calcium Aspartate Anhydrous

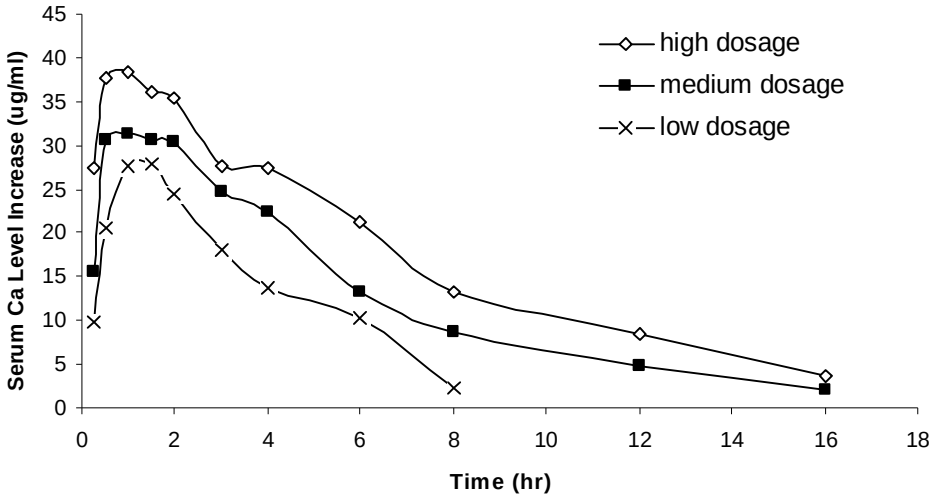
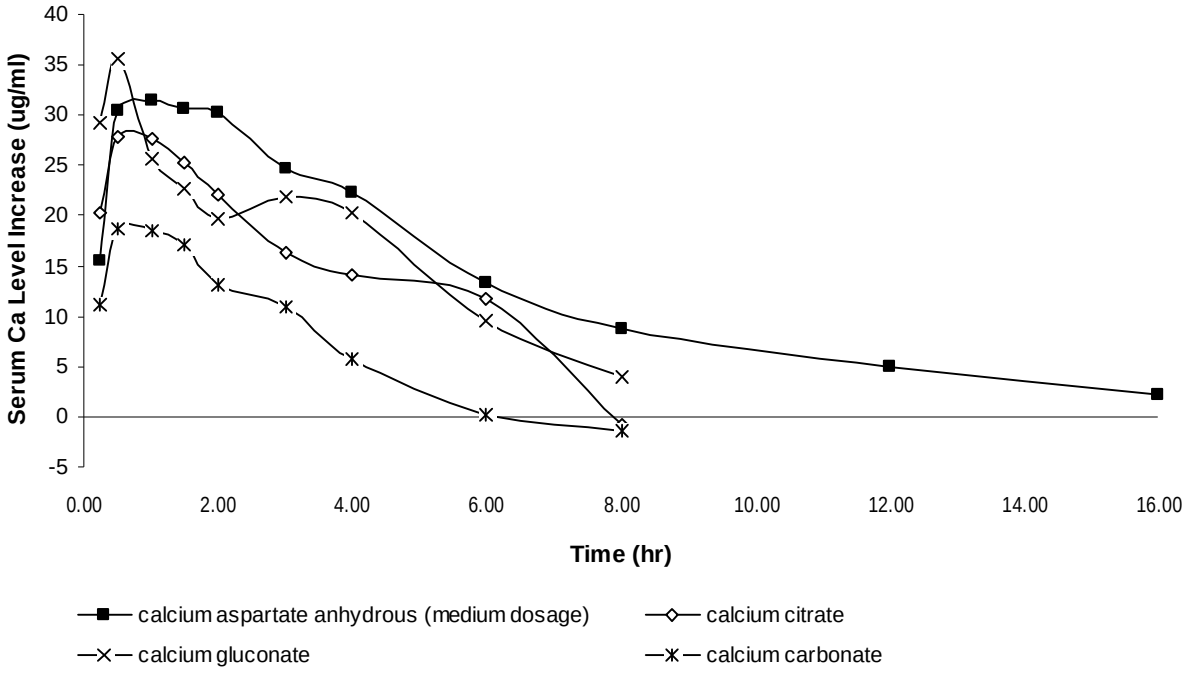


Fig. 2 Serum Ca Level Increase Over Time



(ii) The experimental data was fitted by computer with SAS Statistical Software, and the following pharmacokinetics parameters was obtained: half-life of clearance $t_{1/2}$ =4.22 hr, area under the curve AUC=201.75 (μg/ml)·hr, maximum value of serum Ca C_{max} =32.30 μg/ml, time for arriving the maximum t_{max} =0.74 hr.

Table II. Pharmacokinetics parameters of various calcium preparations

Group	$t_{1/2}$ (hr)	AUC_{0_t} [(μg/ml).hr]	c_{max} (μg/ml)	t_{max} (hr)
medium dosage of calcium aspartate anhydrous	4.22	201.75	32.30	0.74
calcium citrate	0.72	117.19	27.86	0.61
calcium gluconate	2.86	131.89	35.72	0.59
calcium carbonate	0.51	55.86	18.67	0.53

(2) Measurement of calcium aspartate anhydrous level in the serum of dog and computation of pharmacokinetics parameters

Serum Ca levels at various time after administration were shown in Table III, the pharmacokinetics parameters fitted were listed in Table IV.

Table III. Serum Ca Levels in Dogs at Various Time After Administration

Serum Ca Level Increase (μg/ml, x/s.d.)											
before	**0.25hr**	**0.5hr**	**1.0hr**	**1.5hr**	**2.0hr**	**3.0hr**	**4.0hr**	**6.0hr**	**8.0hr**	**12hr**	**16hr**
1.56/.1	19.3/1.8	23.1/2.6	36.8/3.8	75.5/3.4	74.2/3.2	46.3/5.4	19.1/4.3	10.2/3.7	6.7/3.2	3.1/2.7	2.7/2.4

Table IV. Pharmacokinetics Parameters of Calcium Aspartate Anhydrous in Dog Body

$t_{1/2}$ (hr)	a.u.c. [(μg/ml).hr]	c_{max} (μg/ml)	t_{max} (hr)
3.53	254.13	78.6	1.15

6. Conclusion

It is demonstrated that calcium aspartate anhydrous has longer metabolic time and higher bioavailability, which make the formation of bone Ca more efficient and effective. This brings about a net increase of bone matrix and realizes the objective to prevent and treat osteoporosis.