VETERINARSKI ARHIV 74 (2), 115-127, 2004

Dynamics of concentrations of Ca, Mg, P, and glucose after intravenous administration of complex solutions of calcium, magnesium, phosphorus, and glucose to rabbits

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DABUŽINSKAS, S., G. DAUNORAS, A. MATUSEVIČIUS: Dynamics of concentrations of Ca, Mg, P, and glucose after intravenous administration of complex solutions of calcium, magnesium, phosphorus, and glucose to rabbits. Vet. arhiv 74, 115-127, 2004.

ABSTRACT

Presented in this article are data of pre-clinical rabbit trials using calcium borogluconate and calcium glycerophosphate injection solution of new composition containing phosphorus and magnesium salts, glucose and caffeine. The dynamics of concentrations of Ca, Mg, P, and glucose in the blood serum were studied. This data was then compared with that of the commercial veterinary medicinal product. When rabbits received an intravenous injection of 21 mg/kg of total calcium, a statistically significant increase in calcium concentration in the blood serum was recorded after 15 and 60 min. It was established that when the inorganic phosphorus contained in sodium dihydrophosphate is administered intravenously it has superior bioavailability than inorganic phosphorus contained in calcium glycerophosphate. Pure phosphorus (7.9 mg/kg) contained in the injected sodium dihydrophosphate salt produced a statistically larger increase in inorganic phosphorus concentration after 15 and 60 min. compared to 10 mg/kg of pure phosphorus contained in the calcium glycerophosphate salt injected. Complex injection solution A1 containing calcium borogluconate, sodium dihydrophosphate, and magnesium chloride, were distinguished by the best bioavailability, and compared to the control solution produced the greatest and longest-lasting increase in concentrations of calcium, magnesium, and inorganic phosphorus in blood serum of rabbits. Newly created complex solutions A1 and A2 of different compositions are suitable for parenteral use and are well tolerated by

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ISSN 0372-5480
Printed in Croatia

rabbit organism, and upon intravenous injection produce an increase in total calcium, magnesium, and inorganic phosphorus in the rabbit blood which lasts for several hours.

Key words: calcium, magnesium, phosphorus, glucose, rabbit, serum

Introduction

Presented in this article are data on component concentration dynamics and tolerance for the newly created complex calcium, magnesium, phosphorus, glucose, and caffeine solutions of various chemical compositions in non-target animals. In collaboration with chemists a number of complex solutions of various chemical compositions (Table 1)

Table 1. Composition of solutions

Amount of active ingredients		Quantities of ions	
100 ml of A1 solution contain			
Calcium gluconate	24 g	Ca^{2+}	2.1 g
Magnesium chloride	6 g	Mg^{2+}	0.72 g
Sodium dihydrophosphate	4 g	P	0.79 g
Sodium tetraborate	3 g	Na^{2+}	0.21 g
Boric acid	1 g	B	0.52 g
Glucose	18 g		
Caffeine	0.4 g		
Water for injection	100 ml		
100 ml of A2 solution contain			
Calcium gluconate	18 g	Ca^{2+} (with calcium glycerophosphate)	3 g
Calcium glycerophosphate	7 g	P	1 g
Magnesium chloride	6 g	Mg^{2+}	0.72 g
Sodium tetraborate	1 g		
Boric acid	0.5 g	B	0.26 g
Glucose	12 g		
Caffeine	0.4 g		
Water for injection	100 ml		
100 ml of C-B-Gluconat mit Coffein u. Traubenzucker (control solution) contain			
Calcium gluconate	38 g	Ca^{2+}	3.3 g
Magnesium chloride	6 g	Mg^{2+}	0.72 g
Boric acid	5 g	B	2.6 g
Glucose	20 g		
Caffeine	0,5 g		
Water for injection	100 ml		

suitable for treatment of animals suffering from metabolic disorders were created in the Experimental Pharmacology Laboratory of the Veterinary Academy of Lithuania. In the event of the aforementioned pathology (milk fever, pasture and transportation tetany, osteodystrophy, etc.) homeostasis of a number of substances is often disordered. Thus, application of complex solutions is advantageous as the animal organism is provided with a number of necessary substances and thus the possibilities for relapse are reduced (FENWICK, 1990; MALC and MAYER, 1993; VERKERK et al., 1997). The originality of the preparations studied lies in the fact that combined in the single solution are both calcium and phosphate salts, which usually precipitate and discard as sediments. These solutions also include analeptic substance (caffeine). Studying glucone acid interaction with trihydroxiborane, and by using various methods, we succeeded in producing a stable water-based solution of calcium and magnesium salts on a buffer of sodium borate-phosphates. This production technology is patented in Lithuania (STANKEVIČIUS et al., 1999). After producing several formulas of complex solutions, tests of their toxicity, pirogenicity, tolerance, and suitability for parenteral use were conducted. It was found that LD_{50} of the complex calcium, magnesium, inorganic phosphorus, and glucose solution A1 when it was injected subcutaneously into white mice was 24.1 ml/kg of mouse weight. After subcutaneous injection the solution did not irritate tissues. Also, a trial series of this solution produced for rabbits was found to be non-pyrogenic and had no negative effect during the functional load study applying hunger diet (MATUSEVIČIUS et al., 2000).

On the basis of the commonly accepted principles of creation of new medicines, before commencing field trials with the target animals, pre-clinical studies are required to establish pharmacological activity and tolerance of the new drug (Dir. 2001/82/EC). Thus, the aim of the present work was to establish suitability for parenteral use and tolerance of newly created complex solutions of differing compositions A1 and A2, dynamics of the total amount of calcium, magnesium, inorganic phosphorus, and glucose in the rabbit blood serum upon intravenous administration of these solutions, and to compare these solutions with a well-known and widely used control multi-component solution of similar composition, C-B-Gluconat mit Coffein u. Traubenzucker (Selectavet, Germany).

Materials and methods

Animals, *housing and feeding*. Twelve female and male crossbred rabbits with masses of 1.950-2.750 g of reproductive age were used in the study. The animals were caged individually, fed commercial rabbit meal and had access to water *ad libitum*. They were housed at a temperature of 20 ± 2 °C with a 12/12 h. light/dark cycle.

Experimental design. The study was performed in spring in a single phase, in accordance with the requirements of E.U. Directive 86/609/EEC (Dir. 86/609/EC). Experimental rabbits were divided into 3 groups, 4 rabbits of each sex in each group. In this study multi-component experimental solutions A1 and A2, as well as C-B-Gluconat mit Coffein u. Traubenzucker (Selectavet, Germany) were used. Composition of these solutions is presented in Table 1. The dosage of preparations injected was calculated in such a way that rabbits in different groups would receive equal doses of pure calcium, i.e. 21 mg/kg body weight. Therefore, a different amount of P, Mg and glucose was injected. Rabbits in the first group had 1 ml/kg of A1 injected in the ear vein. Rabbits in the second group received 0.7 ml/kg of A2, while the control group received 0.6 ml/kg of C-B-Gluconat mit Coffein u. Traubenzucker (Selectavet, Germany) solution intravenously. Blood for biochemical tests was collected before injecting solutions and after 15 min., 1 h. and 5 h. post-injection. Blood was then centrifuged at 1,800 rpm for 20 min. Serum free of hemolysis was obtained within 30 min after blood collection. During the study, and 5 days afterwards, all rabbits were observed twice daily in an attempt to identify possible observable symptoms of intolerance or poisoning. Rectal body temperature was measured, heart was auscultated, and breathing rate was assessed.

Analytical assay. The serum total calcium, magnesium, inorganic phosphorus and glucose concentrations (millimoles in litre (mmol/L)) in serum were determined by the photo-colorimetric method using interferential photometer Clin-check plus® (Hospitex Diagnostics S.r.l., Italy). The principle for calcium determination was that calcium ions form a violet complex with O-Cresolphtalein complexone in an alkaline medium. Magnesium reacts with calmagite in alkaline medium to give a purple-coloured complex. Phosphorus forms a coloured phosphomolybdene complex after reaction of ammonium molybdate with sulphuric acid.

Glucose forms a stable colour by enzymatic reaction with glucose oxidase and peroxidase. The method for calcium was linear up to 15 mg/dL, for phosphorus – 20 mg/dL, for magnesium – 4.9 mg/dL and for glucose – up to 500 mg/dL. The apparatus was validated with standard serum.

Statistical analysis. Obtained data was processed by statistical calculations program GrafPad Prism 2.01 (GrafPad Software Inc., 1996). Arithmetical mean (mean), standard deviation (SD) and significance of increase of serum concentration of total calcium, magnesium, phosphorus and glucose were calculated. Significance was accepted at $P<0.05$.

Results

After 15 min. the concentration of calcium in the blood serum of group 1 rabbits was 16 % or (0.53 mmol/L) in 1 h. – 10 % (or 0.35 mmol/L ($P<0.05$)) higher than prior to injecting the preparation. After 5 h., calcium concentration decreased to the level that existed prior to injection of the preparation and was significantly higher than the blood levels of calcium in rabbits in groups 2 and 3 (Table 2).

Table 2. Calcium concentration changes (mmol/L, mean, SD) in rabbit blood serum

Animal group	Before injection	Time after injection		
		15 min	1 h	5 h
1 group (n=4) A1 solution	3.31	3.84*	3.66* ^{2*}	3.34$^{2*\ 3*}$
	0.05	0.17	0.17	0.08
2 group (n=4) A2 solution	3.23	3.78*	3.39*	3.15
	0.10	0.11	0.21	0.09
3 group (n=4) Control solution	3.19	3.71*	3.29	3.12
	0.09	0.05	0.07	0.14

* - statistically significant, compared to pre-injection levels ($P<0.05$)
^{2*} - statistically significant, compared to group 2 levels ($P<0.05$)
^{3*} - statistically significant, compared to group 3 levels ($P<0.05$)

After 15 min. and 1 h. after injection of the A2 solution (group 2) we observed an increase in total calcium levels of 14% and 5% (or 0.55 mmol/

L and 0.16 mmol/L) respectively, compared to pre-injection levels. Mean differences in comparison with initial data are statistically significant ($P<0.05$). Injection of the A1 solution caused a larger and longer-lasting increase in calcium levels than injection of the A2 solution. Injection of the control solution (group 3) caused only a short-lived increase in calcium concentration, which was evident because a statistically significant increase of 16 % (or 0.52 mmol/L) was observed only 15 min. after the injection.

In summary, examination of calcium dynamics reveals that intravenous injections of all of solutions increased the levels of calcium in the blood serum of experimental rabbits. The greatest and the longest-lasting increase in calcium concentration was caused by the A1 solution. No arrhythmias or other functional heart disorders were diagnosed in the rabbits during the study (heart rate was 176-203 bpm).

Analysis of changes in phosphorus levels in rabbit blood serum after injection of the control solution revealed that phosphorus concentration in the blood serum of the rabbits in group 3 did not increase significantly ($P>0.05$), due to the fact that the control solution contained no phosphorus salts (Table 3).

Table 3. Inorganic phosphorus concentration changes (mmol/L, mean, SD) in rabbit blood serum

Animal group	Before injection	Time after injection		
		15 min	1 h	5 h
1 group (n=4) A1 solution	1.49	3.42* [2* 3*]	2.81* [2*]	1.55
	0.20	0.44	0.69	0.42
2 group (n=4) A2 solution	1.62	2.43* [3*]	2.02* [3*]	1.79
	0.17	0.50	0.16	0.33
3 group (n=4) Control solution	0.98	1.38	1.11	1.05
	1.34	1.47	1.33	1.33

* - statistically significant, compared to pre-injection levels ($P<0.05$)
[2*] - statistically significant, compared to group 2 levels ($P<0.05$)
[3*] - statistically significant, compared to group 3 levels ($P<0.05$)

With regard to the solution dosages selected for rabbits in groups1 and 2, rabbits in group 1 were injected with 7.9 mg/kg of weight of pure phosphorus, while those in group 2 received a dosage of 7.0 mg/kg. The greatest increase in concentration of inorganic phosphorus was found after injection of A1 solution. Fifteen min. after injection, phosphorus levels rose by as much as 129% (or 1.93 mmol/L) compared to those prior to injection. After 1 h. following injection, phosphorus concentration remained 88% (or 1.32 mmol/L) higher than at the commencement of the trial. After 5 h. the phosphorus level in the blood serum of group 1 rabbits fell to normal. For group 2 rabbits the amount of phosphorus 15 min. after injection rose by 50% (or 0.81 mmol/L). After 1 h. there remained 25% (or 0.4 mmol/L) more phosphorus than prior to injection. After 5 h., phosphorus levels in both groups practically dropped to pre-trial levels.

Results of the experiment reveal that the greatest effect on increase in inorganic phosphorus levels in the blood serum of the rabbits was produced by injection of the A1 solution. Concentration of inorganic phosphorus in the blood of rabbits increased by more than twice and remained insignificantly increased for up to 5 h. after injection.

Examination of changes in magnesium concentrations (Table 4) revealed that for all groups of rabbits a statistically significant increase in

Table 4. Magnesium concentration changes (mmol/L, mean, SD) in rabbit blood serum

Animal group	Before injection	Time after injection		
		15 min	1 h	5 h
1 group (n=4) A1 solution	1.32	2.10*	1.80	1.09
	0.32	0.37	0.34	0.28
2 group (n=4) A2 solution	1.35	2.06*	1.65	1.24
	0.11	0.17	0.24	0.11
3 group (n=4) Control solution	1.32	1.87*	1.48	1.33
	0.19	0.24	0.09	0.12

* - statistically significant, compared to pre-injection levels ($P<0.05$)

magnesium concentrations in blood serum was found after 15 min. The greatest and most long-lasting increase in magnesium concentrations was found in group 1 rabbits, a smaller increase in the second group, while the smallest was found in group 3 rabbits. This is accounted for by the fact that different groups were administered different amounts of Mg salts. The largest quantity of Mg^{2+} was injected into group 1 animals (7.2 mg/kg); a smaller quantity was injected into group 2 (5.0 mg/kg), and the smallest quantity was administered to rabbits in group 3 (4.3 mg/kg).

Magnesium concentration in all three groups after one h. was higher than prior to injection. However, these differences were not statistically significant. After 5 h., magnesium concentration in rabbits in groups 2 and 3 dropped even below pre-trial levels. All preparations studied produced a statistically significant short-term increase of magnesium concentration in blood serum.

Table 5. Glucose concentration changes (mmol/L, mean, SD) in rabbit blood serum

Animal group	Before injection	Time after injection		
		15 min	1 h	5 h
1 group (n=4) A1 solution	4.71	5.86	4.16	3.99
	0.60	0.85	0.80	0.44
2 group (n=4) A2 solution	4.51	5.19	4.00	3.32*
	0,15	1.17	1.01	0.46
3 group (n=4) Control solution	5.11	5.98	4.82	4.73
	0.54	0.89	0.55	0.56

* - statistically significant, compared to pre-injection levels ($P<0.05$)

Increase in glucose concentration was proportionate to the injected amount in all groups (Table 5). Rabbits in different groups were injected with a different amount of glucose: group 1 - 180 mg/kg, group 2 - 84 mg/kg, and group 3 - 108 mg/kg. Accordingly, the greatest increase in glucose

concentration after 15 min. was observed in group 1 - 24%, a smaller increase was observed group 3 - 17%, while the smallest was in group 2 - 15%. Even though all of the solutions studied undoubtedly produced an increase in glucose concentrations in rabbit blood serum, however, due to the large dispersion of individual data and high standard deviation no statistically significant increase in glucose concentration was recorded in any of the groups.

During the experiment and for five days afterwards, no visible symptoms of preparation intolerance or intoxication were observed in the experimental rabbits. Heart rate was 176-203 bpm and breathing rate, 56-64 ×/min, increased only during manipulation. No increases in body temperatures were found (38.6-39.2 °C).

Discussion

In modern veterinary practice many kinds of calcium preparations are used for treatment and prevention of animal metabolic disorders. Such preparations include various mono calcium salts, or their combination with phosphorus, magnesium, hydrocarbons, analeptic substances, etc. These preparations are administered through oral or parenteral routes. However, the search for new effective combinations in ongoing (CHIEZE and BAUDET, 1992; MULEN, 1977; GOFF and HORST, 1996). Results of the preliminary pre-clinical research performed with non-target animals using calcium borogluconate and glycerophosphate solutions with phosphorus, magnesium, glucose, and analeptic substance, with respective code names A1 and A2, indicate that solution constituents are well tolerated and produce an increase in total calcium, phosphorus, magnesium, and glucose in the bloodstream. In our study neither constituents of the trial solutions A1 and A2, nor those of the control solution, caused disorders in heart activity. No undesirable effects of calcium on the rabbit organism were observed, due to the fact that a small, safe dose of calcium salts was used (21 mg/kg animal body weight), while the undesirable side-effects of calcium on rabbits are observed with injections of 75 mg of pure calcium per 1 kg of body weight of an animal (HAPKE, 1993).

When rabbits where injected with 21 mg/kg of pure calcium, a statistically significant increase in calcium concentration in blood serum

was recorded after 15 min. Due to the homeostasis maintenance mechanisms of the organism and elimination, this amount later decreased, and after 5 h. reached initial levels. Similar findings were reported by ITON and HATANO (1961a), who conducted a research with rabbits. They found that when radiocalcium is administered intravenously, as early as 15 min. after injection of the isotope, radioactivity in blood calcium decreased to about 10 per cent. The intravenously administered radiocalcium rapidly disappeared from the blood of the mature rabbit, just as it did in the younger animal (ITON and HATANO, 1961b).

When injected parenterally, calcium, magnesium, phosphorus salts, and glucose in the A1 solution increase the ion concentration of the aforementioned elements in blood serum, and provide the animal organism with necessary substances in the event of acute shortage or imbalance.

Calcium glycerophosphate salt contained in the A2 solution is rarely used in veterinary practice. However, results of our study revealed that this salt, as well as calcium borogluconate, has good bioavailability and statistically significantly increases concentration of calcium and inorganic phosphorus in blood serum without causing any side effects. However, solution with this composition turned out to be unstable, and sediments appeared after prolonged storage.

The results of our study indicate that multi-component injection solution A1 containing calcium borogluconate, sodium dihydrophosphate and magnesium chloride salts was distinguished by the best bioavailability and produced the greatest and most long-lasting increase in Ca, P, and Mg concentrations in blood serum of rabbits.

Even though similar amounts of phosphorus salts were injected into rabbits in groups 1 and 2, however, compared to the increase in phosphorus levels in group 2, for rabbits in group 1 a significantly larger increase in phosphorus levels was recorded after 15 min. and after 1 h. It was found that when administered intravenously, inorganic phosphorus in the form of sodium dihydrophosphate had better bioavailability than inorganic phosphorus in the form of calcium glycerophosphate. Pure phosphorus (7.9 mg/kg) injected in the form of sodium dihydrophosphate salt produced a statistically larger increase in inorganic phosphorus levels after 15 and

60 min. than 10 mg/kg of pure phosphorus injected in the form of calcium glycerophosphate. It is likely that the sodium dihydrophosphate salt contained in A1 solution dissociates releases phosphorus ions easier and is more slowly eliminated from blood serum than calcium glycerophosphate salt contained in A2 solution.

We believe than a significant and long-lasting increase in P concentration in blood serum could be particularly beneficial in the treatment of cows suffering from milk fever. According to KLIMIENE (2001), the amounts of both calcium and phosphorus in blood serum decrease during milk fever. FENVICK (1990) also found a significant decrease in phosphorus concentration in blood serum of those cows resistant to calcium borogluconate treatment.

It is planned to introduce A1 solution in veterinary practice with healthy cows and for treating milk fever in cattle.

Conclusion

Newly created complex solutions A1 and A2 of different composition suitable for parenteral use are well tolerated by the rabbit organism, and when administered intravenously produce an increase in total calcium, magnesium, inorganic phosphorus, and glucose in rabbit blood serum.

Multi-component injection solution A1 was distinguished by the best bioavailability and produced the greatest and the longest lasting increase in calcium, magnesium and inorganic phosphorus in rabbit blood serum compared to the control solution.

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Received: 16 July 2003
Accepted: 15 March 2004

DABUŽINSKAS, S., G. DAUNORAS, A. MATUSEVIČIUS: Kretanje koncentracije Ca, Mg, P i glukoze nakon intravenskog davanja kompleksne otopine kalcija, magnezija, fosfora i glukoze kunićima. Vet. arhiv 74, 115-127, 2004.

SAŽETAK

U radu su iznijeti podaci pretkliničkih istraživanja na kunićima koristeći injekcijske otopine kalcijeva boroglukonata i kalcijeva glicerofosfata u novoj smjesi s fosfornim i magnezijevim solima, glukozom i kofeinom. Istraživano je kretanje koncentracije Ca, Mg, P i glukoze u krvnom serumu. Rezultati su potom uspoređivani s rezultatima polučenim upotrebom komercijalnih veterinarsko medicinskih proizvoda. Statistički značajan porast koncentracije kalcija u krvnom serumu zabilježen je 15-60 minuta nakon intravenske injekcije ukupnog kalcija u količini 21 mg/kg. Potvrđeno je da neorganski fosfor sadržan u natrijevu dihidrofosfatu primijenjenom intravenski ima bolju bioraspoloživost od neorganskog fosfora sadržanog u kalcijevu glicerofosfatu. Čisti fosfor (7,9 mg/kg) sadržan u injiciranoj soli natrijeva dihidrofosfata doveo je nakon 15 do 60 minuta do statistički većeg povečanja koncentracije neorganskog fosfora u usporedbi s 10 mg/kg čistog fosfora sadržanog u danoj soli kalcijeva glicerofosfata. Sastavljena injekcijska otopina A1 koja je sadržavala kalcijev boroglukonat, natrijev dihidrofosfat i magnezijev klorid odlikovala se najboljom bioraspoloživošću i u usporedbi s kontrolnom otopinom potaknula najveće i dugotrajno povećanje koncentracije kalcija, magnezija i neorganskog fosfora u krvnom serumu kunića. Pripravljene otopine A1 i A2 različitog sastava prikladne su za parenteralnu upotrebu. Kunići ih dobro podnose, a intravenski primijenjene dovode do porasta ukupnog kalcija, magnezija i neorganskog fosfora u krvi u trajanju od nekoliko sati.

Ključne riječi: kalcij, magnezij, fosfor, glukoza, kunić, serum