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FURTHER STUDIES ON THEOPHYLLINE-INDUCED HYPOCALCAEMIA IN SHEEP

By

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PERSSON, J. and J. LUTHMAN: *Further studies on theophylline-induced hypocalcaemia in sheep.* Acta vet. scand. 1975, *16*, 39—50. — The effects of various doses of theophylline on the plasma levels of calcium, inorganic phosphorus and magnesium were studied in sheep. The dose of 0.25 mg/kg/min. during 40 min. produced a hypocalcaemia, which was abolished by thyroidectomy. At a higher dose, 1.0 mg/kg/min., thyroidectomy reduced, but did not block, the hypocalcaemic effect of theophylline. Young sheep showed a greater calcium response than did adult ewes. The decrease in plasma calcium was in no case accompanied by hypophosphataemia. Plasma magnesium decreased in all groups after 1.0 mg/kg/min. and was not influenced by thyroidectomy. Theophylline increased the urinary excretion of calcium and magnesium. It is concluded that theophylline-induced hypocalcaemia in sheep is in part a result of increased calcitonin secretion but that also other mechanisms must be involved, e. g. a direct effect of theophylline on bone.

theophylline; hypocalcaemia; sheep; thyroidectomy; urinary calcium.

It is now well established that cyclic adenosine 3′,5′-monophosphate (cyclic AMP) is the intracellular mediator of the action of parathyroid hormone (PTH) on bone (*Aurbach & Chase* 1970, *Chase & Aurbach* 1970). PTH activates membrane-bound adenyl cyclase which enhances the synthesis of cyclic AMP from ATP, and the increased intracellular concentration of cyclic AMP is then intimately involved in the further steps in cell activation, eventually leading to resorption of bone. According to the hypothesis proposed by *Rasmussen* (1972), also calcium ions play an important role in this mechanism and when PTH acts upon bone

cells, the release of calcium from bone is preceded by an increased concentration of the ion in the bone cell cytosol (*Parsons & Potts* 1972).

The phosphodiesterase system is responsible for the degradation of cyclic AMP. Methyl xanthines are potent phosphodiesterase inhibitors and cause a rise in the intracellular concentration of cyclic AMP. The dibutyryl derivative of cyclic AMP is also a phosphodiesterase inhibitor (*Heersche & Aurbach* 1971), and both theophylline and dibutyryl cyclic AMP have been found to mimic some of the actions of PTH on bone. *Wells & Lloyd* (1967) showed that single injections of theophylline at a dose of 120 mg/kg caused a rapid, marked and relatively long-lasting elevation of serum calcium in parathyroidectomized rats, while it was without effect in intact animals. The drug also retarded the fall in serum calcium which is seen after para- or thyroparathyroidectomy. Simultaneous administration of rather high doses of theophylline and parathyroid extract (PTE) produced a smaller rise in serum calcium than that caused by either agent alone. Later, *Wells & Lloyd* (1968) reported that theophylline inhibited the hypocalcaemic action of calcitonin. When small doses of theophylline and PTE were given simultaneously, the increase in serum calcium was greater than that obtained after either drug or extract alone, a finding which was in contrast to their earlier report.

In a study with cultured foetal bones, *Klein & Raisz* (1971) found that dibutyryl cyclic AMP, at concentrations of 0.1—0.3 mM, mimicked the calcium-releasing action of PTH. The effect was, however, lost at higher concentrations. Theophylline was found not to increase the release of calcium, but an increase was obtained in the presence of low doses of PTH. Dibutyryl cyclic AMP has also been shown to be effective in vivo (*Wells & Lloyd* 1969).

Contradictory effects of theophylline on calcium metabolism have been reported from studies in sheep. *Barlet* (1971) and *Luthman et al.* (1972a) independently found that intravenous infusion of theophylline caused hypocalcaemia in intact sheep. The dose used by *Barlet* was 0.33 mg/kg/min. during 90 min. Since the hypocalcaemia was suppressed by thyroidectomy, he suggested that theophylline increased the rate of calcitonin secretion. The study of *Luthman et al.* (1972a) was performed in view of the fact that methyl xanthines are lipolytic in sheep

and that heavy lipolysis is associated with increased uptake of calcium into adipose tissue and sometimes a decrease in serum calcium (*Akgün & Rudman* 1969, *Luthman et al.* 1972b). The doses used were 1.0 and 2.0 mg/kg/min. during 40 min. The results showed that the lipolytic and hypocalcaemic effects were not coupled, since lipolysis was blocked by nicotinic acid, whereas the decrease in serum calcium was unaffected.

The aim of the present investigation was to study the effects of different doses of theophylline on the pasma levels of calcium, inorganic phosphorus and magnesium in intact and thyroidectomized sheep and also to measure the urinary excretion of calcium and magnesium.

MATERIAL AND METHODS

In total, 49 sheep were used in the study. All sheep were of the Swedish landrace and animals of both sexes were used. They were kept indoors and fed according to the routine with hay and grain twice a day and they had free access to tap water. Adult ewes (3—5 years old) were used in the urinary excretion study, while the animals in all other groups were young (7—10 months old). The young female sheep were all non-pregnant, while the adult ewes were in the first month of pregnancy. All animals were non-fasted when used in the experiments.

The effects of theophylline at various doses were studied in young sheep. Theophylline (Teofyllamin, ACO, Stockholm, Sweden) was diluted with saline to a final volume of 70 ml and was given intravenously at a constant rate during 40 min. by means of a peristaltic pump. The doses used were 0.06, 0.13, 0.25 and 1.0 mg/kg/min. Control animals were given the same volume of saline. Blood was drawn in heparinized tubes (Heparinrör, Vitrum, Stockholm, Sweden) at 0, 40, 70, 100 and 160 min. after start of the infusion, and plasma was analysed for calcium, inorganic phosphorus and magnesium.

Thyroidectomy was performed in 13 young sheep as was described earlier by *Luthman et al.* (1972b). After about 24 hrs. they were used in the experiment. Five animals received 0.25 mg/kg/min. and 8 animals received 1.0 mg/kg/min. of theophylline. The drug was administered as above. The observation period was extended with another 2 observations at 200 and 240 min. Plasma was analysed as above.

The effect of theophylline on the urinary excretion of calcium and magnesium was studied in 6 adult intact ewes. A balloon catheter (Rüsch Silkolatex, Rüsch, Rommelshausen, Germany) was placed in the urinary bladder on the day before the experiment. Urine was collected hourly for 4 hrs., beginning 2 hrs. before start of the theophylline infusion, which was performed as above. The dose of theophylline was 1.0 mg/kg/min. and the infusion was given as above. Four adult ewes served as controls and were given saline. Blood was collected as in the young intact group and plasma was analysed for calcium and magnesium. The concentrations of calcium and magnesium in the urine samples were determined and from the obtained sample volumes the amounts of calcium and magnesium excreted during each collecting period were calculated.

Plasma calcium was determined according to *Skerry* (1965), while urinary calcium was analysed in a Marius Calcium Titrator (Canalco Europe, Vlaardingen, Netherlands). Commercial reagent kits were used for the determination of inorganic phosphorus (Sigma Kit 670, Sigma Chemical Company, St. Louis, USA) and magnesium (Merckotest Magnesium, E. Merck, Darmstadt, Germany).

The pretreatment levels of the measured parameters given in the Tables are the mean of 2 determinations, at —30 min. and immediately before start of the experiment.

Student's t-test was used for the statistical calculations.

RESULTS

Table 1 shows the effects of different doses of theophylline on the plasma concentrations of calcium, inorganic phosphorus and magnesium in intact young sheep. Theophylline at the dose of 0.25 mg/kg/min. caused significant hypocalcaemia at 40 min., while at the higher dose (1.0 mg/kg/min.) the decrease in plasma calcium was more pronounced and persisted throughout the observation period.

The doses of the drug which caused hypocalcaemia did not influence the plasma phosphate level. A small rise was obtained after a lower dose (0.13 mg/kg/min.).

Plasma magnesium was lowered by the highest dose of theophylline.

Thyroidectomy did not change the plasma levels of calcium and magnesium, while a highly significant ($P < 0.001$) decrease

Table 1. Changes in the plasma levels of calcium, inorganic phosphorus and magnesium in intact young sheep after 40 min. intravenous infusion of theophylline. Mean±s.

Dose	Pretreatment level (mg/100 ml)	Minutes			
		40	70	100	160
			Δ Calcium (mg/100 ml)		
Controls (n=5)	9.62±0.26	—0.10±0.00	—0.20±0.10	—0.14±0.16	—0.02±0.13
0.06 mg/kg/min. (n=6)	9.95±0.43	—0.18±0.16	—0.28±0.26	—0.22±0.26	—0.28±0.23
0.13 mg/kg/min. (n=5)	9.40±0.38	—0.18±0.36	—0.18±0.36	—0.12±0.33	+0.10±0.37
0.25 mg/kg/min. (n=5)	9.62±0.58	—0.88±0.76	—0.96±0.40**	—0.52±0.34	—0.13±0.33
1.0 mg/kg/min. (n=5)	9.38±0.20	—1.64±0.80**	—2.54±0.59***	—2.40±1.02**	—1.74±0.59***
			Δ Inorganic phosphorus (mg/100 ml)		
Controls (n=5)	6.76±0.35	—0.30±0.37	—0.52±0.38	—0.46±0.45	—0.87±0.83
0.06 mg/kg/min. (n=6)	7.23±0.72	—0.18±0.35	—0.08±0.85	—0.95±0.60	—0.80±0.44
0.13 mg/kg/min. (n=5)	6.86±0.76	+0.20±0.27*	—0.20±0.54	—0.02±0.50	—0.18±0.85
0.25 mg/kg/min. (n=5)	6.34±1.28	+0.06±0.50	—0.42±0.76	—0.70±1.18	—1.08±1.24
1.0 mg/kg/min. (n=5)	7.46±0.67	—0.24±0.41	—0.74±0.38	—0.98±0.52	—0.78±0.65
			Δ Magnesium (mg/100 ml)		
Controls (n=5)	2.52±0.19	—0.08±0.10	—0.16±0.20	—0.12±0.19	—0.10±0.17
0.06 mg/kg/min. (n=6)	2.65±0.18	—0.12±0.10	—0.07±0.10	—0.18±0.07	—0.05±0.08
0.13 mg/kg/min. (n=5)	2.48±0.16	—0.15±0.13	—0.26±0.05	—0.22±0.23	—0.16±0.16
0.25 mg/kg/min. (n=5)	2.48±0.21	—0.08±0.13	—0.28±0.08	—0.20±0.07	—0.26±0.09
1.0 mg/kg/min. (n=5)	2.36±0.23	—0.08±0.18	—0.30±0.12	—0.40±0.17*	—0.46±0.16**

* $0.05 > P > 0.01$
** $0.01 > P > 0.001$
*** $P < 0.001$

was obtained for inorganic phosphorus. The values before thyroidectomy were for calcium 10.19±0.68, for magnesium 2.24± 0.19 and for inorganic phosphorus 7.86±2.19 mg/100 ml. Corresponding values obtained 24 hrs. after surgery were 10.25±0.87, 2.17±0.21 and 4.78±1.41 mg/100 ml, respectively.

Table 2. Changes in the plasma levels of calcium, inorganic phosphorus and magnesium in thyroidectomized young sheep after 40 min. intravenous infusion of theophylline. Mean±s.

Dose (mg/kg/min.)	Pretreatment level (mg/100 ml)	Minutes					
		40	70	100	160	200	240
				Δ Ca (mg/100 ml)			
0.25 (n=5)	10.36±0.71	0.00±0.07	—0.02±0.18	—0.02±0.24	+0.16±0.15		
1.0 (n=8)	10.19±0.99	—0.89±0.58	—0.84±0.45	—0.83±0.62	—0.24±0.59	+0.14±0.80	+0.27±0.84
				Δ P (mg/100 ml)			
0.25 (n=5)	5.32±1.81	+0.02±0.66	—0.66±0.63	—0.44±0.39	—1.28±0.62		
1.0 (n=8)	4.44±1.11	—0.28±0.25	—0.85±0.29	—1.10±0.51	—1.40±0.42	—1.20±0.70	—1.20±0.70
				Δ Mg (mg/100 ml)			
0.25 (n=5)	2.06±0.11	—0.04±0.11	—0.08±0.16	—0.14±0.13	—0.52±0.78		
1.0 (n=8)	2.26±0.18	—0.10±0.18	—0.30±0.13	—0.38±0.09	—0.46±0.18	—0.39±0.22	—0.37±0.11

Table 3. The plasma levels of calcium and magnesium (mg/100 ml) in intact adult ewes after intravenous infusion of theophylline (1.0 mg/kg/min. during 40 min.).

Animal no.		Minutes				
		0	40	70	100	160
				Controls		
1	Ca	9.3	9.2	9.2	9.3	9.2
	Mg	2.5	2.6	2.6	2.5	2.4
2	Ca	10.4	10.3	10.4	10.3	10.4
	Mg	2.7	2.7	2.7	2.6	2.7
3	Ca	9.6	9.7	9.6	9.7	9.7
	Mg	2.4	2.4	2.5	2.4	2.4
4	Ca	9.9	9.8	9.8	9.8	9.9
	Mg	2.3	2.3	2.2	2.1	2.2
				Theophylline		
5	Ca	9.2	8.7	8.5	8.5	8.9
	Mg	2.4	2.5	2.0	1.8	1.8
6	Ca	8.9	9.0	8.1	8.2	9.1
	Mg	2.2	2.2	2.0	1.8	1.7
7	Ca	9.8	9.2	9.2	9.1	9.3
	Mg	2.2	2.2	2.0	1.8	1.7
8	Ca	9.4	9.4	9.4	9.4	—
	Mg	2.3	2.1	2.0	1.9	1.7
9	Ca	9.8	9.7	9.0	8.5	9.4
	Mg	2.3	2.2	2.0	1.9	1.8
10	Ca	10.8	10.7	10.5	10.2	10.3
	Mg	2.2	2.1	1.8	1.8	1.6

The 2 doses of theophylline that caused hypocalcaemia in intact animals were tested also in thyroidectomized animals and the results are given in Table 2. Thyroidectomy completely abolished the decrease in plasma calcium after 0.25 mg/kg/min., while the hypocalcaemia, though reduced, was still present after the higher dose. This hypocalcaemia was most pronounced just after the infusion, was then reduced, and in some animals plasma calcium exceeded the pretreatment level at the end of the observation period.

The plasma phosphate level was not changed in the thyroidectomized sheep, and the only change in the magnesium level was a small decrease when the higher dose was used.

Table 4. The urinary excretion of calcium and magnesium after intravenous infusion of theophylline (1.0 mg/kg/min. during 40 min.) in intact adult ewes.

Animal no.		—120 min. to —60 min.	—60 min. to 0	0 to 60 min.	60 min. to 120 min.
			Controls		
1	Ca mg	16.2	12.4	22.0	21.5
	Mg mg	28.4	31.0	34.8	34.2
2	Ca mg	7.7	12.6	16.2	18.0
	Mg mg	29.2	34.0	28.0	26.0
3	Ca mg	6.4	7.8	2.4	2.0
	Mg mg	41.6	39.6	24.6	37.1
4	Ca mg	20.1	30.1	13.6	13.7
	Mg mg	35.3	33.7	34.7	28.1
			Theophylline		
5	Ca mg	4.8	4.5	36.6	20.3
	Mg mg	37.6	40.1	62.8	41.8
6	Ca mg	13.8	17.7	20.3	13.6
	Mg mg	20.7	27.6	41.0	35.6
7	Ca mg	27.8	30.1	36.8	34.3
	Mg mg	37.5	37.8	46.8	51.6
8	Ca mg	9.8	12.0	42.9	20.6
	Mg mg	29.1	31.8	44.8	28.7
9	Ca mg	1.2	0.9	11.2	7.2
	Mg mg	27.3	22.6	44.5	31.3
10	Ca mg	9.4	12.1	45.7	20.1
	Mg mg	24.4	24.5	53.8	32.6

Table 3 shows the effects of theophylline (1.0 mg/kg/min.) on plasma calcium and magnesium in adult intact ewes, and the urinary excretion in the same animals is given in Table 4. The drug produced a decrease in plasma calcium in all animals except 1 (no. 8), the decrease was, however, smaller than in the young intact sheep, and the difference in response between the groups was highly significant ($P < 0.001$) throughout the observation period. Plasma magnesium declined in all animals. The difference in magnesium response between adult and young animals was not significant ($P > 0.05$). Theophylline showed a marked diuretic effect, and the urinary excretion of calcium and magnesium was also increased. The increase in urinary calcium was most

pronounced in animals with a low excretion during the pre-infusion periods.

DISCUSSION

It is known from the literature that theophylline causes an increase of the cyclic AMP concentration in bone cells by inhibiting the activity of the enzyme phosphodiesterase (*Chase & Aurbach* 1970). On the basis of this finding and accepting that increased cyclic AMP concentration leads to bone resorption, one might expect that theophylline would mimic the plasma calcium-raising effect of PTH. From the reports by *Wells & Lloyd* (1967, 1968, 1969) it is clear that theophylline increases serum calcium in parathyroidectomized, hypocalcaemic rats. They also found that the drug was without effect in intact animals and attributed this to a compensatory release of calcitonin. Increased calcitonin secretion was also suggested as the explanation to the ineffectiveness of dibutyryl cyclic AMP in intact, normocalcaemic animals. It was further observed that the simultaneous administration of low doses of theophylline and PTE changed serum calcium in an additive fashion, whereas an auto-inhibition became apparent when higher doses were used. Similar results were reported by *Klein & Raisz* (1971) from in vitro studies on the release of labelled calcium from foetal bone. Recently, *Herrmann-Erlee & v.d.Meer* (1974) found that theophylline acted in a biphasic way on the release of calcium and inorganic phosphorus from cultured foetal mouse calvaria. Low concentrations stimulated the release, while higher concentrations increasingly stimulated the uptake from the incubation medium.

In the present study, theophylline produced hypocalcaemia in the intact sheep at the doses of 0.25 and 1.0 mg/kg/min. In the thyroidectomized animals the lower dose was ineffective and the calcium response to the higher dose was reduced. *Barlet* (1971) found theophylline-induced hypocalcaemia in sheep to be thyroid-dependent, since the response was inhibited in thyroidectomized animals. The dose used by *Barlet* was 0.33 mg/kg/min. during 90 min. The results obtained in the present study may in part be explained along the same line, i.e. that theophylline increases the rate of calcitonin secretion. This is also supported by the fact that the hypocalcaemia was greater in the young animals than in the adult ewes after the same dose of the drug. It is well known that young animals are more responsive

to calcitonin because of their higher rate of skeletal calcium turnover. It is, however, obvious that also some other mechanism, or mechanisms, must be involved, since the decrease in plasma calcium after the higher dose was only reduced but not blocked in the thyroidectomized animals.

As shown in Table 4, theophylline increased urinary calcium in all animals. It seems, however, uncertain whether increased urinary calcium plays an important role in theophylline-induced hypocalcaemia, as in sheep no. 8 no plasma calcium decrease was obtained in spite of a marked increase in the urinary calcium excretion. It is thus only possible to speculate about the nature of the thyroid-independent effect of theophylline. It has earlier been observed that theophylline and also dibutyryl cyclic AMP cause an increase of the intracellular concentration of calcium in kidney and muscle cells (*Bianchi* 1968, *Borle* 1972). As discussed above, the effects of theophylline on bone calcium seem to be dose-dependent, and in the study of *Herrmann-Erlee & v. d. Meer* high doses of theophylline were found to increase the uptake of calcium into bone instead of stimulating the release.

Hypocalcaemia was in no case accompanied by hypophosphataemia, which is in contrast to the results obtained in other species, where hypocalcaemic agents usually also produce a decrease in the plasma phosphate level. It has earlier been shown in sheep that the hypocalcaemic agents toluidine blue and neutral red do not influence the level of plasma inorganic phosphorus (*Luthman & Persson* 1974, *Persson & Luthman* 1974) and even that protamine, another hypocalcaemic drug, is accompanied by hyperphosphataemia (*Luthman et al.* 1973).

It was reported by *Larvor & Rayssiguier* (1972) that intravenous infusion of theophylline (30 mg/kg during 90 min.) in intact ewes caused increased urinary magnesium associated with hypomagnesaemia. They concluded that the decrease in plasma magnesium was not a renal effect, since furosemide, like theophylline a potent diuretic, produced increased urinary magnesium with only a small effect on plasma magnesium. They also found that thyroidectomy did not influence the theophylline-induced hypomagnesaemia. In the present study, 1.0 mg/kg/min. of theophylline produced hypomagnesaemia in all groups of animals and also increased urinary magnesium in the adult ewes. The nature of the hypomagnesaemia remains unknown.

It may be concluded from the present study that theophylline

induces hypocalcaemia in sheep by at least 2 mechanisms. It obviously releases calcitonin from the thyroid gland. The other mechanism is, however, obscure, even though there is some evidence in the literature that theophylline has a direct action on bone.

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SAMMANFATTNING

Fortsatta studier över teofyllininducerad hypokalcemi hos får.

I den föreliggande undersökningen användes får för att studera effekterna av varierande teofyllindoser på plasmakoncentrationerna av kalcium, oorganiskt fosfor och magnesium. Dosen 0,25 mg/kg/min under 40 minuter medförde en hypokalcemi, vilken ej kunde reproduceras på thyreoidektomerade djur. Vid en högre dos, 1,0 mg/kg/min, medförde thyreoidektomin endast en reduktion av kalciumsänkningen. Hypokalcemin åtföljdes icke av hypofosfatemi. Plasmamagnesium sjönk i samtliga grupper efter dosen 1,0 mg/kg/min. Denna sänkning påverkades icke av thyreoidektomi. Teofyllin ökade urinutsöndringen av kalcium och magnesium. Teofyllininducerad hypokalcemi hos får tycks således till viss del bero på ökad kalcitoninsekretion. Även andra mekanismer måste emellertid vara inblandade, mekanismer vars natur ännu är oklara, även om det i litteraturen finns ett visst stöd för att teofyllin skulle ha en direkt effekt på skelettet.

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