No effect of verapamil on calcium stimulated calcitonin release

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Summary: We investigated the effect of infusing 5 mg/h of verapamil on calcitonin release in normal males. After 60 minutes of infusion, ionized calcium and calcitonin levels were unchanged. At 60 minutes we infused 3 mg/kg of body weight of elemental calcium over 10 minutes and we found that calcitonin release was no different from when the subjects were receiving verapamil. These results suggest that, despite blocking calcium channels, acute hypercalcaemia produces normal calcitonin release.

Introduction

Calcium channel blockers are widely used in the treatment of different cardiovascular disorders. In addition to their effect as inhibitors of calcium influx into the cells they can inhibit the availability of Ca^{++} for excitation contraction coupling at an intracellular site.¹ Recent studies have suggested that some calcium antagonists may diminish insulin, glucagon, follicle stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), thyroid stimulating hormone (TSH) and ACTH release after different stimuli both *in vitro* and *in vivo*.^{2,3,4} Since calcium is the major regulator of the function of C-cells of the thyroid we evaluated the effect of verapamil, a well-known calcium antagonist, on basal and calcium-stimulated calcitonin release.

Material and methods

Fifteen normal males, aged 20–42 years, were studied after they gave their informed consent. None of them was obese, had evidence of diseases known to affect calcium metabolism or was taking any kind of drug. We excluded four of them because basal calcitonin levels were lower than the sensitivity of our assay. We excluded two further subjects because no calcitonin response was found after calcium infusion. So results are given of nine subjects in whom basal calcitonin levels were detected in our assay and who showed a measurable calcitonin response to calcium infusion.

All subjects were studied on two different days at 08.30 h after an overnight fast (0 time). Protocol A consisted of infusing normal saline at a rate of 100 ml/h over 2 hours. At 60 minutes 3 mg/kg of body weight

of elemental calcium as calcium gluconogalactogluconate (Calcium Sandoz [TM]) was infused over 10 minutes. Blood samples were obtained from a different vein for ionized calcium and calcitonin at 0, 60, 70, 80, 90, 105 and 120 minutes. Protocol B consisted of infusing 5 mg/h verapamil i.v. (Manidon Knoll [TM]) diluted in normal saline 100 ml/h over 2 hours. At 60 minutes calcium was infused as in protocol A and blood samples were obtained at the same times as in protocol A. Cardiac rate and blood pressure were evaluated at 0, 60 and 120 minutes. To begin with either protocol A or B was chosen at random and the second protocol was performed a week after the first.

Serum was obtained anaerobically and stored on ice until it was used for determination of ionized calcium with a Space Stat 20 ionized calcium analyzer (Orion Biomedical, Cambridge MA).⁵ Calcitonin was measured in duplicate by a direct RIA using a kit furnished by Immunonuclear Corp., Stillwater MN. Interassay coefficient of variation for ionized calcium was 1.3% at a concentration of 1.1 mmol/l. To avoid interassay variations in calcitonin all samples from one subject were measured in a single assay. Intra-assay coefficient of variation was 5% at 100 pg/ml. Sensitivity was 25 pg/ml.

Results are given as mean $\pm$ s.e.m.. Statistical analysis was done using paired Student's *t* test. Results were considered significant if $P < 0.05$.

Results

Ionized calcium and calcitonin levels are shown in Table I. We found no significant effect of verapamil on calcium or calcitonin after 60 minutes infusion. Likewise calcium-stimulated calcitonin release was not significantly different during verapamil infusion.

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Table I Calcium and calcitonin responses to calcium infusion during saline (protocol A) and saline-verapamil infusion (protocol B).

	Time (minutes)						
	0	60	70	80	90	105	120
Ionized calcium	1.16 ± 0.007	1.15 ± 0.007	1.39 ± 0.016	1.33 ± 0.013	1.32 ± 0.010	1.29 ± 0.010	1.27 ± 0.010
Protocol A							
Protocol B	1.15 ± 0.007	1.15 ± 0.010	1.39 ± 0.020	1.31 ± 0.023	1.29 ± 0.016	1.27 ± 0.007	1.26 ± 0.007
Statistical significance	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Calcitonin	68.5 ± 4.2	65.2 ± 3.8	119.7 ± 4.4	95.1 ± 8.6	84.7 ± 4.7	80.1 ± 6.1	77.2 ± 5.3
(pg/ml)							
Protocol A							
Protocol B	64.8 ± 3.6	69 ± 4.1	115.1 ± 6.1	93.2 ± 5.4	82.1 ± 5.1	79.7 ± 5.5	78.3 ± 4.3
Statistical significance	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
N.S. – not significant							

N.S. – not significant

Discussion

Calcium antagonists could alter calcitonin release by inhibiting the entry of calcium ions into the C-cells of the thyroid, but in this study we found no significant effects of therapeutic doses of verapamil on calcitonin secretion. At these doses of verapamil the release of other hormones is diminished.⁶ These results are in accordance with that presented by Deedwania *et al.*⁷ who found no effect of oral nifedipine at therapeutic doses on the long-term calcium, calcitonin and parathyroid hormone levels in a group of patients with angina pectoris.

We can only speculate on the possible mechanisms for the failure of verapamil to inhibit calcitonin release, which include (a) the possible selectivity of action of verapamil, i.e. calcium channels in various cells are not affected in the same way, and (b) that the effects of verapamil are overcome by increased concentrations of extracellular calcium, in the case of calcium-stimulated calcitonin release.

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References

1. Zsoter, T.T. & Church, J.G. Calcium antagonist. Pharmacodynamic effects and mechanism of action. *Drugs* 1983, **25**: 93–112.
2. Davis, G., Somers, G., Van Obberghen, E. & Malaisse, W. Calcium antagonists and islet function. I. Inhibition of insulin release by verapamil. *Diabetes* 1975, **24**: 547–551.
3. Eto, S., McMillen-Wood, J., Hutchins, M. & Fleischer, N. Pituitary ⁴⁵Ca uptake and release of ACTH, GH and TSH: effect of verapamil. *Am J Physiol* 1974, **226**: 1315–1320.
4. Barbarino, A. & De Marinis, L. Calcium antagonists and hormone release. II. Effects of verapamil on basal, gonadotropin-releasing hormone and thyrotropin-releasing hormone-induced pituitary hormone-release in normal subjects. *J Clin Endocrinol Metab* 1980, **51**: 749–753.
5. Larsson, L. & Ohman, S. (1985). Effect of silicone-separator tube and storage time on ionized calcium in serum. *Clin Chem* 1985, **31**: 169–170.
6. De Marinis, L. & Barbarino, A. Calcium antagonists and hormone release. I. Effects of verapamil on insulin release in normal subjects. *Metabolism* 1980, **29**: 599–604.
7. Deedwania, P.C., Kukreja, S.C., Mann, L.T. & Williams, G.A. Effects of nifedipine on serum calcium, calcitonin, and parathyroid hormone in man. In Cohn, D.V., Potts, J.T., Jr. & Fujita, T. (eds) *Endocrine Control of Bone and Calcium Metabolism*, Vol 8b. Elsevier Science Publishers BV, Amsterdam, 1984, pp.282–285.