Eur. J. Clin. Pharmacol. 16, 7–9 (1979)

European Journal of
Clinical Pharmacology

Effect of Verapamil on Ionized Calcium Excretion in Human Parotid Saliva*

H. Maier, G. Antonczyk, J. G. Schindler, and A. Heidland

Technical assistance: Ch. Stöhr
Medizinische Universitätsklinik, Abteilung Nephrologie, Würzburg and Institut für angewandte Physiologie der Universität Marburg, Marburg, Federal Republic of Germany

Summary. The effect of Verapamil on ionized calcium transport in the parotid gland and duct system was investigated in eight male volunteers. Transepithelial Ca^{++}-transport was inhibited, as shown by markedly enhanced excretion of calcium in parotid saliva.

Key words: Verapamil, salivary calcium; ionized calcium, parotid gland

In recent years the Ca^{++}-antagonistic action of Verapamil on excitation-contraction coupling in heart muscle [1] vascular smooth muscle [3, 4, 7] and myometrium [2] have been described. However, the mode of action of Verapamil have still not been fully elucidated. It is assumed that it blocks transmembrane Ca^{++} influx into muscle fibers, without affecting the sodium channels.

Until now, no convincing data has been obtained to show whether Verapamil also affects ionized calcium transport in epithelial structures, such as salivary glands.

To examine this question the human parotid gland was chosen as a test model of electrolyte transport, and the concentration of ionized calcium in saliva before and after intravenous injection of Verapamil was measured.

Materials and Methods

Saliva was sampled from 16 healthy male volunteers (aged 20–28 years) after an overnight fast. The experiments were performed at 8–10 a. m. For flow-rate dependent collection of saliva a polyethylene catheter, 8 cm long, was passed 2–2.5 cm into the parotid duct. The secretion of saliva was stimulated by subcutaneous injection of pilocarpine 0.015 mg/kg. In 9 subjects, 10 min after administration of pilocarpine, Verapamil (0.015 mg/kg was injected i. v.) and its effects on the composition of saliva were observed for 35–40 min. In 7 males the time course of flow-rate and electrolyte excretion during pilocarpine stimulation without Verapamil were followed.

The ionized fraction of calcium was measured using an miniaturized version of an electrochemical multi-measuring-system [9], fitted with a calcium-selective disk electrode [8]. A detailed description of saliva sampling and the measurement of ionized calcium under these conditions is given by Maier et al. [6].

Total calcium was measured by atomic absorption spectrophotometry (AAS Beckman), sodium was analyzed by flame photometry and total protein was measured by the method of Lowry [5].

Results

The time-course of the flow-rate of saliva was not influenced by Verapamil (Fig. 1). The excretion of sodium in parotid saliva also did not show significant variations. It decreased within 30 min from 67.0 ± 4.0 mmol SEM (control 62.0 ± 2.5 mmol SEM) to 35.0 ± 2.5 mmol (control 37.5 ± 2.0 mmol; Fig. 2). The excretion of ionized calcium in parotid saliva was significantly ($p < 0.01$); enhanced 30 min after the injection of Verapamil it increased from 0.87 ± 0.04 mmol (control 0.93 ± 0.03 mmol) to 1.32 ± 0.05 mmol (control 0.7 ± 0.02 mmol). Total calcium concentration was also enhanced by Verapamil; it rose from 1.77 ± 0.07 mmol (control 1.81 ± 0.09 mmol) to 2.01 ± 0.06 mmol (control 1.44 ±

* Supported by "Deutsche Forschungsgemeinschaft SFB 92 Biomund".

0031-6970/79/0016/0007/$01.00

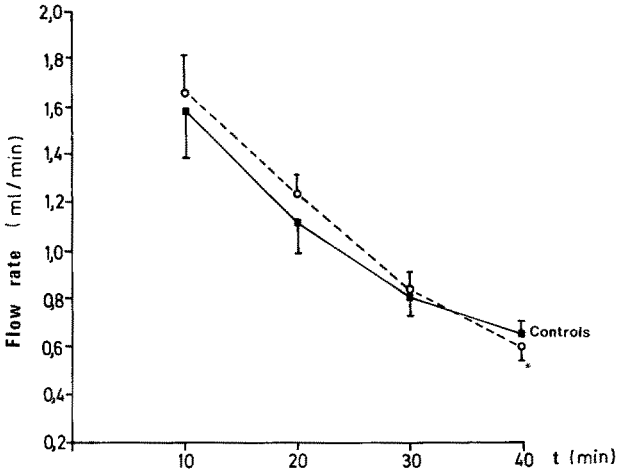


Fig. 1. Flow-rate of pilocarpine-stimulated parotid saliva 30 min after verapamil i. v.* and in controls

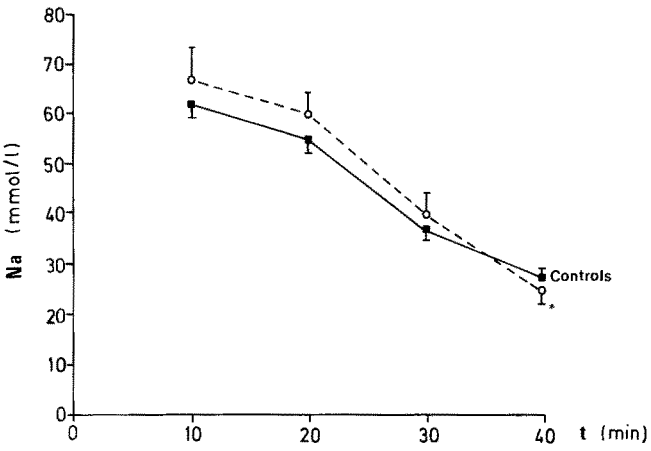
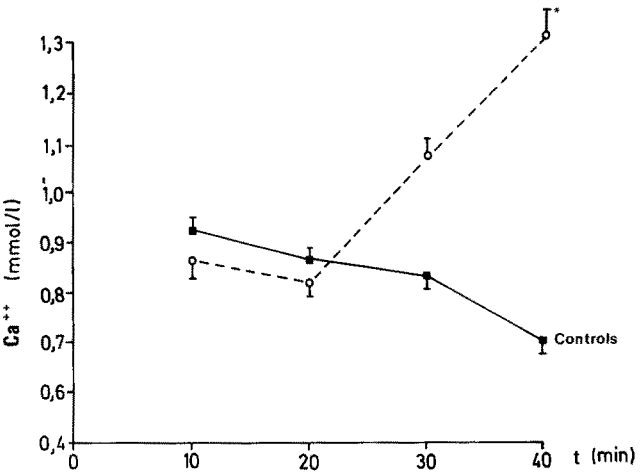
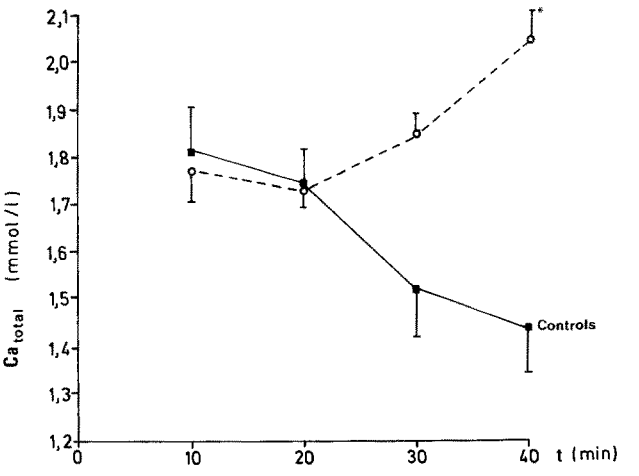


Fig. 2. Concentration of sodium in pilocarpine-stimulated saliva 30 min after verapamil i. v.* and in controls



a



b

Fig. 3a; b. Concentration of ionized and total calcium ($p < 0.01$) in pilocarpine-stimulated parotid saliva 30 min after verapamil i. v.* and in controls

0.1 mmol; Fig. 3b). Protein excretion in these experiments was not influenced by flow-rate, and it did not change after the administration of Verapamil (244.6 ± 22.3 mg/dl; control 252.4 ± 24.3 mg/dl).

Discussion

The investigation has shown that transport of ionized calcium in the parotid gland and duct system is affected by Verapamil. During the action of Verapamil, the concentration of ionized calcium in parotid saliva rose significantly to become as high as in plasma. Arguing from the idea that Ca^{++} concentration in plasma is almost equal to that of the primary secretion produced in the acinar cells, as has been postulated for sodium [8], it is reasonable to assume that the reabsorption of calcium ions in the parotid duct system is markedly diminished by Verapamil. The rise in total calcium concentration is likely to represent an increase in the ionized calcium fraction. Both calcium fractions were increased to the same extent and the total concentration of protein, to which is bound a large proportion of salivary calcium, was not affected by Verapamil.

For a more detailed examination of these results, microperfusion and micropuncture experiments in animals would be necessary. However, the volume of saliva samples obtained from the rat is too small for measurement of the ionized calcium fraction using the electrochemical multimeasuring system.

Transport of sodium, unlike calcium was not affected by Verapamil. The present results agree well with the concept of Fleckenstein, who postulated that Verapamil inhibits the transmembrane influx of calcium ions, without affecting sodium channels.

From the clinical viewpoint, possible pathological consequences of a Verapamil-induced increase in Ca^{++} excretion in human parotid saliva must be taken into consideration. It is conceivable, for instance, that a long-acting Verapamil medication might favour the development of tartar and salivary calculi.

References

1. Fleckenstein, A.: Die Zügelung des Myokardstoffwechsels durch Verapamil. Angriffspunkte und Anwendungsmöglichkeiten. Drug Res. **20**, 1317–1322 (1970)
2. Fleckenstein, A., Grün, G., Tritthart, H., Byon, K., Harding, P.: Uterus-Relaxation durch hochaktive Ca^{++} antagonistische Hemmstoffe der elektro-mechanischen Kopplung wie Isoptin (Verapamil, Iproveratril), Substanz D 600 und Segontin (Prenylamin). Klin. Wochenschr. **49**, 32–41 (1971)
3. Grün, G., Fleckenstein, A.: Ca antagonism, a new principle of vasodilatation. Naunyn-Schmiedebergs Arch. Pharmacol. **270**, Suppl., R 48 (1971)
4. Haeusler, G.: The effect of verapamil on excitation-contraction coupling in smooth muscle and excitation-secretion coupling in adrenergic nerve terminals. Naunyn Schmiedebergs Arch. Pharmacol. **269**, 446–447 (1971)
5. Lowry, O. H., Rosebrough, N. Y., Farr, A. L., Randall, R. J.: Protein measurement with the Folin phenol reagent. J. Biol. Chem. **193**, 265–275 (1951)
6. Maier, H., Coroneo, M. T., Heidland, A., Wigand, M. E.: Ionisiertes Calcium und Totalcalcium im Parotisspeichel bei Normalpersonen und essentiellen Hypertonikern. Laryngol. Rhinol. Othol. **57**, 1013–1017 (1978)
7. Rydén, L., Saetre, H.: The haemodynamic effect of verapamil. Eur. J. Clin. Pharmacol. **3**, 153–157 (1971)
8. Schindler, J. G., Riemann, W.: Calciumselektive Scheiben-Elektrode für Durchflußmessungen. Biomed. Tech. **20**, 76–77 (1975)
9. Schindler, J. G.: Multimeßsystem für die elektrochemische Analyse strömender Flüssigkeiten und Gase. Biomed. Tech. **22**, 235–244 (1977)
10. Thaysen, J. H., Thorn, N. A., Schwartz, I. L.: Excretion of sodium, potassium, chloride and carbon dioxide in human parotid saliva. Am. J. Physiol. **178**, 155–159 (1954)

Received: January 23, 1979
accepted in revised form: May 4, 1979

Prof. Dr. A. Heidland
Abteilung Nephrologie
der Medizinischen Universitätsklinik
Josef Schneider Straße 2
Luitpold-Krankenhaus
D-8700 Würzburg
Federal Republic of Germany