Calcium antagonists and endocrine status: lack of effect of oral verapamil on pituitary-testicular and pituitary-thyroid function

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Calcium ions seem to be essential for the release of many hormones. The calcium antagonist verapamil which is used as an anti-arrhythmic and anti-anginal agent has an inhibitory effect on the release of follicle stimulating hormone (FSH), luteinising hormone (LH), and thyrotrophin stimulating hormone (TSH) when given as an intravenous infusion to normal volunteers. As verapamil is usually given orally we studied pituitary-testicular and pituitary-thyroid function before and after completing a 4-week course of oral verapamil. The oral preparation did not have any significant effect on the endocrine parameters studied.

Keywords verapamil calcium antagonists endocrine status

Introduction

The presence of calcium ions is essential for the release of a variety of hormones. With regard to anterior pituitary hormone secretion, *in vitro* studies have suggested a role for calcium ions in the release of FSH, LH, TSH, and growth hormone (GH) (Vale *et al.*, 1967; Wakabayashi *et al.*, 1969; Milligan *et al.*, 1973). The anti-anginal effects of calcium antagonists such as verapamil and nifedipine are probably due to inhibition of calcium ion influx into myocardial cells through the slow calcium channels (Karlsberg, 1982). That an intracellular calcium ion influx is involved in hormone release is suggested by the *in vitro* finding that nifedipine reduces stimulated release of LH, prolactin and insulin (Takahara *et al.*, 1979). Verapamil has a similar inhibitory effect on insulin release (Devis *et al.*, 1975) and adrenocortical steroidogenesis (Podesta *et al.*, 1981).

The relevance of these *in vitro* findings to the *in vivo* situation remains as yet uncertain. Higher doses of nifedipine may suppress the insulin response to a glucose load with subsequent glucose intolerance (Charles *et al.*, 1981). A single oral dose of nifedipine has no effect on basal or stimulated levels of FSH, LH, TSH, prolactin or cortisol (Struthers *et al.*, 1983). An intravenous infusion of verapamil suppresses stimulated release of FSH, LH, TSH and insulin (Barbarino

& De Marinis, 1980; DeMarinis & Barbarino, 1980).

In clinical practice verapamil is often used orally and it therefore seemed to us of some importance to investigate the effect, if any, of the oral preparation on endocrine function. We have previously reported that oral verapamil has no effect on glucose tolerance (Semple *et al.*, 1983). As Barbarino & DeMarinis (1980) had previously shown an adverse effect on FSH, LH and TSH secretion we decided to investigate the effect of the oral preparation on the pituitary-testicular and pituitary-thyroid axes.

Methods

Eight male patients (mean age 51.8, range 47–57 years) were selected by a cardiologist (A.R.L.) as being suitable for verapamil therapy. All patients gave informed consent to the study and local Ethical Committee approval was obtained. Patients were given verapamil 120 mg/day in three divided doses for 1 week increasing thereafter to 240 mg/day for a further 3 weeks.

Before starting treatment and 2 h after the final dose the following procedure was performed: an indwelling venous cannula was in-

serted into the antecubital fossa of the fasted subject between 09.00 and 10.00 h; 30 min later a resting sample was withdrawn for estimation of serum verapamil, thyroxine (T₄), triiodothyronine (T₃), TSH, FSH, LH, testosterone and prolactin: thereafter 100 µg gonadotrophin releasing hormone and 200 µg thyrotrophin releasing hormone (Relefact LHRH/TRH—Roche) were injected intravenously with further samples withdrawn at 30, 60, 90 and 120 min for TSH, FSH, LH and prolactin levels.

Serum specimens were kept stored below -20°C prior to assay. Assay variability was kept to a minimum throughout the study by ensuring that all samples from any one patient were measured in a single assay batch (CV < 8% in all cases). Serum LH and FSH were quantitated using double antibody radioimmunoassays that are based on reagents recommended by the UK National External Quality Assessment Scheme, including standardisation against MRC 68/40 and MRC 78/549, respectively. The limits of detectability of the LH and FSH assay are 0.5 u/l and 0.3 u/l, respectively, and all results were obtained within the working ranges of the standard curves. Serum prolactin was measured with a radioimmunoassay of similar design that employs highly purified human prolactin for standardisation (calibrated against MRC 75/504) and radioiodination (Friesen) and a goat anti-human prolactin serum kindly provided by Corning Medical. The mean sensitivity of the prolactin assays is 30 mu/l and the working range extends

to 2000 mu/l before specimen dilution is required. Testosterone was measured in ether extracts of serum using a radioimmunoassay which employs an ovine antiserum to testosterone-3-(*o*-carboxymethyl) oxime-BSA, an ¹²⁵I-histamine derivative of testosterone-3-*o*-carboxymethyl) oxime as radioligand and a double antibody separation system. Serum TSH was estimated by a radioimmunoassay that is standardised against MRC 68/38, has a limit of detectability of 0.5 mu/l and employs a rabbit anti-human TSH serum kindly donated by Professor W. R. Butt. Serum T₄ and T₃ were measured using conventional solid phase radioimmunoassay technology. Verapamil was measured by a rapid high performance liquid chromatographic method (Cole *et al.*, 1981). Statistical analyses were performed using the Wilcoxon rank test for paired data.

Results

Verapamil was detected in the serum of all patients on the completion of 1 month of therapy (range 25–162 µg/l; mean ± s.e. mean 78.9 ± 19.6 µg/l).

There was no significant change in any basal hormonal parameter measured before and after therapy (Figure 1). Two patients had quite pronounced elevation of serum prolactin on completion of therapy (350 → 650; 570 → 1000; normal range 60–360 mu/l). Serum FSH, LH, TSH and prolactin responded in a similar fashion

Figure 1 Basal endocrine parameters before and on completion of verapamil therapy.

Figure 2 Levels of FSH, LH, prolactin and TSH after the injection of gonadotrophin and thyrotrophin releasing hormone. There was no difference before (----) or after (—) therapy.

to the appropriate releasing hormone before and after therapy (Figure 2).

Discussion

Although all our subjects had detectable verapamil levels, there was considerable inter-subject variability, a phenomenon seen by other workers (Woodcock *et al.*, 1980). However, even those subjects who achieved the highest drug concentrations showed no evidence of suppression of pituitary hormone release.

Our findings contrast with those of Barbarino & DeMarinis (1980) who demonstrated significant suppression of pituitary hormone release by intravenous verapamil but gave no details of drug levels attained in their study. This drug is known to have a very high first pass metabolism and it is probable that higher concentrations would have been attained by their intravenous infusion than by the oral route used in our study. The differences in drug level attained might account for the lack of effect of oral verapamil on pituitary hormone release.

Two patients had abnormally elevated serum prolactin concentrations while taking verapamil, one of whom also had a high level prior to therapy. An isolated case of hyperprolactinaemia and galactorrhoea attributable to verapamil has been reported in a female patient; both features resolved on stopping therapy and returned on reintroducing the drug (Gluskin *et al.*, 1981). Modest hyperprolactinaemia (< 1000 mu/l) in stressed subjects is common and although precautions were taken in this protocol to minimise the effect of stress, it is possible that the hyperprolactinaemia in the two subjects was stress related. However, the possibility that hyperprolactinaemia may occur in some patients on this drug should be considered.

Oral verapamil in the standard dose has no significant effect on pituitary-testicular or pituitary-thyroid function. Our study would not support the view of Struthers *et al.* (1983) that nifedipine is preferable to verapamil in patients with pituitary malfunction.

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References

- Barbarino, A. & DeMarinis, L. (1980). Calcium antagonists and hormone release. II. Effects of verapamil on basal, gonadotrophin-releasing hormone and thyrotrophin-releasing hormone induced pituitary hormone release in normal subjects. *J. clin. Endocrinol. Metab.*, **51**, 749–753.
- Charles, S., Ketelslegers, J. M., Buyschaert, M. & Lambert, A. E. (1981). Hyperglycaemic effect of nifedipine. *Br. med. J.*, **283**, 19–20.
- Cole, S. C. J., Flanagan, R. J., Johnston, A. & Holt, D. W. (1981). Rapid high-performance liquid chromatographic method for the measurement of verapamil and norverapamil in blood, plasma or serum. *J. Chromatogr.*, **218**, 621–629.
- DeMarinis, L. & Barbarino, A. (1980). Calcium antagonists and hormone release. I. Effects of verapamil on insulin release in normal subjects and patients with islet cell tumour. *Metabolism*, **29**, 599–604.
- Devis, G., Somers, G., Van Obberghen, E. & Malaisse, W. J. (1975). Calcium antagonists and islet function. I. Inhibition of insulin release by verapamil. *Diabetes*, **24**, 547–551.
- Gluskin, L. E., Strasberg, B. & Shah, J. H. (1981). Verapamil-induced hyperprolactinaemia and galactorrhoea. *Ann. int. Med.*, **95**, 66–67.
- Karlsberg, R. P. (1982). Calcium channel blockers for cardiovascular disorders. *Arch. int. Med.*, **142**, 452–455.
- Milligan, G. V., Kraicer, J., Fawcett, C. P. & Illner, P. (1972). Purified growth hormone releasing factor increases ^{45}Ca uptake into pituitary cells. *Can. J. Physiol. Pharmacol.*, **50**, 613–617.
- Podesta, E. J., Milani, A., Steffan, H. & Neher, R. (1980). Steroidogenic action of calcium ions in isolated adrenocortical cells. *Biochem. J.*, **186**, 391–397.
- Semple, C. G., Thomson, J. A., Beastall, G. H. & Lorimer, A. R. (1983). Oral verapamil does not affect glucose tolerance in non-diabetics. *Br. J. clin. Pharmacol.*, **15**, 570–571.
- Struthers, A. D., Millar, J. A., Beastall, G. H., McIntosh, W. B. & Reid, J. L. (1983). Calcium antagonists and hormone release: effect of nifedipine on luteinising hormone-releasing hormone and thyrotrophin-releasing hormone-induced pituitary hormone release. *J. clin. Endocrinol. Metab.*, **56**, 401–404.
- Takahara, J., Yunoki, S., Yamane, Y., Yamauchi, J., Yakushiji, W., Kageyama, N., Fujino, K. & Ofuji, T. (1979). The effects of nifedipine on prolactin, growth hormone, and luteinising hormone release by rat anterior pituitary *in vitro*. *Proc. Soc. exp. Biol. Med.*, **162**, 31–33.
- Vale, W., Burgus, R. & Guillemin, R. (1967). Presence of calcium ions as a requisite for the *in vitro* stimulation of TSH release by hypothalamic TRF. *Experientia*, **23**, 853–855.
- Wakabayashi, K., Kamheri, I. A. & McCann, S. M. (1969). *In vitro* response of the rat pituitary to gonadotrophin releasing factors and to ions. *Endocrinology*, **85**, 1046–1056.
- Woodcock, B. G., Hopf, R. & Kaltenbach, M. (1980). Verapamil and norverapamil plasma concentrations during long-term therapy in patients with hypertrophic obstructive cardiomyopathy. *J. cardiovasc. Pharmacol.*, **2**, 17–23.

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