Failure of Amantadine to Modify Serum Growth Hormone and Insulin Levels

Amantadine hydrochloride, an antiviral agent effective against influenza virus[1], has recently been used, either alone or in combination with L-dopa, in the treatment of Parkinson's disease[2–4]. Its mode of action, however, has not been fully clarified: recent studies would indicate that amantadine increases the concentration of available dopamine and other catecholamines in the central nervous system (CNS), either by stimulating their release from an extragranular intraneuronal pool and enhancing their new synthesis, or by preventing their uptake in the storage sites[5–8]. Since it has been demonstrated that dopamine as well as adrenaline and noradrenaline stimulates hypophysial release of growth hormone (GH)[9], in the present work the effects of acute administration of amantadine on serum GH levels were studied. Changes in serum insulin, plasma free fatty acids (FFA) and blood glucose levels were also evaluated.

Material and methods. 6 healthy, non-obese subjects, aged 23–33 years, volunteered for this study. One of them had previously been hyperthyroid but was eumetabolic when the study was performed, Amantadine hydrochloride (Mantadan and TF 648, De Angeli) 300 mg was administered to each subject both by mouth (in a single dose) and i.v. (over a 5 min period), on 2 separate occasions, after an overnight fast. For the oral test, venous blood samples were taken trough an indwelling catheter at –30, 0, 30, 60 min and then every 15 min for the following 2 h; for the i.v. test blood samples were obtained at –30, 0, 10, 20, 30 min and then every 15 min until 180 min. Serum GH and insulin concentrations were determined by radioimmunoassay[10], employing CEA-CEN-SORIN kits. Plasma FFA were estimated according to Dole and Meinertz[11], and blood glucose levels by a glucose-oxidase method[12]. On no occasion were symptoms related to amantadine administration observed while the tests were in course.

Results. Amantadine, administered either by mouth or i.v., did not induce any significant modification of serum GH and insulin levels (see Table). Only 2 subjects exhibited an increase of serum GH concentration to 14.0 ng/ml and 11.5 ng/ml 30 and 60 min, respectively, after the infusion of the drug. In the first of these subjects, a rise of serum GH level to 9.0 ng/ml was also observed 30 min after the oral administration of amantadine.

A late elevation of plasma FFA was recorded during both tests; the mean values at 0 and 180 min were 580 ± 28.1 (SE) and 885 ± 29.5 μEq/l, respectively, during the oral test and 540 ± 25.3 and 850 ± 18.2 μEq/l during the i.v. test. Blood glucose levels remained unchanged.

Discussion. Dopamine and its precursor L-dopa have been shown to elicit hypophysial GH release[9,13,14]. Since amantadine is believed to increase the concentration of available dopamine in the CNS, it was thought that, like dopamine, amantadine could also stimulate GH secretion. However, this study has shown that acute administration of amantadine does not modify serum GH levels. The increase exhibited by 2 subjects is probably non-specific; it could be the result of spontaneous elevations or the effect of venipuncture.

This result is not necessarily in conflict with the assumption that amantadine potentiates dopamine activity in the CNS: the increase of available dopamine concentration produced by amantadine, although effective in improving certain symptoms of Parkinson's disease, could be inadequate for eliciting GH release. Insulin and glucose levels were also unchanged after amantadine administration, suggesting that the drug does not alter the balance between the inhibiting and stimulating factors regulating basal insulin secretion. The late raise of plasma FFA observed in most of the subjects can be attributed to the prolonged fast.

The fact that amantadine does not modify serum GH and insulin concentrations may be of advantage when this drug is administered, alone or in combination with L-dopa, for prolonged periods, as in the treatment of Parkinson's disease. In fact, in patients under chronic therapy with L-dopa, the repeated daily spurts of GH induced by the drug, might lead to still undefined metabolic disorders[15,16].

Highest serum growth hormone (GH) and immunoreactive insulin (IRI) levels after amantadine administration

Subject	Sex	Oral administration		Intravenously	
		GH ng/ml	IRI μU/ml	GH ng/ml	IRI μU/ml
1	♂	4.0 (3.0)	16.7 (19.8)	1.5 (1.2)	26.0 (11.0)
2	♂	1.2 (2.0)	24.3 (25.0)	11.5 (1.6)	22.3 (25.3)
3	♂	9.0 (1.0)	17.3 (19.0)	14.0 (1.5)	18.1 (21.3)
4	♂	3.5 (1.0)	25.5 (17.5)	2.0 (1.7)	15.3 (13.2)
5	♀	2.5 (1.6)	15.5 (17.0)	1.5 (2.3)	23.6 (18.4)
6	♂	1.5 (2.0)	16.2 (10.5)	2.0 (1.2)	16.0 (18.6)

Basal values in brackets.

Riassunto. In sei volontari normali, la somministrazione acuta, sia orale che e.v. di 300 mg di amantadina non ha causato modificazioni dei livelli serici di GH. Anche i valori di insulinemia, glicemia e di FFA plasmatici non hanno subito variazioni.

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