Effect of amantadine on the urinary excretion of some monoamines and metabolites in normal and parkinsonian subjects

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Amantadine is of benefit in Parkinson's disease, producing a prompt improvement with few side effects in most patients (Schwab, England, Poskanzer & Young, 1969; Fieschi, Nardini, Casacchia, Tedone & Robotti, 1970; Parkes, Zilkha, Marsden, Baxter & Knill-Jones, 1970). However, its mode of action remains undetermined. Experiments in laboratory animals suggest that amantadine releases catecholamines from stores in the peripheral (Grelak, Clark, Stump & Vernier, 1970) and central (Stromberg, Svensson & Waldeck, 1970) nervous systems. We have therefore measured several monoamines and their metabolites in the urine of both parkinsonian patients and normal subjects given amantadine. The results are presented in this demonstration.

Twenty-four hour urine specimens were collected from ten hospitalized patients with Parkinson's disease immediately before the start of amantadine therapy. A second collection from each patient was made within the first 4 days of taking the drug, 200 mg daily. Collections were also made from six patients who received L-dopa plus amantadine and from four patients receiving L-dopa alone. All patients continued to receive their normal anticholinergic drugs. In addition, the urines of five healthy volunteers who took amantadine (200 mg) daily for up to 12 days were also analysed. Aliquots of the collections were assayed for histamine (Oates, Marsh & Sjoerdsma, 1962) 1,4-methylhistamine (extracted by the method of White, 1966 with assay by the method of Fram & Green, 1965), 5-hydroxyindole-3 acetic acid (McFarlane, Dalgliesh, Dutton, Lennox, Nyhus & Smith, 1956), adrenaline and noradrenaline (Anton & Sayre, 1962), dopamine (Anton & Sayre, 1964) and 4-hydroxy-3-methoxyphenylacetic acid (Sato, 1965).

The excretion of 1,4 methylhistamine and 5-hydroxyindole-3 acetic acid was significantly higher in parkinsonian patients when measured during the first few days of taking amantadine than immediately before starting the drug. The excretion of dopamine and 4-hydroxy-3-methoxyphenylacetic acid was also increased, but the changes were not statistically significant. In contrast, the urinary excretion pattern in normal subjects was not affected by amantadine. The reason for this different effect in normal and parkinsonian patients is not apparent at the present time but is the subject of further investigation. L-Dopa, alone or in combination with amantadine produced the expected increases in dopamine and 4-hydroxy-3-methoxyphenylacetic acid excretion but also significantly reduced output of 5-hydroxyindole-3 acetic acid. In those patients receiving the drug combination, the excretion of 5-hydroxyindole-3 acetic acid was reduced to pre-amantadine levels. Brune & Pflughaupt (1971) also found 5-hydroxyindole-3 acetic acid excretion to be lower in parkinsonian patients on L-dopa therapy. Our finding that L-dopa reduced the excretion of 5-hydroxyindole-3 acetic acid but not that of methylhistamine supports their suggestion that the decrease may not simply be due to competition between amino-acids for absorption or for a decarboxylase enzyme.

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Haemodynamic effects of indoramin: a non-invasive technique for the cardiovascular evaluation of drugs

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Non-invasive techniques for assessing cardiovascular function have the advantage of safety, simplicity, sensitivity and relatively low costs. They are being increasingly applied to the problems of diagnosis and the relevance of these techniques in the assessment of the cardiovascular effects of pharmacological interventions will be demonstrated.

A non-invasive technique was used in the cardiovascular evaluation of indoramin, a new hypotensive agent with cardio-inhibitory and α-adrenoceptor blocking properties in animals (Alps, Johnson & Wilson, 1970) and the latter in man (Coltart, Lockhart, Royds & Turner, 1971). Five healthy male subjects were studied at the same time of day, semifasting and lying on a bed with a 15° head-up tilt for a period of 2 h after the intravenous administration of indoramin (10 mg); blood pressures were taken with a London School of Hygiene sphygmomanometer (Rose, Holland & Crowley, 1964).

The systolic time intervals of left ventricular systole were obtained at 15 min intervals from simultaneous recordings of the electrocardiogram, phonocardiogram and carotid artery pulse trace, using a multi-channel photographic recorder at a paper speed of 100 mm/second. Left ventricular ejection time (LVET), Q-S_2 and R-R interval were measured and the pre-ejection period (PEP) was derived from Q-2_2 interval less LVET (Weissler, Harris & Schoenfeld, 1968). The ratio PEP/LVET