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Letter to the Editor

Autonomic Neuropathy Following Treatment with Flavone Acetic Acid

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FLAVONE ACETIC ACID (LM 975) (FAA) is the second in a series of compounds based on the flavonoid aglycone ring structure and is currently being assessed in Phase II studies in a variety of malignancies including renal, colon and breast cancer, and melanoma. Dose limiting toxicity in Phase I studies was identified as acute reversible hypotension occurring during drug infusion [1]. The mechanism of this hypotension is unclear but may be related to the drug's underlying mechanism of action, which probably involves changes in tumour vasculature [2]. We now report a case of (non-reversible) cardiovascular autonomic neuropathy which followed FAA administration.

A 57-year-old female underwent an abdomino-perineal resection for Duke's Stage B adenocarcinoma of the rectum in July 1986. In January 1987 she developed multiple hepatic metastases and recurrence in the perineal scar. The patient denied any weight loss and there was no other significant prior medical history. She was not taking any regular medication. Physical findings included a resting pulse rate of 88 and b.p. of 120/70 with no postural variation. Performance status (WHO criteria) was 0.

The patient received six courses of FAA at a dose of 8.6 g/m^2, administered at weekly intervals as part of a Phase II study being conducted by the Cancer Research Campaign Phase II Committee and supplied by Lipha Pharmaceuticals. The drug was diluted in 1 l of N-saline and given intravenously over 6 h. During the fourth course of treatment, the patient became hypotensive, the b.p. falling from 130/80 (pre-treatment) to 95/70. She remained asymptomatic and the b.p. returned to pre-treatment levels when the infusion was ceased. The final two courses were also complicated by asymptomatic hypotension, in spite of a 25% dose reduction of FAA.

Four weeks after completing the chemotherapy, the patient developed symptoms of postural dizziness and tachycardia. Significant postural hypotension was noted, the b.p. falling from 140/80 (lying) to 95/75 (standing). The pulse rate was 80/min, in sinus rhythm. There were no other symptoms of autonomic neuropathy.

Simple non-invasive autonomic function tests [3, 4] demonstrated mixed sympathetic and parasympathetic abnormality in the response of the heart rate and blood pressure to standing, deep breathing, Valsalva and stress. Intravenous atropine (0.6 mg) raised the heart rate from 72 to 120 beats/min confirming parasympathetic efferent activity at rest. During controlled head-up tilting, increasing 15 degrees every 5 minutes, blood pressure fell from 127/77 to 94/76 at 60 degrees and heart rate rose from 81 to 106/min. After 5 min at 60 degrees, b.p. became undetectable and the patient lost consciousness. Simultaneous blood samples demonstrated a rise in plasma renin activity from 14 μU/l at 0 to 40 μU/l at 60, adrenaline rose from 0.2–0.7 nmol/l and noradrenaline from 1.9–4.5 nmol/l, the increase insufficient to maintain blood pressure. Abnormal adrenoceptor function was excluded by a normal pressor response to isoprenaline but edrophonium (10 mg) i.v. produced a 55% increase in circulating noradrenaline, consistent with a central sympathetic abnormality [5].

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Overall the findings are consistent with an incomplete mixed sympathetic parasympathetic autonomic neuropathy.

An abdominal CT scan did not reveal adrenal metastases and a short synacthen test, to exclude adrenal insufficiency, showed a normal response. The patient has now been commenced on 1-α-fludrocortisone, with a symptomatic and clinical improvement in the postural hypotension.

Autonomic neuropathy in cancer patients is well recognized. Isolated reports in the literature suggest it may occur as a paraneoplastic phenomenon. Park *et al.* [6] described a patient with bronchial carcinoma and autonomic neuropathy which subsequently disappeared after radiotherapy to the tumour. The incidence of cardiovascular autonomic insufficiency was assessed in a group of patients with advanced breast cancer [7] and was more frequently abnormal in patients with poor performance status, malnutrition and a basal heart rate of greater than 100, none of which are applicable to our patient.

More commonly, autonomic neuropathy may be associated with chronic disorders, including chronic renal disease and diabetes mellitus [4]. Morphine and tricyclic antidepressant drugs may cause autonomic changes and, of the anti-cancer agents the vinca alkaloids most frequently cause autonomic neuropathy [8].

Our findings in this patient are consistent with a mixed, predominantly sympathetic efferent, cardiovascular autonomic neuropathy. The temporal relationship between the administration of the FAA and the onset of the neuropathy are very suggestive of a drug effect, although, clearly, a paraneoplastic relationship cannot be excluded. Nevertheless, this may represent a long term side-effect of FAA, quite distinct from the acute, transient hypotension and should be considered in the patient who presents with postural hypotension while, or after, receiving FAA. The mechanism for the autonomic neuropathy is unclear.

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