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Clinical Study

Cisplatin-induced autonomic neuropathy: does it really exist?

W.P. Vandertop,[1] W.B. de Vries,[1] N.C. Notermans,[2] M.J.M.A. Nijsen,[3] D.J. de Wildt,[3] C.A.F. Tulleken,[1] and W.H. Gispen[3]
[1] *Department of Neurosurgery,* [2] *Department of Neurology,* [3] *Department of Medical Pharmacology, Rudolf Magnus Institute and University Hospital, Utrecht, The Netherlands*

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Abstract

The neurotoxic side-effects of cisplatin affect predominantly the large, myelinated fibres of peripheral nerves, leading to a sensory neuropathy. Several reports of cisplatin-associated autonomic neuropathy have been published. Autonomic dysfunction however, is caused by a neuropathy of small unmyelinated nerve fibres.

By using the absolute pupil diameter as a parameter of autonomic nervous system function, we studied autonomic neuropathy in the eye of cisplatin-intoxicated rats. In addition, we examined autonomic cardiovascular function by measuring the change in heart rate (HR) and mean arterial blood pressure (MAP) in response to intravenous phenylephrine (PHE) and tyramine (TYR). No significant differences in mean pupil diameter developed in cisplatin-intoxicated rats ($n = 12$) in the course of 9 weeks (total cumulative dose cisplatin 18 mg/kg) compared with normal controls ($n = 9$) (MANOVA, $F_{1,19} = 0.88$, $P < 0.36$). The PHE- and TYR-induced changes in MAP and HR were virtually the same in cisplatin-intoxicated rats when compared with normal controls.

We conclude that cisplatin probably does not cause autonomic dysfunction, at least not in rats, in doses commonly used and which are known to cause a peripheral, sensory neuropathy.

Introduction

Cisplatin is a cytotoxic drug with substantial gastrointestinal, nephrotoxic and neurotoxic side effects. Many patients will develop a peripheral sensory neuropathy, predominantly of large myelinated fibres [1].

The first report of a cisplatin-associated autonomic neuropathy was by Rosenfeld and Broder [2]. Several reports of autonomic neuropathy after cisplatin-based chemotherapy have been published since [1, 3–5]. In order to cause an autonomic dysfunction, a neuropathy of small unmyelinated nerve fibres would be required. As cisplatin affects the large, myelinated fibres of peripheral nerves predominantly [6], an autonomic neuropathy would not be expected to develop.

Using an animal model, where the pupil diameter of the eye in the rat serves as a parameter of autonomic function, we have documented the development of an autonomic neuropathy in streptozotocin-induced diabetic rats and the beneficial effect of systemic Org 2766, an $ACTH_{4-9}$ analogue, in preventing this autonomic neuropathy [7]. Furthermore, we have shown the beneficial effect of systemic, as well as topical, application of $ACTH_{4-9}$ analogue on oculomotor nerve regeneration in the early stages after a crush lesion [8–9].

In the present study we used the same model to examine whether an autonomic neuropathy devel-

ops in the eye of cisplatin-intoxicated rats (*experiment 1*). In addition, we examined autonomic cardiovascular function by measuring the change in heart rate (HR) and mean arterial blood pressure (MAP) in response to intravenous phenylephrine (PHE) and tyramine (TYR) in controls and cisplatin-intoxicated rats (*experiment 2*). Thereby, the PHE-induced pressor response and reflectory bradycardia reflects postsynaptic sympathetic and baroreceptor reflex activity, respectively. The TYR-induced pressor response and tachycardia will be a measure for presynaptic sympathetic activity at vascular and cardiac level, respectively.

Materials and methods

Male young adult rats of an inbred Wistar strain, weighing approximately 220 g at the onset of the experiment, were used. The animals were housed in Makrolon cages on sawdust, with food and water ad libitum. The rats were randomised into two groups.

Experiment 1: pupil diameter in controls and cisplatin intoxication

One group of animals (n = 14) received an intraperitoneal injection of cisplatin (Platinol[R], Bristol-Myers Squibb, Woerden, The Netherlands), twice a week, in a dose of 1 mg/kg total body weight (b.w.) for the period of nine weeks, leading to a cumulative dose of 18 mg/kg. Twenty minutes prior to the cisplatin injection, the rats received a subcutaneous injection of furosemide in a dose of 12,5 mg/kg b.w., to protect against nephrotoxicity. A second group (n = 12) of weight-matched non-cisplatin-intoxicated rats served as contols.

Measurement of all pupil diameters was carried out under general anaesthesia (Hypnorm[R], Duphar, Weesp, The Netherlands, containing fluanisone 10 mg/ml and fentanyl citrate 0,315 mg/ml, dose 0,1 ml/rat, administered intramuscularly). The rats were placed under an operating microscope (Zeiss OpMi-1; lens focal distance 200 mm, magnification ratio 16 ×). A Canon EOS-650 35 mm reflexcamera with electronically-controlled automatic exposure, focal plane shutter and built-in motor drive was side-mounted to the operating microscope. The left eye of each rat was manually brought into focus in a plane parallel with the microscope lens, after which a supramaximal light stimulus was directed at that eye with an electronic flashlight. Using the camera self-timer, the flash was given after 8 s, and the shutter was released after 10 s, i.e. at the point of maximal pupillary constriction, as this represents a constant, maximal parasympathetic action. That the photograph was taken at the moment of maximal pupillary constriction was checked every time under direct visual control. Kodak Ektachrome 160T professional colour reversal film was used.

Prior to all measurements the focal distance of the microscope lens was tested by taking a photograph of calibrated millimeter paper. All pupil measurements were based on this calibration. The baseline measurements were performed one day after the animals received their first dose of cisplatin. Thereafter, all animals were photographed at one week intervals.

After developing the exposed films, all colour slides were projected onto a white screen using a Zeiss Ikon 129 slide-projector. By first projecting the slide of calibrated millimeter paper, a magnification ratio could be calculated. Then absolute pupil diameters were measured on the white screen and calculated using the magnification ratio. Slides showing a pupil not in focus were omitted as calculation of these pupil diameters would be inaccurate. All slides were measured independently by two investigators (WPV;WBdV), on separate occasions (limits of agreement – 0.06 to + 0.06 mm) [10]. All measurements were carried out in a blind fashion.

Electrophysiological measurements of the H-reflex related sensory nerve conduction velocity (SNCV) were performed at the beginning of the experiment and after 9 weeks in order to quantify the peripheral neuropathy. The technique is described in detail elsewhere [6].

Experiment 2: PHE/TYR-induced changes in MAP and HR

One group of animals (n = 14) received an intraperitoneal injection of cisplatin, as described above. A second group (n = 15) of age-matched non-cisplatin-intoxicated rats, received only saline injections and served as controls. After six weeks (= cumulative dose of cisplatin 12 mg/kg) all rats were brought under general anesthesia (urethane 1,3 ml/100 mg b.w., administered intraperitoneally) and cannulated with indwelling arterial (carotid) and venous (jugular) polyethylene cannulae. The arterial cannula was connected to a pressure transducer and the blood pressure (systolic/diastolic) was directly recorded on a Wekagraph (WK-821 AR, Dépex, de Bilt, The Netherlands). HR was recorded by a cardiotachometer coupled to the pressure transducer. A syringe was connected to the venous cannula for intravenous drug administration.

Firstly, resting blood pressure and HR were recorded. Secondly, PHE and TYR were administered in bolus injections and dose-response curves were determined for PHE over the range of 0.5, 1, 3, 10, 30 and 50 μg/kg b.w., and for TYR over the range of 30, 100, 300, 500, 700 and 1000 μg/kg b.w. The rats were allowed to respond to each dose of PHE or TYR and to stabilise before the next dose was administered.

Electrophysiological measurements of the H-reflex related sensory nerve conduction velocity (SNCV) were performed at the beginning of the experiment and after 6 weeks in order to quantify the peripheral neuropathy. The technique is described in detail elsewhere [6].

Data analysis

The pupil diameter measurements were analysed by an analysis of variance for repeated measurements (MANOVA), using the Statistical Package for the Social Sciences (SPSS) computer program. The H-reflex related sensory nerve conduction velocities were analysed using supplemental t tests.

MAP was calculated by adding the systolic pressure and twice the diastolic pressure, and dividing the sum by three:

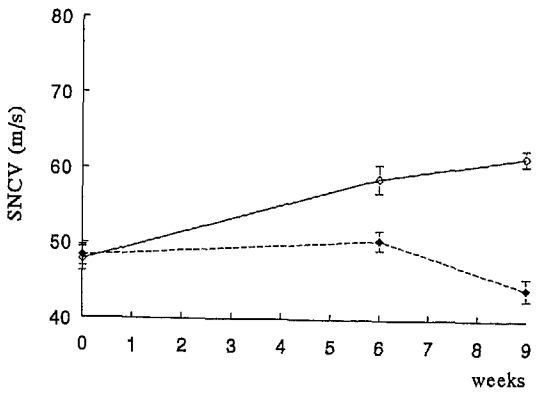

Fig. 1. H-reflex related sensory nerve conduction velocity (mean with SE) in weight-matched control rats (◇; n = 9, open diamonds), compared with cisplatin-intoxicated rats (◆; n = 12, filled diamonds). After 9 weeks there is a clear increase in SNCV in the control group, whereas the SNCV in the cisplatin-treated group has dropped significantly.

$$MAP = \frac{systolic\ pressure + 2 \times diastolic\ pressure}{3}$$

Dose-response curves for PHE and TYR were determined for cisplatin-intoxicated and control rats and graphed as a function of the change in MAP (Δ MAP) and the change in HR (Δ HR) that corresponded to a single bolus injection of either agent. The Δ MAP and Δ HR were analysed by an analysis of variance (one-way ANOVA).

The codes, disclosing which animals were cisplatin-intoxicated and which were controls, were broken only after analysis of all data had been performed. Data obtained from rats that died during the course of the experiment were excluded. The cause of death was usually suffocation during induction of general anaesthesia.

Results

Experiment 1: pupil diameter in controls and cisplatin intoxication

Twelve rats in the cisplatin group and nine rats in the control group were used for final analysis.

The H-reflex related SNCV at the onset of the experiment was 47.8 m/s (SE 1.6) for the control group and 48.3 m/s (SE 1.4) for the cisplatin-group. After 6 weeks the SNCV in the control group had

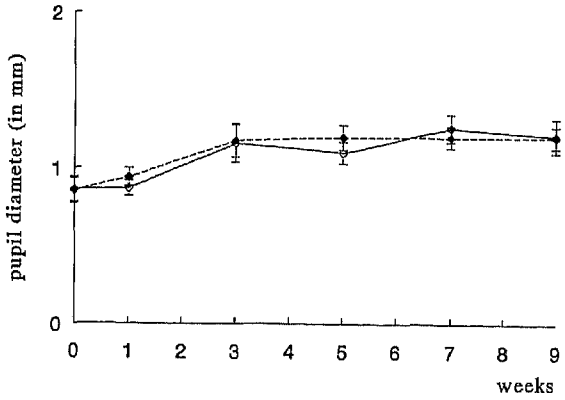

Fig. 2. Development in time of pupil diameter (mean with SE) in weight-matched control rats (◇; n = 9, open diamonds), compared with cisplatin-intoxicated rats (◆; n = 12, filled diamonds). No significant differences in mean pupil diameter of both groups develops in the course of 9 weeks (total cumulative dose cisplatin 18 mg/kg) (MANOVA, $F_{1,19} = 0.88$, $p < 0.36$).

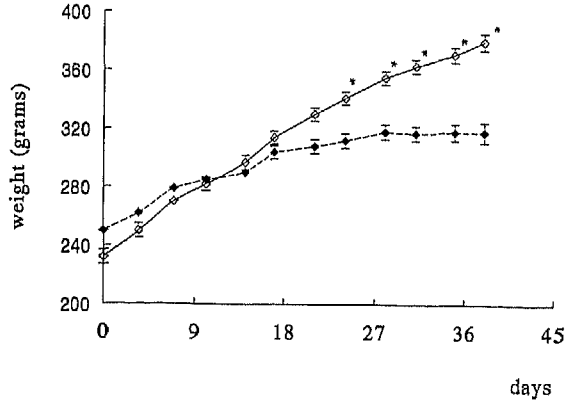

Fig. 3. Development in time of total body weight (mean with SE) in weight-matched control rats (◇; n = 15, open diamonds), compared with cisplatin-intoxicated rats (◆; n = 14, filled diamonds). The absence in weight gain in the cisplatin-intoxicated group is apparent after 3 weeks. The difference between both groups is significant (* = $p < 0.001$).

increased to 58.9 m/s (SE 1.3), whereas the SNCV in the cisplatin-intoxicated group was 50.6 m/s (SE 1.9) ($P < 0.035$). After 9 weeks the SNCV in the control group had further increased to 61.9 m/s (SE 1.1), whereas the SNCV in the cisplatin-intoxicated group had significantly dropped to 44.2 m/s (SE 1.5) ($P < 0.001$) (Fig. 1). This confirms the presence of a peripheral sensory neuropathy after a cumulative cisplatin intoxication of 18 mg/kg.

The mean pupil diameter at the onset of the experiment was 0.86 mm (SE 0.08) for the control group and 0.84 mm (SE 0.09) for the cisplatin-intoxicated group (t test, $t = 0.13$, $df = 19$, $P < 0.90$). After three weeks the mean pupil diameter in both groups increased to 1.16 mm (SE 0.12) and 1.11 mm (SE 0.11) respectively, and remained more or less stable (Fig. 2).

From week 0 to week 9 there was no significant difference in mean pupil diameter between the rats in the control group and the cisplatin-intoxicated rats (MANOVA, $F_{1,19} = 0.88$, $P < 0.36$). This result implies that cisplatin intoxication up to 18 mg/kg body weight does not cause an autonomic neuropathy in the eye of the rat.

Experiment 2: PHE/TYR-induced changes in MAP and HR

At the onset of the experiment the rats weighed 210–270 g. Initially, the rats in the control group weighed less than in the cisplatin-intoxicated group, but an absence of further weight increase in the group of cisplatin-intoxicated rats became apparent after the third week (Fig. 3). These differences in body weight between the cisplatin-intoxicated rats compared with the age-matched control group were significant (t test, $t = 6.67$, $df = 27$, $P < 0.001$).

The H-reflex related SNCV at the onset of the experiment was 47.8 m/s (SE 1.6) for the control group and 48.3 m/s (SE 1.4) for the cisplatin-group. After 6 weeks the SNCV in the control group had increased to 59.5 m/s (SE 1.2) whereas the SNCV in the cisplatin-intoxicated group was only 51.0 m/s (SE 2.1) $P < 0.034$). This confirms the presence of a peripheral sensory neuropathy after a cumulative cisplatin intoxication of 12 mg/kg.

The resting MAP in both groups before any administration of vasopressor agents showed no difference: 81 (SE 3.4) and 79 (SE 5.2) mmHg for the control and cisplatin group, respectively. The administration of i.v. saline led to only a slight increase in MAP of 5 mmHg in the control group and 3 mmHg in the cisplatin-intoxicated group. This dif-

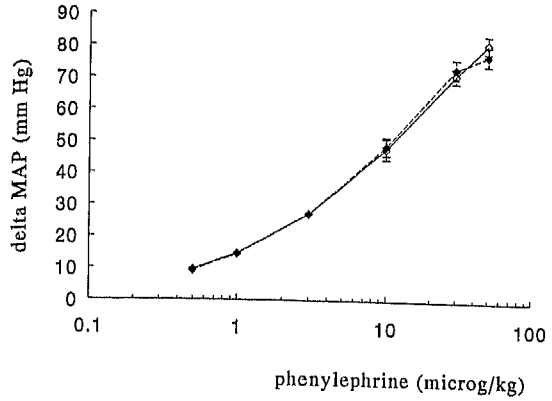

Fig. 4a. Dose-response curve illustrating the change in mean arterial pressure after intravenously administered phenylephrine over a range of 0.5–50 µg/kg, for controls rats (◇; n = 15, open diamonds), and cisplatin-intoxicated rats (◆; n = 14, filled diamonds).

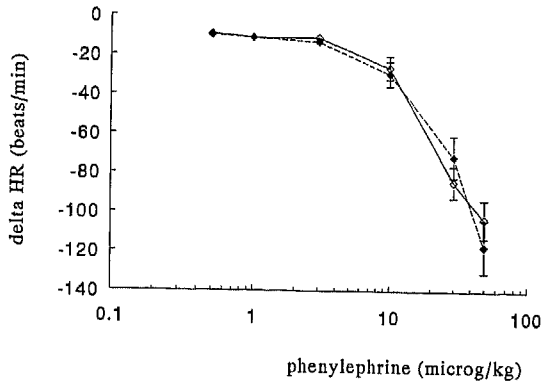

Fig. 4b. Change in heart rate (reflectory bradycardia) after intravenously administered phenylephrine over a range of 0.5–50 µg/kg, for controls rats (◇; n = 15, open diamonds), and cisplatin-intoxicated rats (◆; n = 14, filled diamonds).

ference was not statistically significant (t test, t = 1.26, df = 27, P < 0.22). The PHE-induced change in MAP (Fig. 4a) and HR (Fig. 4b) over the range of 0.5–50 µg/kg was virtually the same in both the control group and the cisplatin-intoxicated group. The TYR-induced change in MAP (Fig. 5a) and HR (Fig. 5b) over the range of 30–1000 µg/kg showed also no differences when both groups were compared. These results imply that cisplatin intoxication up to 12 mg/kg b.w. does not cause an autonomic neuropathy, as measured by cardiovascular responsiveness to vasopressor agents.

Discussion

Simply by photographing the rat's pupil under standardised circumstances, the absolute pupil diameter can be used as a parameter of autonomic nervous system function [7–9]. The present study shows that the mean pupil diameter in cisplatin-intoxicated rats does not differ significantly compared with normal control rats, up to a cumulative dose of 18 mg/kg. In humans, a major side-effect of cisplatin is a sensory neuropathy which occurs at cumulative doses of 350 to 600 mg/m^2, corresponding to at least 3 courses of cisplatin. At conventional doses of 400 mg/m^2, many patients complain of mild to moderate numbness and paraesthesias [11]. With an estimated length of 15 cm and an average weight of 220 g, the total body surface of a Wistar rat is estimated at 0.0030 m^2. A cumulative dose of 11 mg/kg means a cumulative dose of 3.3 mg per rat of 300 g, which in turn would mean a cumulative dose of 1100 mg/m^2. In experiments by De Koning *et al.* [6] and Hamers *et al.* [12] these doses have been shown to cause a peripheral neuropathy in 100% of rats. A cumulative dose of 18 mg/kg means a cumulative dose of 5.4 mg per rat of 300 g, which in turn would mean a cumulative dose of 1800 mg/m^2. Nevertheless, despite these massive doses, it is still conceivable that it would take more time or would require even higher doses for an autonomic neuropathy to develop, as animal data cannot simply be extrapolated from the human state.

Cisplatin-intoxication in mature rats gives a marked reduction of the sensory nerve conduction velocity, whilst the SNCV in age-matched controls remains more or less unchanged [13]. It is well known however, that the SNCV in young adult rats increases as the animals more fully mature [6]. The fact that this normal increase in SNCV does not occur in cisplatin-intoxicated young adult rats indicates a relative slowing of the SNCV, demonstrating the development of a sensory neuropathy.

Experimentally, it has been shown that vasopressor-induced changes in blood pressure and heart rate are effective for the evaluation of cardiovascular autonomic nervous system functioning [14–15].

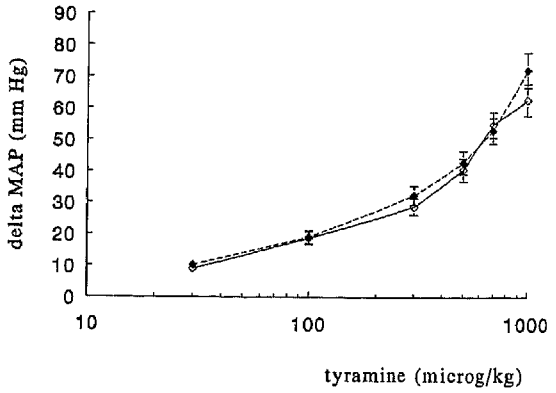

Fig. 5a. Dose-response curve illustrating the change in mean arterial pressure after intravenously administered tyramine over a range of 30–1000 μg/kg, for controls rats (◇; n = 15, open diamonds), and cisplatin-intoxicated rats (◆; n = 14, filled diamonds).

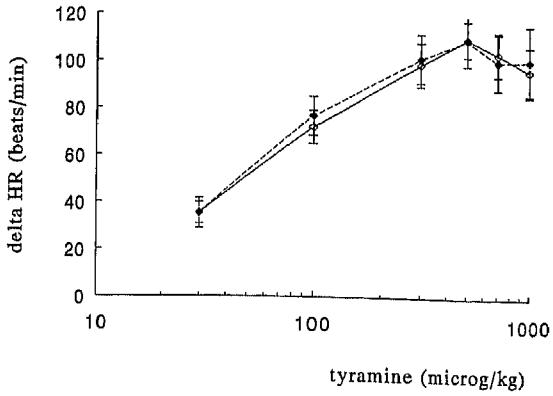

Fig. 5b. Change in heart rate (tachycardia) after intravenously administered tyramine over a range of 30–1000 μg/kg, for controls rats (◇; n = 15, open diamonds), and cisplatin-intoxicated rats (2 mg/kg/week) (◆; n = 14, filled diamonds).

Jackson *et al.* showed that short-term diabetic rats were hypotensive and had lower heart rates when compared with control rats [14]. Furthermore, blood pressure responses to norepinephrine and angiotensin II were depressed in the diabetic rats, whereas the baroreceptor reflexes in these rats were more sensitive. Phenylephrine, a directly acting, selective activator of the (postsynaptic) α_1-receptor causes a dose-related increase in peripheral vascular resistance leading to a rise in blood pressure, has few or no cardiac effects, and is regarded superior to angiotensin II for the evaluation of cardiovascular responsiveness [16,17]. Tyramine, an indirectly (presynaptic) acting non-selective adrenergic drug causes an increase in blood pressure (α-effect) and an increase in heart rate (β-effect). Van der Zee *et al.* have demonstrated a severely reduced responsiveness of blood pressure to i.v. tyramine, and a decreased responsiveness to i.v. phenylephrine in streptozotocin-induced diabetic rats with a documented peripheral neuropathy, indicating the additional presence of an autonomic neuropathy [15].

In the present investigation, we found an excellent dose-response curve for the mean arterial pressure after phenylephrine, in both control and cisplatin-intoxicated rats. An equally intact baroreceptor function was present in both groups, as the rise in blood pressure was immediately followed by a significant reflex bradycardia. Both these findings indicate an intact postsynaptic adrenergic function. The rise in mean arterial pressure (indirect α-effect) and increase in heart rate (indirect β-effect) after tyramine show that presynaptic adrenergic mechanisms are also not adversely affected in cisplatin-intoxicated rats. This implies that cisplatin does not cause an autonomic neuropathy.

De Koning *et al.* found that the first sign of neurotoxicity in cisplatin-intoxicated rats was a decreased sensitivity of Ia-fibres to electrical stimulation, that motor nerves were seldom affected and that small unmyelinated fibres conducting pain sensation were not impaired [6]. In humans, cisplatin affects predominantly thick myelinated nerve fibres responsible for propriocepsis and vibration sense [12, 18], while pain and temperature sense remain relatively spared [19, 20]. Krarup-Hansen *et al.* found no evidence of autonomic neuropathy in an electrophysiological and histological study of cisplatin-induced neuropathy in man [11].

Analysis of the anecdotal reports on cisplatin-induced autonomic neuropathy shows that the majority relies on the clinical symptoms and signs for diagnosing autonomic neuropathy, without corroboration with autonomic function tests [2–4]. The two reports that have performed autonomic function tests are quite inconclusive. Boogerd *et al.* suggest some involvement of the autonomic nerves based

solely on a Valsalva ratio dropping below 1.3 during chemotherapy in two out of 12 patients [5]. No other autonomic function tests were performed. Nine of the twelve patients received cisplatin (20 mg/m^2/day) in combination with doxorubicin (35 mg/m^2), cyclophosphamide (100 µg/m^2) and hexamethylamine (150 mg/m^2), and three patients received cisplatin (75 mg/m^2) in combination with cyclophosphamide (750 mg/m^2). Only one patient was treated with cisplatin as the single chemotherapeutic agent. Doxorubicin is known to produce selective damage of dorsal root ganglia in rats [21], and hexamethylamine causes a sensorimotor neuropathy in man [5]; to our knowledge, no data on the toxicity of these drugs on the autonomic nervous system exists. Both patients with suspected autonomic involvement, received combined schedules. It is conceivable that the combination of these drugs could be at least partly responsible for the symptoms. In addition, one of the two patients with an abnormal result on Valsalva's manoeuver had no clinical symptoms (and was not examined for signs), while the total dose of cisplatin received by this patient was only 300 mg/m^2. Usually, signs of a peripheral sensory neuropathy become apparent only after a cumulative dose of 350 to 600 mg/m^2. Finally, the other patient, a 72-year-old, had a borderline Valsalva ratio (1.31) even before cisplatin treatment started, indicating a possible autonomic dysfunction from the onset. Hansen observed a dysfunction of the parasympathetic nerves in 10 out of 28 patients, based on the heart rate response to standing, to Valsalva's manoeuvre and to deep breathing [1]. Eight of the ten patients however, had an abnormal result in one out of the 3 tests, indicating only minimal damage, whilst the only complaint related to autonomic dysfunction was impotence in three patients. All patients received combined chemotherapy schedules (cisplatin, vinblastine and bleomycin in unknown doses).

In conclusion, one must always bear in mind that the cause of autonomic neuropathy in patients with cancer is probably multifactorial, and that cytotoxic agents may be only one factor [4]. Our animal model data suggest that the autonomic nervous system is relatively insensitive to cisplatin, at least in rats, and in doses usually required to induce a peripheral, sensory neuropathy. Although animal data cannot simply be extrapolated to the human state, it is conceivable that an autonomic neuropathy may not be an expected side-effect of cisplatin therapy in man. Before diagnosing autonomic neuropathy in patients treated with cisplatin, extensive laboratory evaluation of autonomic reflex function is warranted, determining whether sympathetic or parasympathetic pathways, or both are involved.

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Address for offprints: W.P. Vandertop, Department of Neurosurgery, University Hospital, G.03.124, P.O. Box 85500, 3508 GA Utrecht, The Netherlands