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Vibration perception and thermoperception as quantitative measurements in the monitoring of cisplatin induced neurotoxicity

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SUMMARY

In 20 ovarian cancer patients treated by cisplatin-based chemotherapy quantitative investigations of the vibration and the thermoperception were performed. Following the administration of cisplatin of 300 mg/m^2 and more the vibration perception threshold (VPT) was shown to be significantly elevated in all patients, despite the absence of clinical symptoms and signs in a number of patients. The VPT returned within 8 monhts to its original level in the 2 patients who were followed after cessation of therapy (cumulative dose of cisplatin 450–525 mg/m^2). The changes seen in hands and in feet were comparable. There was no significant difference between the left and the right hand side. Thermoperception thresholds did not change during the treatment period. This study shows that quantitative measurement of vibration perception thresholds in patients treated with cisplatin is a relatively simple, accurate and reliable technique. Measurement is only required at the hand. It is concluded that this technique is a valuable tool in the assessment of cisplatin neurotoxicity and may be used in the monitoring of drugs that claim to be of benefit in the prevention and treatment of this affliction.

Key words: Cisplatin; Neuropathy; Vibration sense

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INTRODUCTION

Cisplatin is widely used in chemotherapeutic regimens for ovarian, testicular and bladder carcinoma. A major side-effect of cisplatin treatment is a dose-dependent, sensory, peripheral neuropathy (Thompson et al. 1984; Ongerboer de Visser and Tiessens 1985; Ozols et al. 1985; Roelofs et al. 1985). Studies indicate that, depending on the dose of cisplatin, 40–100% of the patients are affected by this neuropathy. Patients complain of tingling and numb feelings following cumulative doses of 300–600 mg/m^2. Higher doses may induce a severely disabling sensory ataxia. On clinical examination tendon reflexes are diminished or absent. Vibration sense, proprioceptsis and fine touch perception are diminished, whilst perception of pain remains unaffected (Ongerboer de Visser and Tiessens 1985). Muscle weakness does not develop and motor nerve conduction is normal. Sensory nerve conduction velocity and sensory nerve action potentials decrease (Thompson et al. 1984; Gastaut et al. 1985). The number of thick myelinated fibers has been shown to be decreased in sural nerve biopsies, which is in agreement with the clinical and electrophysiological observations. Upon cessation of treatment the severity of the neuropathy generally decreases, but recovery may take from several months to 2 years and is often incomplete (Gastaut et al. 1985; Ozols et al. 1985).

Quantification of signs of a neuropathy is required in order to be able to follow in a stepwise fashion the development of and recovery from the disorder. Quantification also enables the monitoring of the effects of drugs aimed at the prevention and treatment of neurotoxic side effects.

In this study the vibration and thermoperception were measured before, during and after treatment of patients with cisplatin. The objective of the study was to establish whether the development of the neuropathy and subsequent recovery could be accurately quantified and whether changes in the VPT have a predictive value. It will be shown that measurement of vibration sense allows the registration of subclinical neuropathy. The vibration perception threshold raises with increasing cumulative doses of cisplatin and tends to decrease in the period of clinical recovery.

METHODS

Measuring techniques

Vibration perception threshold (VPT) was measured according to the "method of limits" using a Vibrameter type III (Somedic AB, Stockholm, Sweden). A discussion of the pros and cons of the "method of limits" compared to the "forced choice method" is given in Secular et al. (1973), Dyck et al. (1978), Stern et al. (1980). The underlying physical mechanism, technical features and functioning of the Vibrameter type III have been described previously (Lindblom 1974; Goldberg and Lindblom 1979; Dyck 1984). Briefly, the vibrameter is a hand-held instrument, and the vibration stimulus is applied by means of a rod with a diameter of 13 mm. The stimulus consists of sinusoidal pulses with a frequency of 100 Hz. The application pressure of the rod can be adjusted and

visually controlled during the measurement. Therefore, effects due to changes in pressure are minimized. By means of a transducer in the stimulator, the vibration amplitude is measured directly at the stimulation site, which eliminates the variable damping effect of the underlying tissues, and is presented in micrometers peak to peak on a calibrated digital display. The stimulus strength, therefore, is expressed in actual displacement of the skin in micrometer. The investigator can increase and decrease the amplitude of the displacement of the rod gradually. The measurements were performed on the left and right os metacarpal II and os metatarsal I, while the patient was lying on a couch, with the extremity placed on a cushion filled with rice grains. Test–retest variability was shown to be small in a large series of healthy subjects (Goldberg and Lindblom 1979).

The thermoperception threshold (TPT) was assessed with a method slightly modified from Früstorfer (Früstorfer et al. 1978). A Peltier element probe with a stimulation surface of 6.25 cm^2 was used. The temperature was changed with a speed of 0.5 °C per second. The current reverser of the Peltier element could be controlled by the patient, who was asked to press the button changing this current when a change in temperature was felt. The latency between pressing the button and the subsequent reversal in temperature change was variable, in order to avoid response bias caused by rhythmical pressing. Also, measurements were taken at both sides, and only accepted after the appearance of a consistent saw-tooth curve with respect to both upper and lower thresholds.

Both techniques were performed in a quiet place at room temperature. In accordance with the "method of limits" as put forward by Goldberg and Lindblom (1979) the stimulus is increased until it is perceived by the patient and subsequently decreased until it is no longer perceived. This procedure is repeated 3 times. The average of the perception and extinction values obtained in this way yields the perception threshold.

The VPT values were corrected for age, since extensive investigation in healthy subjects has shown a clear logarithmical correlation between age and VPT (Halonen et al. 1986). The mean values for different age categories were provided by Somedic AB (manual for vibrameter type III, Somedic AB, Stockholm, Sweden, 1985). Values obtained with the Vibrameter in our hospital closely resembled the values given by Goldberg and Lindblom. The means of TPT values obtained before the start of cisplatin treatment was used as reference value for TPT test results.

One investigator (A.E.) examined all the patients. In addition to the above mentioned tests a complete neurological examination was also done. This included an interview and the recording of muscle strength, tendon reflexes, pin-prick perception, touch perception, vibration perception with the tuning fork, position sense and the Romberg sign. The results were classified quantitatively on ordinal scales.

Patients and statistics

In total 20 ovarian cancer patients were included in the study. Only patients with FIGO stage III/IV were considered eligible. No further selection was employed. All received a combination of cisplatin and cyclophosphamide (75 mg/m^2 and 750 mg/m^2 i.v. respectively, on day 1; this treatment was repeated every 3 weeks). The VPT's, TPT's and the neurological status were determined on one or more occasions, before,

during and after treatment. Patients who were examined after completion of treatment had received 6–7 treatment courses (450–525 mg/m^2 cisplatin).

The study consisted of 2 parts. In the first part 15 patients were included. The patients were all in different stages of therapy at the start of the study. Hence only a limited number of test results was obtainable in these patients. In order to allow statistical evaluation of these results, only one measurement of each of these patients was used. The values obtained were put in a correlation matrix against the cumulative dose of cisplatin they had received at that point. Statistical significance was calculated using a regression analysis.

In the second part 5 patients were followed from the beginning up till 6 treatment courses. In these patients measurements were only done on the left and the right second

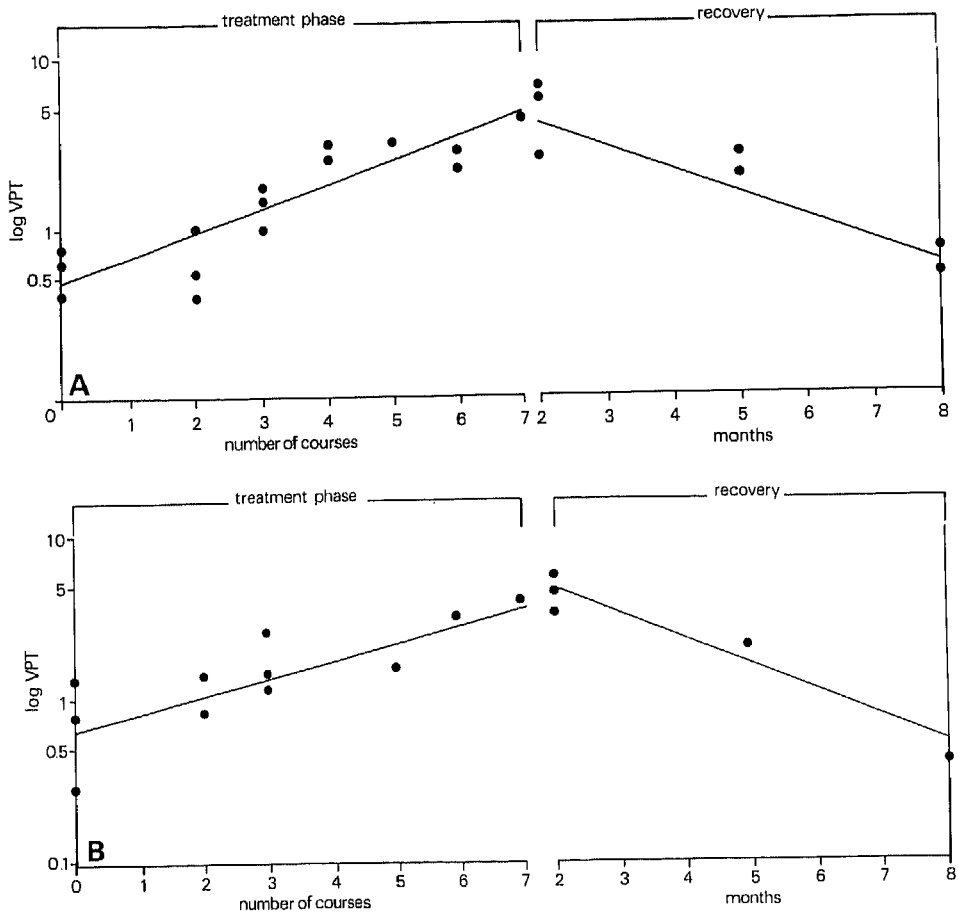

Fig. 1. Relation between cumulative doses of cisplatin or months after cessation of treatment and Vibration perception thresholds (VPT) in hands (a) and feet (b) in 15 patients. The VPT's were corrected for age and log-transformed with the formula supplied by Goldberg and Lindblom (1979): N (corrected value) = (log(VPT) − b*Age − a)/s. For the hands the values a = −0.933, b = 0.0068, s = 0.266, and for the feet a = −1.204, b = 0.026, s = 0.344. The correlation coefficients calculated, using the measurements in the treatment period are $r = 0.65$ ($P < 0.008$) and $r = 0.78$ ($P < 0.004$) respectively.

metacarpal bone. An ANOVA for repeated measures was applied to these results to calculate statistical significance. The SPSS statistics package was used for all calculations.

RESULTS

A correlation matrix between cumulative dose of cisplatin and corresponding vibration perception threshold values is depicted in Fig. 1a and b. The correlation found was significant both for measurements at the metacarpal and at the metatarsal level. Results from the left and the right side were closely comparable and no evidence was found for a consistent difference between the two sides. Paresthesiae were reported by 5 out of 6 patients who were measured after receiving 4 courses of chemotherapy or more. Three of them had decreased tendon reflexes. Other symptoms and signs were less prominent. No effect of cisplatin treatment was seen on thermoperception.

Three patients were examined after cessation of cisplatin therapy, 2 of them repeatedly. The values recorded in these patients are also given in Fig. 1. A normalization of both vibration perception thresholds and clinical signs was seen in the latter patients after 8 months, which indicates a tendency to recover (Table 1). The cold perception threshold, which remained unchanged during the treatment period, increased in the follow-up period.

The results of vibration perception measurement in the 5 patients, prospectively followed, are given in Fig. 2. The corresponding clinical parameters are shown in Table 2. The increase in VPT was dose-dependent as calculated by MANOVA

TABLE 1

SYMPTOMS AND SIGNS IN 2 PROSPECTIVELY FOLLOWED PATIENTS DURING A FOLLOW-UP OF 8 MONTHS AFTER CESSATION OF TREATMENT

	2 months	8 months
Symptoms		
Paresthesiae	2	0
Loss of dexterity	1	0
L'Hermitte's sign	0	0
Signs		
Decreased or absent tendon reflexes	1	0
Loss of strength	0	0
Pain perception	0	0
Fine touch perception	2	0
Vibration perception[a]	1	0
Cerebellar dysfunction	0	0
Positive Romberg	1	0

[a] With tuning fork.

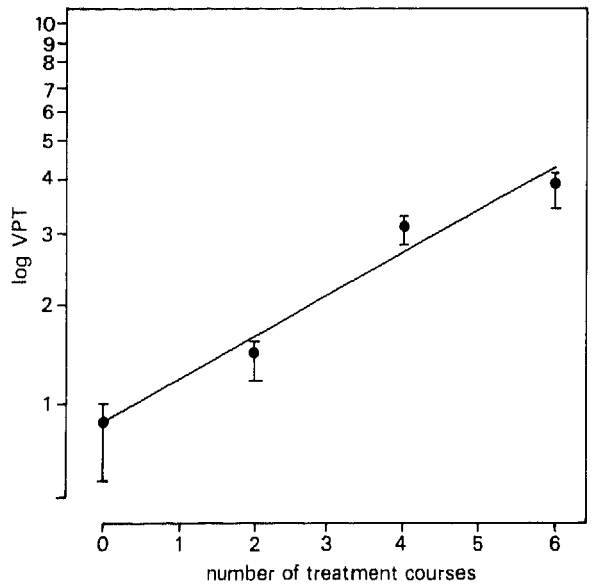

Fig. 2. Vibration perception thresholds (VPT) in 5 patients before treatment and after 2, 4 and 6 treatment courses. The VPT's were corrected for age and log-transformed, using the formula described in the legend of Fig. 1. ANOVA for repeated measures gave a significance of $P < 0.01$.

TABLE 2

SYMPTOMS AND SIGNS IN 5 PROSPECTIVELY FOLLOWED PATIENTS AFTER 4 (300 mg/m^2) AND 6 (450 mg/m^2) TREATMENT COURSES OF CISPLATIN

	300 mg/m^2	450 mg/m^2
Symptoms		
Paresthesiae	2	4
Loss of dexterity	0	2
L'Hermitte's sign	0	0
Signs		
Decreased or absent tendon reflexes	1	3
Loss of strength	0	0
Pain perception	0	0
Fine touch perception	0	1
Vibration perception[a]	1	4
Cerebellar dysfunction	0	0
Positive Romberg	0	2

[a] With tuning fork.

($P < 0.01$). Two patients at 4 courses, and 4 patients at 6 courses complained of paresthesia; 1 patient developed symptoms only after 9 courses of CP treatment. In all these cases striking changes in VPT's had been noted at the investigation that took place 2 courses earlier. Likewise, an increase in VPT also preceded changes in other clinical symptoms and signs (loss of dexterity, loss of tendon reflexes, decrease in vibration perception as measured with the tuning fork, and the appearance of a positive Romberg sign).

DISCUSSION

In this study vibration perception and thermoperception thresholds were measured quantitatively in ovarian cancer patients treated with cisplatin, using relatively simple techniques. A good correlation was found between cumulative dose of cisplatin and age-related vibration perception thresholds both in the hands and in the feet. In the 5 prospectively followed patients symptoms and signs only became apparent after a cumulative dose of cisplatin of 450 mg/m^2, whereas changes in vibration perception could be detected 6 weeks to 2 months earlier. Measurement of the vibration sense at the feet was no more sensitive than at the hands and since changes did appear at the same time both in hands and in feet, measurements can be limited to either extremity. The results are in line with earlier findings by Roelofs et al. (1984). These authors assessed the time a tuning fork was felt to vibrate. Using this method as a semi-quantitative measure, they observed a decrease in vibration perception with increasing cumulative doses of cisplatin. The vibrameter is however to be preferred to a tuning fork as it allows adjustment of application pressure and accurate regulation of increase and decrease of amplitude. With the method used no significant changes were observed in thermoperception thresholds during therapy.

In conclusion this study shows that quantitative testing of vibration perception thresholds can be of benefit in the assessment of neurotoxicity in patients treated with cisplatin. The examination can be restricted to the hands. Though no consistent differences were noted between the left and right side, differences can however occur when local pathology (carpal tunnel syndrome, recent infusion) is present. We advise therefore to measure both sides. The method enables the registration of subtle changes in an early phase of sensory nerve fibre affliction and may be of value in explanatory trials of drugs with a potentially protective effect on the peripheral nervous system.

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