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PERIPHERAL NEUROPATHY RELATED TO MISONIDAZOLE: INCIDENCE AND PATHOLOGY

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Summary.—The human tolerance to multiple dosages of misonidazole (Ro-07-0582) was studied in 28 patients with different types of malignant neoplasias. The mean total dose for this group of patients was 16·2 g. The main toxicity was peripheral neuropathy with an overall incidence of 35%.

This neuropathy occurred more frequently and with greater severity when the drug was administered 3 times a week and when patients received total doses of over 18 g. The best tolerated schedule appears to be once or twice a week up to total dosages of 18 g or less (approximately 11 g/m^2).

Electron microscopy of a sural nerve biopsy from an affected patient revealed residual of previous distal axonal degeneration, with some segmental demyelination and remyelination, which affected both large and small myelinated nerve fibres.

CONSIDERABLE interest has developed to assess the use of misonidazole (1-(2)-nitro-1-imidazolyl-3-methoxy-2-propanol), in combination with radiation therapy in human solid tumours. The rationale of its application is to be able to inflict a higher radiation damage to the radioresistant hypoxic tumour cells, assuming that they in fact represent one of the relevant factors that determine the radiation response in some human solid tumours.

Drug toxicity in the form of peripheral neuropathies has been reported when using multiple doses of this compound (Urtasun *et al.*, 1976; 1977; Dische *et al.*, 1977).

In an effort to elucidate the incidence and severity of this toxicity a group of patients with different types of malignant neoplasias have been studied during multiple administration of misonidazole.

MATERIALS AND METHODS

Twenty-eight patients with different types of malignant neoplasias were entered into this study (Table I). They all received multiple doses of misonidazole either once a week, twice a week or 3 times a week schedule. Normal bone marrow reserve as assessed by peripheral smear, haemoglobin, haematocrit, WBC, differential and platelet count, normal liver function tested by serum glutamic oxalacetic transaminase, alkaline phosphatase, direct and indirect bilirubin, and renal function tested by blood urea nitrogen and serum creatinine were the conditions of eligibility.

TABLE I.—*Patient Composition*

Patient composition Multiple doses—Ro 07-0582	
Soft tissue sarcoma	14
CA of lung	8
Kidney	1
Seminoma	1
Melanoma	1
Primary brain tumour	3
Total	28
Mean dose = 16 g	

In addition, the following baseline studies were done before initiating the drug administration:

neurological examination,
nerve conduction studies and electromyography,
zinc–iron ratio in blood as pointed out by Willson, 1976.

The haematological and blood chemistry parameters were repeated twice a week during the period of drug administration and once a month thereafter for up to 6 months. Electromyography and nerve conduction studies were repeated only in those patients developing clinical evidence of neuropathy.

Determination of blood levels of the drug was performed by a previously described spectrophotometric assay (Urtasun *et al.*, 1974). Assays were done in whole blood at 4–5 h after drug administration and recently before administering the drug to assess any evidence of residual drug in blood.

All patients received concomitant daily fractionated radiation therapy and were treated between 4 and 5 h after drug administration.

RESULTS

Table II shows the mean maximum blood concentration (3rd column) for the different schedules of administration. The mean dose varied according to the schedule and escalation of the dose.

TABLE II.—*Schedules of Administration with Mean Blood Concentrations Obtained 4 to 5 h after Drug Ingestion and Incidence of Toxicity*

Schedule	Mean concentration (μM)	Toxicity	No. of patients
1 g/m² 2. wk/2 wks	228	0	2
2 g/m² 2. wk/2 wks	235	0	1
1 g/m² 2. wk/3 wks	259	0	1
2 g/m² 2. wk/3 wks	448	0	2
0·75 g/m² 3. wk/2 wks	145	0	1
2 g/m² 3. wk/2 wks	344	2	4
1 g/m² 3. wk/3 wks	236	2	4
1·5 g/m² 3. wk/3 wks	311	1	2
2 g/m² 3. wk/3 wks	423	2	2
2·5 g/m² 1. wk/4 wks	541	0	3
4 g/m² 1. wk/4 wks	832	2	3
2·5 g/m² 1. wk/6 wks	488	1	3
Total patients = 28			
Mean dose = 16 g			

Seventeen patients received a total cumulative dose of over 18 g. Ten of these patients developed no neuropathy, 6 of them were on a once a week schedule. The highest concentrations were obtained in the once a week schedule, however the tumour was exposed to the drug for a shorter period of time when compared with 2 or 3 times a week administration.

Seven patients developed GI toxicity consisting of mild to moderate nausea and vomiting, and was equally distributed in all schedules. Only 2 out of 10 patients that developed neuropathies had mild nausea and vomiting.

A clinical sensory peripheral neuropathy developed in 10 patients. This neuropathy lasted in 3 patients for periods of over 7 months with only partial recovery. A neuropathy of mild severity lasted for 3 months in 7 patients. They were not incapacitated, and the clinical and neurological symptoms disappeared. The neurological assessment with electromyography and nerve conduction studies revealed a mixed peripheral neuropathy predominantly of the sensory type. The early symptoms of this neuropathy are decreased pinprick sensations with preservation of the other qualities. Of the 10 patients who developed this neuropathy 3 had low serum iron levels and 1 a low serum zinc level.

No immediate or long term bone marrow toxicity or alteration of liver and kidney function was seen in any of the 28 patients with the exception of 1 patient who showed a temporary moderate increase of glutamic oxalacetic transaminase.

A peripheral nerve biopsy was performed in 1 patient at approximately 3 months from the time of the onset of a persistent neuropathy affecting both feet and hands. In this patient there had been no residual accumulative drug in blood from day to day or unusual high drug blood values.

Case Report

A 54 year old man who has been receiving treatments with radiation for Kaposi's sarcoma since 1973 was entered on the study because of recurrence of the tumour on the amputation stump of the right second toe that failed to respond to 2 previous courses of radiotherapy. Misonidazole at a dose of 4 g/day was administered 3 times a week for 2 weeks 4–5 h prior to radiation treatments. The patient received a total

cumulative dose of 24 g. Serum alkaline phosphatase, glutamic oxalacetic transaminase, bilirubin, urea nitrogen, creatinine, uric acid and total and differential white cell count, platelet count, haemoglobin, haematocrit were normal before drug administration. Serum iron, iron binding capacity and zinc in serum were all within normal limits. Muscle power and examination of all sensory qualities of upper and lower extremities was normal. There were no dysaesthesias or paraesthesias. On the days of the drug administration the mean maximum blood concentration of misonidazole at $4\frac{1}{2}$–5 h was 335 μM (range 308–367). Approximately 2 weeks after the last dose of the drug the patient developed burning pain in both upper and lower extremities with glove and stocking distribution, more so affecting the lower legs and feet. He did not notice any muscle weakness. At that time muscle power in the upper and lower extremities was normal. Arm and knee reflexes were preserved, but the ankle reflexes were absent. Pinprick sensation, position sense and vibration sense were decreased in both hands, feet and legs below the knees. The sense of temperature was also decreased in the above described areas. Fine touch was intact and pin and temperature sensation were relatively more affected. Nerve conduction studies at the early onset of the symptoms were normal: motor conduction in the right ulnar nerve was 52 m/s, motor conduction on right peroneal nerve 52 m/s, sensory conduction right ulnar nerve 48 m/s, sensory conduction right sural nerve 33 m/s. Two weeks later these findings were: motor conduction right ulnar nerve 56 m/s, motor conduction in right peroneal 36 m/s, sensory conduction right ulnar 48 m/s, sensory conduction right sural nerve no response.

There was no cerebral, cerebellar or cranial nerve abnormality evident.

Serum vitamin B-12 was 660 pg/ml (normal 300–1000). Folic acid 2·2 mg/ml (normal 4–16 mg/ml). Folic acid 5 mg tablets were administered 3 times a day, but after 1 month the paraesthesias and dysaesthesias were still present. At approximately 3 months from the onset of the neuropathy a right sural nerve biopsy was performed. This area was not previously treated with irradiation and was not involved with Kaposi's sarcoma.

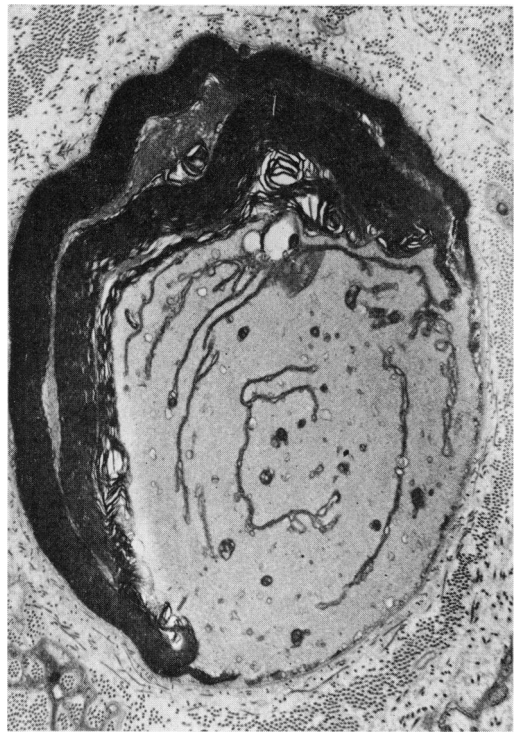

FIG. 1.—Damaged large myelinated nerve fibre showing axonal swelling, an increase in neurofilaments, and partial denudation of the myelin sheath.

Transverse sections of the sural nerve biopsy showed a mild reduction in the number of myelinated fibres of all diameters. Electron microscopy revealed residual abnormalities in approximately 5–10% of large myelinated fibres, which included axonal swelling with an increase in neurofilaments, and splitting, thinning or partial loss of the myelin sheath (Fig. 1). Similarly, approximately 5% of the small myelinated fibres were either hypomyelinated, or displayed myelin debris or granular degeneration (Figs. 2, 3 and 4). The foregoing findings were taken as evidence of a previous episode of distal

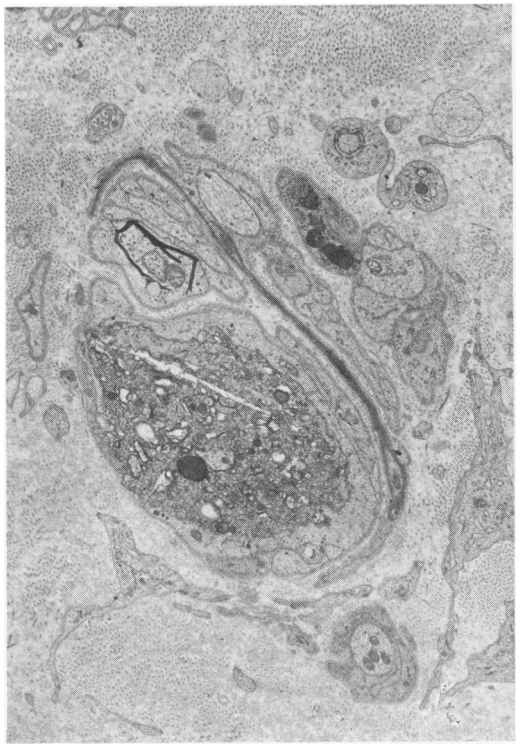

FIG. 2.—Granular degeneration; small myelinated nerve fibre.

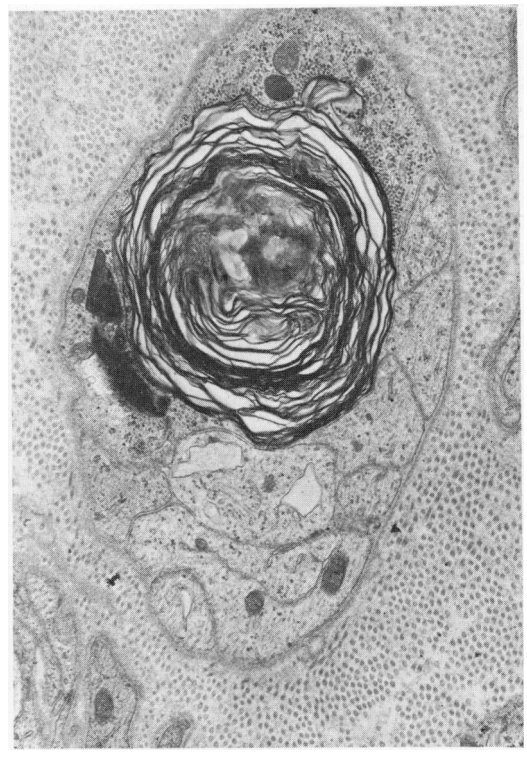

FIG. 3.—Myelin debris; small myelinated nerve fibre.

axonal degeneration ("dying back" neuropathy), with some segmental demyelination and remyelination. The pattern appears to be similar to that found in other toxic neuropathies, as described by Cavanagh (1973).

In Table III the peripheral neurotoxicity is analysed with respect to total cumulative dose and schedule of drug administration. It is clear that the combination of 3 times a week administration and total dose in excess of 18 g is not well tolerated. Cases exhibiting none or mild toxicity received total cumulative doses of less than 18 g and were on a once or twice a week schedule.

CONCLUSION

Peripheral sensory polyneuropathy appears to be a significant toxicity of misonidazole when administered in multiple doses. In 2 groups of patients previously reported (Gray *et al.*, 1976; Urtasun *et al.*, 1977) no neurotoxicity was observed when administering single doses of up to 7 g.

The combination of multiple doses at 3 times a week or more and total cumulative doses in excess of 18 g has a high incidence of peripheral neuropathy. The drug is better tolerated by individuals receiving it once or twice a week and at total doses of less than 18 g. It appears that the total

TABLE III.—*Neurotoxicity in* 10 *Patients Analysed by Total Dose of the Drug and its Schedule of Administration*

	Neurotoxicity					
	Once or twice weekly			Thrice weekly		
Total dose	None	Mild	Severe	None	Mild	Severe
<18 g	6	0	0	3	2	0
>18 g	6	3	0	3	2	3

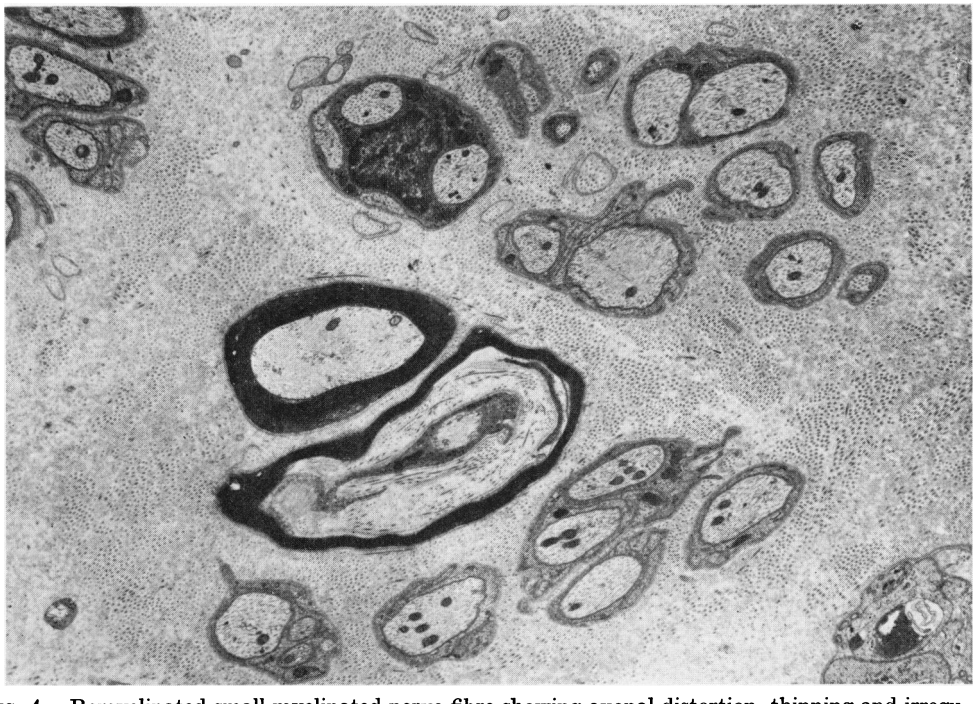

FIG. 4.—Remyelinated small myelinated nerve fibre showing axonal distortion, thinning and irregularity of the myelin sheath and a peri-axonal deposit of collagen. Adjacent non-myelinated nerve fibres are of normal appearance.

dose alone does not account for the toxicity exhibited since the frequency of its administration has some direct relationship.

Pathologic examination of a sural nerve biopsy, taken from an affected patient approximately 3 months after the onset of a sensory neuropathy, revealed residual changes from a previous distal axonal degeneration with some segmental demyelination and remyelination, which affected both large and small myelinated nerve fibres.

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