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Direct delivery of platinum-based antineoplastics to the central nervous system: a toxicity and ultrastructural study

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Summary. Platinum drugs are playing an increasingly major role in cancer treatment, but systemic administration of these agents has resulted in significant toxicity. To examine the effects of cisplatin and two newer agents, iproplatin and carboplatin, we injected the agents directly into the cerebrospinal fluid of rats and found that neurotoxic reactions resulted from doses of cisplatin (10 nmol) much lower than those of iproplatin (40 nmol) or carboplatin (80 nmol). Moreover, central nervous system tissue appeared to be less adversely affected by direct exposure to carboplatin since chronic toxicity was not observed in any of the animals receiving carboplatin until a lethal dose was reached. Furthermore, only the animals receiving cisplatin showed histologic damage in their spinal cords, and ultrastructural studies confirmed that while significant abnormalities were observed in the spinal cords of rats receiving 40 nmol cisplatin, no architectural changes were detected in the spinal cords of animals receiving 240 nmol carboplatin. We conclude that platinum drugs can be delivered intrathecally to achieve a much greater concentration of active drug than can be achieved by intravenous administration and that carboplatin appears to be the most suitable platinum-based drug for use in systems delivering drugs directly to the brain and spinal cord.

Introduction

The direct administration of drugs into cerebrospinal fluid (CSF) increases the subarachnoid and intraventricular exposure to the drug while reducing unnecessary systemic exposure. Patients with documented neoplastic invasion of the subarachnoid spaces (i.e., carcinomatous meningitis) are preferentially treated with intrathecal chemotherapy [31]. Among the drugs clinically tested intrathecally are methotrexate, cytarabine, and thioTEPA [15, 33]. Recently, two additional drugs, diaziquone (AZQ) and 6-mercaptopurine (6-MP), have undergone phase I/II clinical trials for intrathecal administration in refractory meningeal malignancies [1, 4].

Platinum-derived drugs are playing an increasingly important role in the treatment of a variety of neoplasms [22]. The use of cisplatin (*cis*-diamminedichloroplatinum), however, is limited by significant dose-related toxicity, notably, nephrotoxicity, emesis, ototoxicity, and peripheral neuropathy [5, 29, 36]. Seizures, leukoencephalopathy, memory loss, and tremors have also been observed [7, 25, 29, 36].

To improve the therapeutic index of platinum compounds, new analogs have been developed [6, 16]. Carboplatin [*cis*-diammine-1,1-cyclobutanedecarboxylate platinum(II)] and iproplatin [*cis*-dichloro-*trans*-dihydroxy-*bis*-isopropylamine platinum(IV)] are second-generation platinum derivatives recently introduced into clinical practice. Initial studies of these platinum derivatives have revealed a relative reduction in systemic toxicity as compared with that of cisplatin but antitumor activity equivalent to that of the parent drug [2, 9, 34].

In the present study we examined the effects of intrathecal administration of various platinum-based compounds on neurologic function and central nervous system (CNS) tissue in a rat model. This information is needed for selection of the most suitable agent to be used for intrathecal therapy of CNS tumors.

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Materials and methods

Male Fischer 344 rats weighing 200–250 g were used. Cisplatin was purchased from Sigma Chemical Co. (St. Louis, Mo.; lot 18F-3551), and carboplatin (CBDCA, JM-8; lot 82F428) and iproplatin (CHIP, JM-9; lot S84M004) were supplied by Bristol Myers Pharmaceutical Corporation (Syracuse, N.Y.)

Intrathecal catheter implantation. Small spinal subarachnoid catheters were placed according to the technique described by Kooistra et al. [24]. Briefly, rats were anesthetized intraperitoneally with a ketamine/xylazine solution (ketamine HCl, 50 mg/kg; xylazine, 5 mg/kg; in 14% ethanol and normal saline). They were then placed in a stereotactic frame with the neck flexed 90°. A midline incision from the inion to the cervical spine was made. Sharp dissection was carried out to expose the atlanto-occipital membrane. A PE 10 polyethylene catheter (Intramedic, Clay Adams, Parsipanny, Pa.) filled with 10 µl 0.9% NaCl was introduced into the subarachnoid space of the cisterna magna through a small incision in the membrane and underlying dura. The catheter was then passed down to the posterior aspect of the spinal cord for 5–6 cm. The catheter was anchored to the subcutaneous tissue by applying methyl methacrylate cranioplast cement (Howmedica Inc., Rutherford, N.J.) to a loose knot and externalizing it through the skin lateral to the incision by the use of a 19-gauge needle. The catheter was then occluded with a 30-gauge stainless-steel wire stylet.

Drug injection and evaluation of toxicity. At 3 days after catheter implantation, the rats were evaluated and only those remaining neurologically intact (80%) were entered into the study. The animals that developed even slight neurologic deficits as a result of the surgical placement of the catheter were euthanized.

The three agents tested, cisplatin, CBDCA, and CHIP, were dissolved in normal saline at different concentrations. A 20-µl volume of drug was injected through the indwelling catheter via a Hamilton microsyringe connected with a 30-gauge needle. This was followed by a 10-µl rinse with 0.9% NaCl. An initial dose of 20 nmol was given. Animals were observed and monitored carefully for any neurologic changes (i.e., seizures, tremors, motor deficits) in the immediate postinjection period and twice daily during the ensuing 5 weeks. If no sign of toxicity was observed, the dose was doubled in the successive group of animals; if neurologic problems were detected, the dose was halved. For each drug, the highest dose of the drug at which no toxicity occurred (HNTD, highest nontoxic dose) and the lowest dose at which toxicity was seen (TDlow) were recorded. Five animals received only 30 µl 0.9% NaCl and served as controls. We chose this method because it provides direct contact of the tested drug with the CNS tissues and allows immediate detection of neurologic toxicities. Furthermore, this method ensures that the drugs are initially almost exclusively confined to the CSF spaces of the CNS and that there is minimal, if any, systemic exposure. In addition, even in the unlikely event that the entire single dose might spill into the bloodstream, no systemic toxicity would be expected because of the relatively small quantity of drug involved.

Neuropathologic examination. All rat brains and spinal cords were excised and placed in formalin at the time of death or when sacrificed after development of severe neurotoxicity. Paraffin-embedded sections were stained with hematoxylin and eosin and luxol fast blue (LFB) for neuropathologic examination.

Electron microscopy preparation. Six rats (two treated with cisplatin; two with carboplatin; and two controls) were subjected to a perfusion-fixation treatment for ultrastructural analysis by electron microscopy. The animals were anesthetized and perfused with 0.9% NaCl via intracardiac infusion. This was followed by fixation with 1% paraformaldehyde/1% glutaraldehyde in 0.1 *M* phosphate buffer. Sections of the cerebrum, pons, cerebellum, spinal cord, and cauda equina were post-fixed in 1% OsO_4 and embedded in Epon by standard techniques. Thin sections were stained with uranyl acetate and lead citrate and examined by electron microscopy.

Table 1. Intrathecal toxicity of platinum-based drugs

Total single dose (nmol)	Acute toxicity	Chronic toxicity	Survivors
Cisplatin:			
10	0/4	0/4	4/4
20	0/4	1/4	4/4
40	1/4	1/4	3/4
80	3/3	1/3	1/3
Iproplatin:			
20	0/4	0/4	4/4
40	0/4	0/4	4/4
80	2/4	1/4	3/4
160	3/4	1/4	1/4
Carboplatin:			
20	0/4	0/4	4/4
40	0/4	0/4	4/4
80	0/4	0/4	4/4
160	2/4	0/4	4/4
240	2/4	0/4	2/4
320	2/2	0/2	0/2

Results

Toxicity

Two types of toxicity were seen in the animals receiving a single intrathecal dose of platinum drugs: (1) acute neurotoxicity manifesting as lethargy, progressive unresponsiveness, seizure-like contractions, and, in most cases, death within 96 h after the injection; and (2) chronic neurotoxicity characterized by a persistent paresis in one or more limbs. The observations on each group of animals receiving escalating doses of the three different platinum compounds are summarized in Table 1. The dose is expressed in nanomoles, because body weight and body surface area are not relevant denominators for administration of drugs to the CSF.

Chronic toxicity (development of permanent paresis) was observed in one of four rats receiving cisplatin at a total dose as low as 20 nmol (TDlow). The highest nontoxic dose (HNTD) for cisplatin was 10 nmol injected intrathecally. The HNTD for iproplatin was 40 nmol whereas three of four rats in the group receiving 80 nmol (TDlow) developed clinical evidence of toxicity (two cases of acute and one case of chronic toxicity). The animals receiving

Table 2. HNTD and TDlow for each platinum compound intrathecally injected

Drug	HNTD (nmol)	TDlow (nmol)	Toxicity at TDlow	
Cisplatin	10	20	Paralysis	(1/4)
			Incontinence	(1/4)
Iproplatin	40	80	Death	(1/4)
			Seizures	(2/4)
			Paralysis	(1/4)
Carboplatin	80	160	Transient seizures	(2/6)

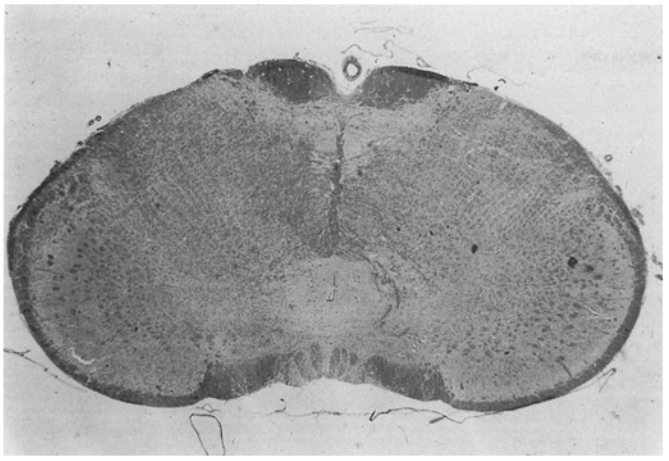

Fig. 1. Photomicrograph of the medulla of a rat that received 80 nmol iproplatin and was killed at 35 days after injection. No pathologic change was seen despite the occurrence of chronic paralysis. No demyelination was seen with any of the three agents tested. LFB/PAS, × 10

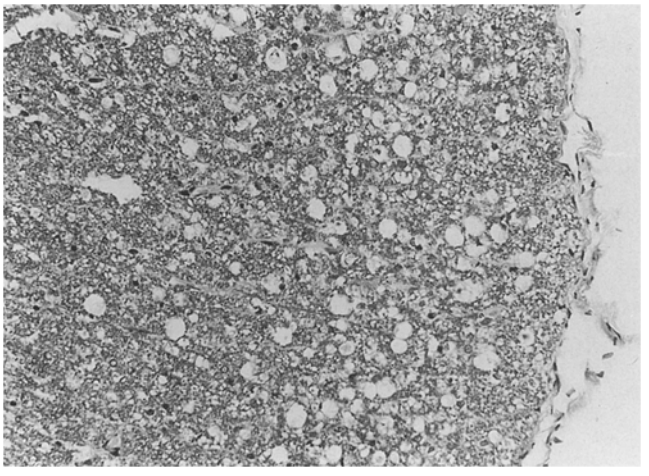

Fig. 2. Photomicrograph of the thoracic spinal-cord white matter of a rat treated with 40 nmol cisplatin. A nonspecific vacuolar pattern is present. LFB/PAS, × 100

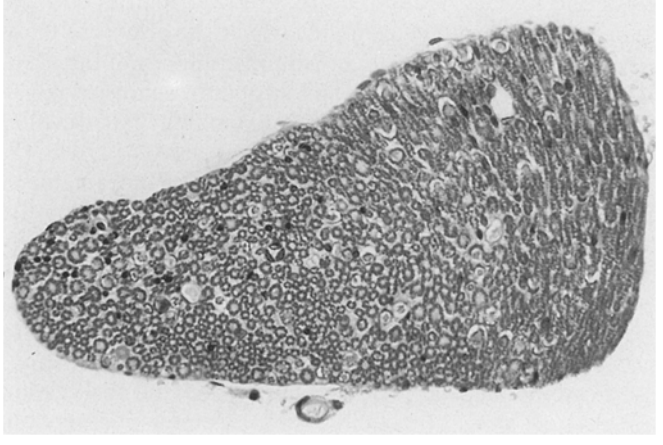

Fig. 3. Photomicrograph of the cauda equina of a rat treated with 160 nmol carboplatin, showing intact myelin and no pathology. LFB/PAS, × 250

carboplatin did not develop clinical toxicity at doses of up to 80 nmol. Two rats injected with 160 nmol carboplatin had brief episodes of clonic contractions lasting for a few minutes, which resolved spontaneously with no neurologic sequelae. These episodes appeared to be different in character and severity from any of the previously observed acute toxicities. The total dose of 320 nmol was acutely lethal. An intermediate total dose of 240 nmol carboplatin was therefore injected into four animals. Two of them developed acute toxicity and died, whereas the other two animals survived with no neurologic deficits. Table 2 summarizes the HNTD and the TDlow of each drug tested.

Histology

Sections of the cortex, pons-cerebellum, medulla, cervical cord, thoracolumbar cord, and cauda equina of each rat were examined under light microscopy. No evidence of demyelination was seen with any of the three agents on the LFB-stained sections (Fig. 1). Sections of cervical cord from two animals receiving 40 nmol cisplatin showed nonspecific vacuolar changes in the white matter (Fig. 2). No pathologic change was observed in tissues from rats receiving iproplatin or carboplatin (Fig. 3).

Ultrastructural studies

Two rats injected with 40 nmol cisplatin, two rats injected with 240 nmol carboplatin, and two controls were perfused at the end of the observation period and their tissues were processed for electron microscopy. The only abnormal ultrastructural findings, axonal shrinkage and neurofibrillar accumulations, were seen in the rats injected with cisplatin (Figs. 4, 5). Again, these changes were detected at the level of the cervical and thoracic cord.

Discussion

The present study shows that currently available platinum drugs can be given intrathecally to achieve neoplastic cytotoxic levels in a rat model. Cisplatin, which is the most potent of the drugs tested, showed the most pronounced toxicity, iproplatin exhibited intermediate toxicity, and carboplatin appeared much less toxic to the CNS.

Intrathecal chemotherapy increases the active concentrations of cytotoxic drugs in certain target regions of the CNS that are normally protected from the effects of antitumor agents by the blood-brain barrier [21]. Nevertheless, justified concern of producing neurotoxicity has considerably limited the use of a number of chemotherapeutic agents suitable for this route. Currently, methotrexate, cytarabine, and thioTEPA are given directly into the CSF for the prevention and treatment of meningeal involvement of leukemias and for meningeal carcinomatosis [15, 31, 33]. These drugs have achieved only partial success and occasionally produce significant neurotoxicities [10, 15, 27].

The recognized need to investigate new agents for intrathecal use has recently resulted in the completion of two clinical studies aimed at establishing the feasibility of the

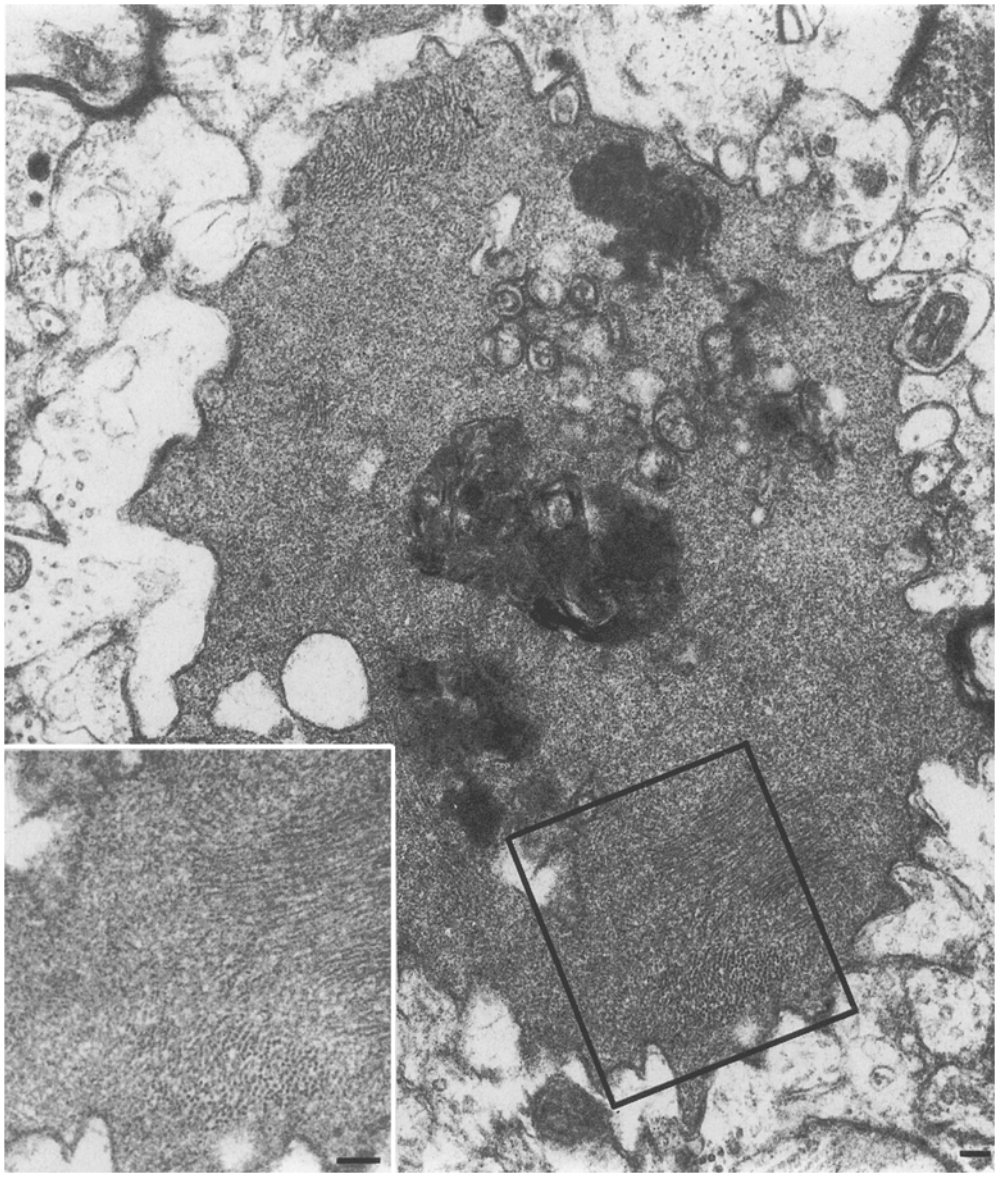

Fig. 4. Electron micrograph of a section of cervical spinal cord obtained from a rat at 35 days after the administration of 40 nmol cisplatin into the CSF. A large filamentous intraaxonal mass is seen, which resulted in marked axonal swelling. Scale bar = 1 μm. *Inset:* Higher magnification of a section of the filamentous mass, showing the disarray of the filaments. Scale bar = 1 μm

intrathecal administration of AZQ and 6-MP [1, 4]. Both agents were found to be safe, well tolerated, and active against meningeal malignancies. Another agent, 4-HC, extensively studied in laboratory models [18], is currently being tested in a clinical trial.

Cisplatin is an active antitumor agent used for the treatment of a variety of solid tumors, including ovarian and testicular carcinomas, bladder transitional carcinoma, head and neck malignancies, and small-cell lung carcinoma [22, 30]. Recently it has been used for both primary and metastatic brain tumors [13, 23, 32, 35, 37]. Dose-related toxicities of cisplatin, however, represent a major limitation to prolonged systemic exposure. Moreover, Neuwelt et al. [28] have reported the development of hemorrhagic encephalopathy in dogs receiving an intracarotid injection of cisplatin with or without previous opening of the blood-brain barrier. Hence, the development and use of new cisplatin analogs such as carboplatin and iproplatin, whose systemic toxicity is reported to be lower than that of the parent drug, prompted us to investigate the effects of these agents following their direct administration into the CSF. The activity of carboplatin and iproplatin against primary brain tumors has recently been tested in both experimental and clinical studies with encouraging results [8, 14, 17, 19]. In addition, carboplatin has proved to be more stable in hydrophilic solutions than is cisplatin, thus providing the theoretical advantage that it might remain longer in its active form in the CSF spaces.

We studied the rat model in which spinal subarachnoid catheters are implanted, which has previously been used to screen new agents for the intrathecal treatment of meningeal carcinomatosis [18, 24]. It allows both the observation of obvious signs of toxicity, such as motor dysfunction, and the examination of the interaction between drug and CNS tissues. Within minutes of its injection, the drug is distributed throughout the entire subarachnoid spaces, al-

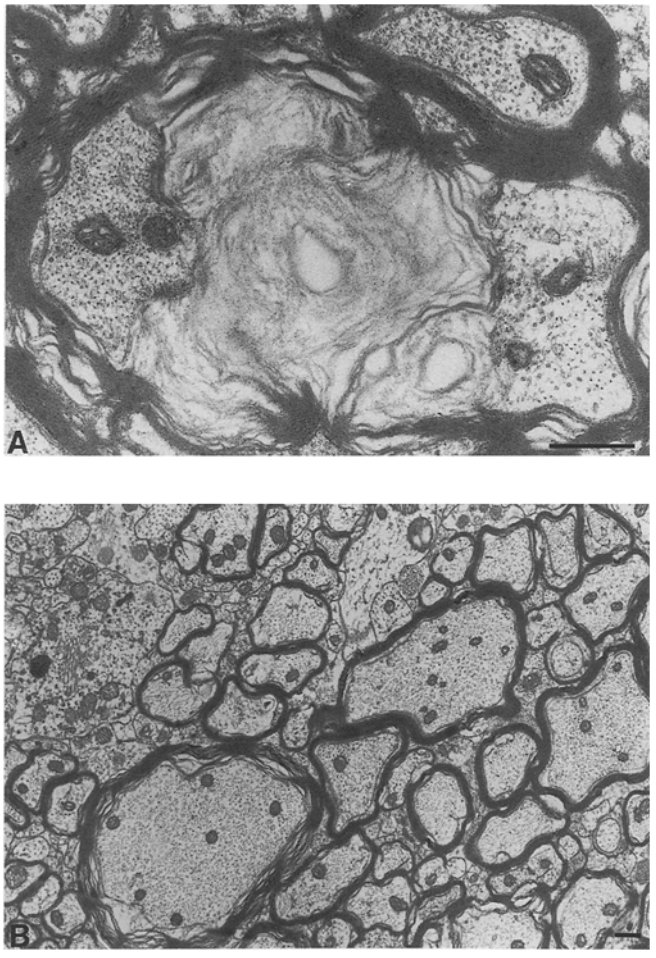

Fig. 5. (A) Electron micrograph of a section of cervical spinal cord obtained from a rat at 35 days after the administration of 40 nmol cisplatin into the CSF. Axonal disruption accompanied by destruction of the myelin sheath is visible in the center of the micrograph. Scale bar = 5 μm. **(B)** Cervical spinal-cord section obtained from a rat at 35 days after the administration of sterile saline into the cerebrospinal fluid (control animal). Normal myelin sheaths and axons are present throughout the section. Scale bar = **5** μm

though a concentration gradient is present, with the highest levels of drug occurring in the CSF spaces of the spinal cord. Previous studies have shown that only small amounts of platinum drugs are found in the CSF after intravenous administration (0.3–0.5 μM) [3, 11, 12, 20].

Assuming that the CSF volume in the rat is about 400–500 μl, the concentration achieved with, for instance, the HNTD cisplatin dose injected intrathecally would be 20 μM, which is 20–80 times higher than the one achieved by intravenous injection and is clearly within the tumoricidal range.

When escalating doses of cisplatin, iproplatin, and carboplatin were injected into the CSF, neurotoxic reactions resulted from doses of cisplatin (HNTD, 10 nmol) much lower than those of iproplatin (HNTD, 40 nmol) or carboplatin (HNTD, 80 nmol). This finding is in accord with the reported drug potencies of cisplatin and its analogs. However, CNS tissue appears to be less adversely affected by direct exposure to carboplatin since no chronic toxicity was observed in any of the animals receiving carboplatin until a lethal dose was reached. In agreement with these findings, only the animals receiving cisplatin showed histologic changes in their spinal cords, and ultrastructural studies confirmed that although significant abnormalities were observed in the spinal cords of animals receiving 40 nmol cisplatin, no architectural changes were detected in the spinal cords of animals receiving 240 nmol carboplatin. No evidence of demyelination was found in any of the animals studied, which supports the theory that the peripheral neuropathy seen in patients undergoing chronic cisplatin treatment is likely to be secondary to axonal degeneration, with subsequent involvement of myelin, rather then representing a direct effect on myelin [26].

In conclusion, platinum-based compounds may be useful in the intrathecal treatment of leptomeningeal malignancies. Carboplatin appears to be the compound least toxic to the CNS and, therefore, the one most suitable for use in systems delivering drugs directly to the brain and spinal cord.

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