CANCER DIAGNOSIS & PROGNOSIS
4: 320-325 (2024) doi: 10.21873/cdp.10327

Oxaliplatin-induced Acute Neurotoxicity Recovers Between Repeat Infusion Cycles: An Axonal Excitability Repeated Multiple Measurements Study

PANAGIOTIS KOKOTIS[1], MICHAIL PAPANTONIOU[1], RICHARD W. CARR[2], MARTIN SCHMELZ[2], DIMITRA SIAKAVELLA[3], EFTHYMIA SKAFIDA[4] and CHRISTOS PAPADIMITRIOU[4]

[1]*Laboratory of Clinical Neurophysiology, First Department of Neurology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece;*
[2]*Department of Experimental Pain Research, MCTN Mannheim, University of Heidelberg, Heidelberg, Germany;*
[3]*Department of Neurology, KAT Hospital, Athens, Greece;*
[4]*Oncology Unit, Aretaieion University Hospital, National and Kapodistrian University of Athens, Athens, Greece*

Abstract. *Background/Aim: Oxaliplatin, a platinum-based chemotherapy used in the treatment of colorectal cancer, induces acute neurotoxicity following infusion. The aim of this study was to establish whether alterations in axonal excitability develop progressively with higher cumulative doses and whether there is a recovery in motor axons after each cycle of treatment. Patients and Methods: Twenty consecutive patients with a colorectal cancer diagnosis, referred from the Oncology Department of Aretaieion Hospital of Athens, were enrolled in this study between October 2018 and May 2019. None of the participants had diabetes, alcohol abuse, known neuropathy or were previously treated with another neo-adjuvant therapy. Threshold Tracking techniques and Qtrac software were used for assessing axonal excitability in motor axons. Excitability recordings were undertaken before and immediately after the end of oxaliplatin infusion. Results: Statistically significant changes were found (p<0.01) in axonal excitability (relative refractory period, refractoriness at 2 ms and 2.5 ms, sub-excitability and super-excitability) before and after oxaliplatin infusion. No statistically significant changes (p>0.05) were found in threshold electrotonus and strength-duration parameters before and after oxaliplatin infusion. We also did not find statistically significant differences (p>0.05) between means of excitability parameters before infusion at each cycle. Conclusion: Our study confirms oxaliplatin-induced acute neurotoxicity following infusion and suggests that motor axons recover between repeat infusion cycles.*

Correspondence to: Panagiotis Kokotis, Laboratory of Clinical Neurophysiology, First Department of Neurology, School of Medicine, National and Kapodistrian University of Athens, Vas. Sofias Avenue 72-74, 11528, Athens, Greece. Tel: +30 2107218093, e-mail: pkokotis@med.uoa.gr

Key Words: Oxaliplatin, neurotoxicity, neuropathy, axonal excitability, threshold techniques.

Oxaliplatin is a platinum-derivative used extensively in the treatment of colorectal cancer (1, 2). Neurotoxicity induced by oxaliplatin has been described as a major side effect and implicates the sustainability of the planned treatment (3). Acute neurotoxicity develops immediately following infusion and manifests with rapid-onset neuropathic symptoms exacerbated by cold exposure, such as transient paraesthesia, fasciculations and muscular spasms in the limbs and perioral region (4, 5). With increasing cumulative dose after several treatment cycles, a chronic axonal neuropathy develops, manifesting with sensory dysfunction, with distal paraesthesia, progressing to sensory ataxia and functional impairment (5, 6).

In vitro experimental studies have suggested that oxaliplatin treatment results in slowing of voltage-dependent Na^+ channel inactivation kinetics, reducing Na^+ current, or shifting the voltage dependence of inactivation to more negative membrane potentials (7-11), consisted with *in vivo* studies showing alterations in voltage-gated Na^+ channel function (12-16). Nerve excitability techniques have been used for detecting these alterations in axonal membrane ion channel function, assessed by threshold tracking techniques (17, 18). However, it remains uncertain if oxaliplatin-induced acute neurotoxicity

following infusion cumulates after each cycle of treatment, contributing to the development of chronic neuropathy.

The aim of this study was to establish whether alterations in axonal excitability develop progressively with higher cumulative doses and whether there is a recovery in neuronal axons after each cycle of treatment.

Patients and Methods

Subjects. In this study, 20 patients (15 males and 5 females, with a mean age of 62.72±13.59 years and range=44-82 years) with diagnosis of colorectal cancer of stage III or IV scheduled to receive the chemotherapy regimen XELOX [oxaliplatin 130 mg/m^2 administered as a 2-h intravenous infusion (IV) in 500 ml of 5% glucose solution and capecitabine 1,000 mg/m^2, orally bid ×2 weeks, followed by 1-week rest period, every three weeks] or mFOLFOX6 [oxaliplatin 85 mg/m^2 IV over 2 h on day 1 plus leucovorin 400 mg/m^2 IV over 2 h on day 1 plus 5-fluorouracil (5-FU) 400 mg/m^2 IV bolus on day 1, then 1,200 mg/m^2/day for two days -total 2,400 mg/m^2 over 46-48 h- continuous infusion, every two weeks] were enrolled, between October 2018 and May 2019. All participants were referred from the Oncology Department of Aretaieion University Hospital of Athens. Each participant was informed and gave his consent for the study, which was held in accordance with the Helsinki Declaration of 1975, as revised in Hong Kong in 1983. None of the participants had diabetes, alcohol abuse, known neuropathy or were previously treated with another neo-adjuvant therapy. Approval for this study was granted by the Bioethics Committee of National and Kapodistrian University of Athens.

Neurophysiological tests. Threshold Tracking techniques and Qtrac software (©Institute of Neurology, London, UK) were used for assessing axonal excitability (16, 17). In excitability studies, the median nerve was stimulated at the wrist and compound muscle action potentials (CMAPs) were recorded from abductor pollicis brevis. Temperature was recorded at the site of stimulation and maintained between 32 and 34˚C, by keeping subjects in a temperature-controlled room with heaters and air-conditioners. Warm water was also used in a few subjects with cold extremities to achieve the intended temperature.

Multiple excitability variables were recorded using an established protocol. The recorded and included excitability indices were the following: strength-duration time constant (SDTC), threshold electrotonus (TE), refractoriness, superexcitability, and late subexcitability of the recovery cycle of axonal excitability after a single supramaximal conditioning stimulus and current-threshold relationship. We used the formulation of Weiss to calculate SDTC from the relationship between stimulus intensity and duration to evoke a target potential (18). A 100 ms sub-threshold polarizing pulse was delivered as a conditioning stimulus at TE, and we measured threshold change to produce a target CMAP response (40% maximus). We recorded the recovery cycle as the recovery of axonal membrane excitability following a supramaximal conditioning stimulus. We used tracking threshold changes to obtain a current-threshold relationship, following a sub-threshold 200 ms polarizing current.

Study design. Excitability recordings were undertaken before and immediately (approximately 10-15 min) after the end of oxaliplatin infusion. Our target was to assess primarily the ability of motor axons to recover after an oxaliplatin infusion during the interval between the cycles and secondarily the acute effect of oxaliplatin on neurophysiological parameters.

The majority of the participants completed the predicted number of therapies, while for 2 (10%) of them therapy was prematurely interrupted due to disease progression. No patient needed adjustment of oxaliplatin dose, due to neurotoxicity. We gathered 85 recordings before and 79 recordings after infusion, as 8 patients withdrew their participation after the 3rd cycle because of either intolerance of the examination procedure or extreme physical exhaustion experienced after infusion. However, their recordings up to 3rd cycle were included in statistical analysis (Figure 1).

Statistical analysis. Nerve excitability data was analyzed with Qtrac Software. Statistical analysis was performed using the STATISTICA (STATISTICA v. 7 for Windows, Statsoft Inc., Tulsa, OK, USA) software package. Data are presented as mean±standard deviation (SD). The Shapiro-Wilk test was used to test for normality. For normally distributed data ANOVA for repeated measures was used, otherwise data was analyzed with Friedmann test. The significance level was set to $p<0.05$.

Results

Extracellular threshold tracking techniques were used to assess axonal excitability in patients undergoing a chemotherapeutic regime with oxaliplatin. To estimate the immediate impact of intravenous infusion of oxaliplatin for each patient, pairs of excitability recordings were performed before and after each infusion. The resulting pre and post excitability measures were compared independent of the cycle from which they were acquired (Figure 2). The relative refractory period (RRP), defined as the time after an action potential required to re-establish an axonal threshold equivalent (threshold reduction=0%) to that immediately before the action potential was prolonged significantly (ANOVA, *post-hoc* test, $p<0.01$). Refractoriness was also increased both at the discrete time points of 2 ms and 2.5 ms after an action potential. These changes in the recovery of excitably during the refractory period are consistent with slower recovery from sodium channel inactivation. At later points in the recovery cycle, the super-excitability that immediately follows the refractory period was reduced, both at 5 ms and 7 ms (Figure 2). In addition, during the third phase of the recovery cycle, late sub-excitability was increased immediately after oxaliplatin infusion (Figure 2).

Depolarizing (TeD) and hyperpolarizing threshold electrotonus (TeH) parameters (TeD 10-20, TeH 10-20, TeD 90-100, and TeH 90-100) were not significantly changed. We also did not find statistically significant changes in the strength-duration parameters (SDTC, Slope and Rheobase), as presented in Table I ($p>0.05$).

To control the behavior of motor axons during the intracycle interval and their ability to recover after oxaliplatin's neurotoxic action, the recordings before infusion were grouped per cycle and paired by patient. Interestingly, no significant

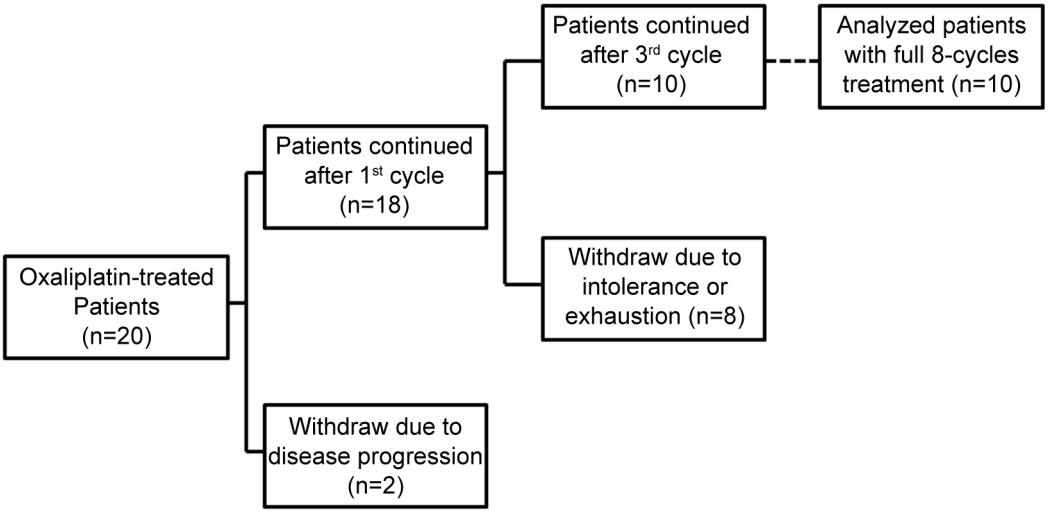

Figure 1. *Flow chart of patients participating in the study.*

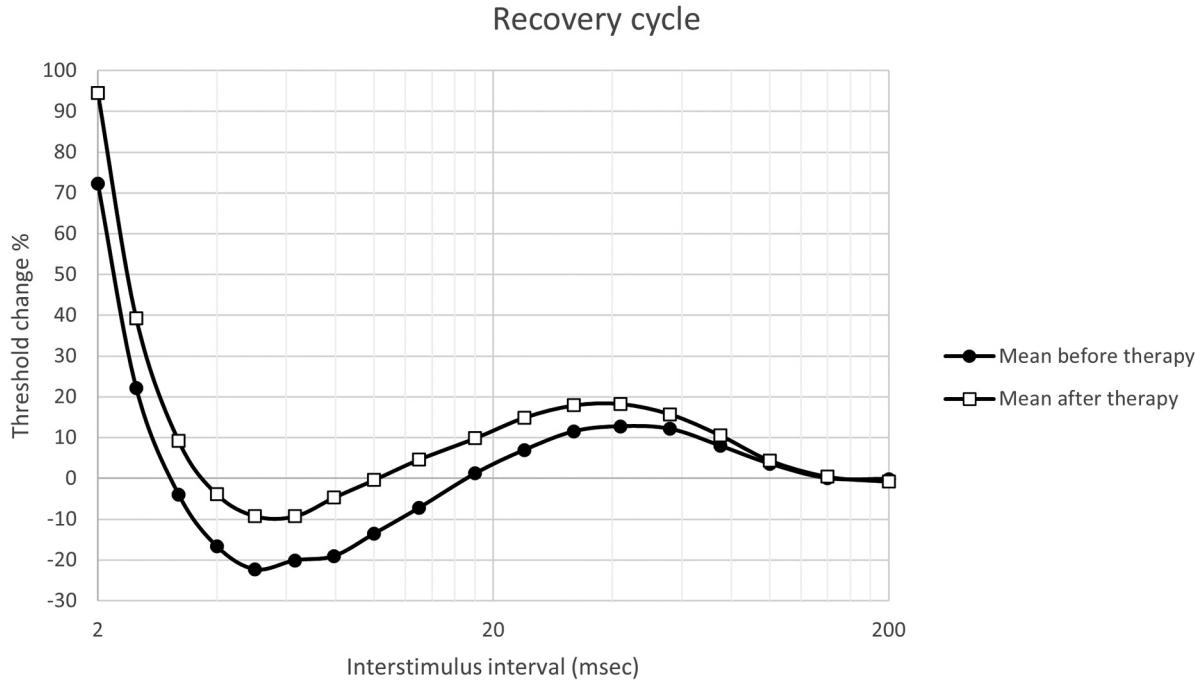

Figure 2. *Summary of changes in axonal excitability parameters for 20 patients tested before and after oxaliplatin infusion.*

difference ($p>0.05$) was found neither for excitability nor for refractoriness between the cycles of treatment (Table II).

Discussion

In this study, we examined axonal excitability parameters in motor axons from 20 patients with diagnosis of colorectal cancer, before and after infusion of chemotherapy with oxaliplatin. We gathered and analyzed 85 recordings before and 79 recordings after infusion, due to withdraw of some patients.

Our results, concerning oxaliplatin-induced acute neurotoxicity following infusion, confirmed findings from previous *in vivo* studies, using nerve excitability techniques (12-16). Prolonged refractoriness, as seen in our results, relates to inactivation of transient Na^+ channels, leading to transient axonal dysfunction and symptoms (17-20). We

Table I. *Excitability parameters before and after oxaliplatin infusion.*

	Before infusion (n=85)	After infusion (N=79)	Before *vs*. after parameters
Refractoriness	Mean (sd)	Mean (sd)	
RRP	3.101 (0.518)	3.516 (0.762)	***p*<0.01**
Refr 2 ms	74.016 (57.83)	92.545 (53.155)	***p*<0.01**
Refr 2.5 ms	23.25 (23.348)	40.41 (32.377)	***p*<0.01**
Superexcitability	–22.652 (5.866)	–12.602 (7.745)	***p*<0.01**
Superexcitability 5 ms	–22.500 (6.456)	–12.597 (8.994)	***p*<0.01**
Superexcitability 7 ms	–20.909 (5.825)	–10.303 (5.825)	***p*<0.01**
Subexcitability	13.001 (3.511)	18.188 (5.671)	***p*<0.01**
Threshold electrotonus			
TeD 10-20 ms	67.174 (6.198)	66.474 (5.844)	p=0.096
TeD 90-100 ms	43.886 (4.500)	43.422 (4.249)	p=0.3173
TeH 10-20 ms	–71.388 (13.297)	–73.083 (14.477)	p=0.222
TeH 90-100 ms	–122.325 (50.403)	–115.256 (25.734)	p=0.908
Strength duration and stimulus response			
SDTC	0.475 (0.103)	0.475 (0.182)	p=0.0325
Rheobase	3.211 (1.004)	3.295 (0.992)	p=0.470
Slope	4.832 (1.422)	4.730 (1.516)	p=0.908

RRP: Relative refractory period; Refr: refractoriness; TeD: depolarizing threshold electrotonus; TeH: hyperpolarizing threshold electrotonus; SDTC: strength-duration time constant. Statistically significant *p*-values are shown in bold.

support the general consensus that acute alterations in axonal excitability recordings, immediately after treatment, are mediated through an effect on axonal voltage-gated transient Na^+ channels and possibly contribute to the development of chronic neuropathy (21).

In contrast, our results showed no significant changes in strength-duration parameters before and after infusion, and also in parameters between the cycles of treatment. It has been described that strength-duration time constant (SDTC) provides a surrogate marker of persistent Na^+ conductance active at threshold (16, 22, 23). The absence of significant alterations in SDTC may indicate that persistent Na^+ current may not be affected significantly during oxaliplatin infusion, or that axons possibly recover after acute neurotoxicity. We suggest that it is highly possible that, even during the short interval of two or three weeks, axons are capable of retrieving their previous neurophysiological values, regarding axonal persistent Na^+ current. However, pronounced changes were observed in recovery cycle parameters following oxaliplatin (Table I and Table II). The relative refractory period was prolonged while refractoriness, superexcitability and late subexcitability were all elevated. This effect of oxaliplatin resembles the recovery cycle parameter changes seen with cooling human median nerve motor (24) and sensory axons (25). In peripheral axons in vitro, both cooling (26) and oxaliplatin slow the kinetics of sodium channel inactivation and thus increase the likelihood of resurgent sodium current and burst firing (11). The observed pattern of change in recovery cycle excitability in patients may thus indicate slowed inactivation of voltage gated sodium channels following oxaliplatin (27, 28).

In our previous study, regarding clinical and neurophysiological follow-up of patients with oxaliplatin-induced neuropathy, we found that chronic sensory cumulative neuropathy developed in most of the patients after the middle of therapy with numbness and was assessed using clinical scales, nerve conduction studies, and the vibration threshold (29). Several other studies, which also pointed out the persistence of chronic large sensory fiber neuropathy and the influence of the cumulative dose of oxaliplatin on the development and severity of the chronic neuropathy, suggested a correlation between acute neurotoxicity and chronic sensory symptoms and severity of neuropathy (30-32). In this study, sensory nerve conduction and excitability studies were not included since it has been well described that toxicity affects sensory nerves and causes sensory symptoms (29). Our results showed that functional and not degenerated axons recover after each cycle of treatment, suggesting that there is a possible different pathological mechanism concerning acute neurotoxicity and chronic neuropathy, as has been proposed by other investigators in the past (3). Moreover, we did not confirm that axonal excitability was affected by chronic axonal degeneration, thus we suggest that it could not be used as a possible biomarker for the prognosis of chronic axonal neuropathy induced by oxaliplatin. In contrary a recent study using neurophysiology together with immune-histochemistry techniques has suggested a link between the acute oxaliplatin neurotoxicity and chronic nerve degeneration in mice, paving the way to a new line of research to prevent oxaliplatin induced neuropathy (33).

A limitation to our study was the small number of subjects that were included, because of the coexistence of diabetic

Table II. *Means of excitability parameters determined before each infusion across eight cycles.*

RRP	3.35 (0.6)	3.12 (0.49)	2.81 (0.75)	2.82 (0.65)	2.79 (0.75)	2.76 (0.78)	2.81 (0.76)	2.75 (0.94)
Refr 2 ms	112.41 (99.36)	73.41 (41.21)	63.98 (37.52)	59.59 (27.19)	61.31 (43.28)	56.71 (39.06)	57.27 (32.76)	62.90 (27.97)
Refr 2.5 ms	33.58 (24.45)	27.68 (26.18)	19.66 (18.76)	18.26 (16.36)	17.67 (24.16)	16.83 (25.01)	18.09 (22.30)	23.46 (17.62)
Super-excitability	–22.46 (7.06)	–23.09 (4.37)	–21.87 (9.23)	–21.40 (9.56)	–19.75 (9.18)	–20.10 (9.90)	–20.50 (10.57)	–16.77 (12.92)
Superx 5 ms	–21.10 (8.19)	–22.15 (5.12)	–21.89 (9.12)	–21.59 (9.47)	–19.97 (9.38)	–20.66 (10.60)	–21.04 (11.36)	–17.02 (13.58)
Superx 7 ms	–22.07 (7.69)	–21.21 (4.69)	–19.88 (9.33)	–19.43 (9.50)	–17.33 (8.76)	–17.14 (8.38)	–18.10 (8.68)	–15.94 (11.38)
Sub-excitability	12.25 (3.27)	12.70 (3.46)	12.69 (3.43)	12.02 (4.67)	13.55 (3.51)	14.22 (3.83)	13.06 (4.15)	10.92 (4.24)
TeD10-20	66.15 (6.2)	67.02 (6.55)	64.45 (17.3)	65.17 (14.26)	65.20 (14.43)	64.74 (14.37)	64.31 (14.43)	57.91 (19.24)
TeD90-100	42.52 (3.64)	44.84 (3.91)	42.44 (11.43)	43.52 (10.02)	42.74 (9.75)	41.97 (9.42)	41.64 (9.80)	37.36 (12.54)
TeH10-20	–72.74 (18.57)	–68.63 (12.03)	–66.12 (24.01)	–64.72 (24.84)	–66.29 (25.33)	–68.94 (29.15)	–68.28 (29.48)	–53.69 (36.10)
TeH90-100	–115.37 (18.5)	–114.84 (18.5)	–105.50 (39.08)	–135.24 (115.39)	–137.59 (125.59)	–113.24 (69.34)	–108.76 (50.50)	–86.79 (63.94)
SDTC	0.52 (0.1)	0.51 (0.14)	0.46 (0.12)	0.41 (0.12)	0.41 (0.11)	0.43 (0.10)	0.43 (0.11)	0.41 (0.14)
Rheobase	2.67 (1.08)	3.09 (1.09)	2.92 (0.98)	3.00 (0.83)	3.17 (1.00)	3.23 (1.01)	3.28 (1.07)	3.04 (1.24)
Slope	4.76 (1.28)	5.10 (1.79)	4.32 (1.13)	4.80 (1.63)	4.91 (1.69)	4.78 (1.52)	4.73 (1.32)	4.39 (1.62)

RRP: Relative refractory period; Refr: refractoriness; TeD: depolarizing threshold electrotonus; TeH: hyperpolarizing threshold electrotonus; SDTC: strength-duration time constant.

neuropathy and previous treatment with another neo-adjuvant therapy, which had to be excluded in the 9-month period of the study. Another limitation was the drop-out of some patients from voluntary participation, due to progress of disease, intolerance of the examination procedure or extreme physical exhaustion experienced after infusion.

Conclusion

Our study confirmed oxaliplatin-induced acute neurotoxicity following infusion and suggested that neural axons recover between infusion cycle intervals. Further long-term follow-up studies in humans need to be carried out with larger populations to confirm these findings and elucidate the pathophysiological mechanisms concerning oxaliplatin-induced acute neurotoxicity and chronic neuropathy, and their possible correlation.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

P.K. and M.P. performed the neurophysiological tests and wrote the manuscript; R.C. and M.S. revised the manuscript; E.S. and C.P. were responsible for patients' clinical care.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18(16): 2938-2947, 2000. DOI: 10.1200/JCO.2000.18.16.2938

2 André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350(23): 2343-2351, 2004. DOI: 10.1056/NEJMoa032709

3 Lehky TJ, Leonard GD, Wilson RH, Grem JL, Floeter MK: Oxaliplatin-induced neurotoxicity: Acute hyperexcitability and chronic neuropathy. Muscle Nerve 29(3): 387-392, 2004. DOI: 10.1002/mus.10559

4 Wilson RH, Lehky T, Thomas RR, Quinn MG, Floeter MK, Grem JL: Acute oxaliplatin-induced peripheral nerve hyperexcitability. J Clin Oncol 20(7): 1767-1774, 2002. DOI: 10.1200/JCO.2002.07.056

5 Grothey A: Oxaliplatin-safety profile: neurotoxicity. Semin Oncol 30(4 Suppl 15): 5-13, 2003. DOI: 10.1016/s0093-7754(03)00399-3
6 Gamelin E, Gamelin L, Bossi L, Quasthoff S: Clinical aspects and molecular basis of oxaliplatin neurotoxicity: Current management and development of preventive measures. Semin Oncol 29(5 Suppl 15): 21-33, 2002. DOI: 10.1053/sonc.2002.35525
7 Adelsberger H, Quasthoff S, Grosskreutz J, Lepier A, Eckel F, Lersch C: The chemotherapeutic oxaliplatin alters voltage-gated Na^+ channel kinetics on rat sensory neurons. Eur J Pharmacol 406(1): 25-32, 2000. DOI: 10.1016/s0014-2999(00)00667-1
8 Wu SN, Chen BS, Wu YH, Peng H, Chen LT: The mechanism of the actions of oxaliplatin on ion currents and action potentials in differentiated NG108-15 neuronal cells. Neurotoxicology 30(4): 677-685, 2009. DOI: 10.1016/j.neuro.2009.04.010
9 Benoit E, Brienza S, Dubois J: Oxaliplatin, an anticancer agent that affects both Na^+ and K^+ channels in frog peripheral myelinated axons. Gen Physiol Biophys 25(3): 263-276, 2006.
10 Grolleau F, Gamelin L, Boisdron-Celle M, Lapied B, Pelhate M, Gamelin E: A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels. J Neurophysiol 85(5): 2293-2297, 2001. DOI: 10.1152/jn.2001.85.5.2293
11 Sittl R, Lampert A, Huth T, Schuy ET, Link AS, Fleckenstein J, Alzheimer C, Grafe P, Carr RW: Anticancer drug oxaliplatin induces acute cooling-aggravated neuropathy *via* sodium channel subtype Na(V)1.6-resurgent and persistent current. Proc Natl Acad Sci USA 109(17): 6704-6709, 2012. DOI: 10.1073/pnas.1118058109
12 Krishnan AV, Goldstein D, Friedlander M, Kiernan MC: Oxaliplatin-induced neurotoxicity and the development of neuropathy. Muscle Nerve 32(1): 51-60, 2005. DOI: 10.1002/mus.20340
13 Krishnan AV, Goldstein D, Friedlander M, Kiernan MC: Oxaliplatin and axonal Na^+ channel function *in vivo*. Clin Cancer Res 12(15): 4481-4484, 2006. DOI: 10.1158/1078-0432.CCR-06-0694
14 Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC: Oxaliplatin-induced neurotoxicity: changes in axonal excitability precede development of neuropathy. Brain 132(10): 2712-2723, 2009. DOI: 10.1093/brain/awp219
15 Park SB, Goldstein D, Lin CS, Krishnan AV, Friedlander ML, Kiernan MC: Acute abnormalities of sensory nerve function associated with oxaliplatin-induced neurotoxicity. J Clin Oncol 27(8): 1243-1249, 2009. DOI: 10.1200/JCO.2008.19.3425
16 Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC: Dose effects of oxaliplatin on persistent and transient Na^+ conductances and the development of neurotoxicity. PLoS One 6(4): e18469, 2011. DOI: 10.1371/journal.pone.0018469
17 Bostock H, Cikurel K, Burke D: Threshold tracking techniques in the study of human peripheral nerve. Muscle Nerve 21(2): 137-158, 1998. DOI: 10.1002/(sici)1097-4598(199802)21:2<137::aid-mus1>3.0.co;2-c
18 Kiernan MC, Burke D, Andersen KV, Bostock H: Multiple measures of axonal excitability: A new approach in clinical testing. Muscle Nerve 23(3): 399-409, 2000. DOI: 10.1002/(sici)1097-4598(200003)23:3<399::aid-mus12>3.0.co;2-g
19 Burke D, Kiernan MC, Bostock H: Excitability of human axons. Clin Neurophysiol 112(9): 1575-1585, 2001. DOI: 10.1016/s1388-2457(01)00595-8
20 Kiernan MC, Baker MD, Bostock H: Characteristics of late Na^+ current in adult rat small sensory neurons. Neuroscience 119(3): 653-660, 2003. DOI: 10.1016/s0306-4522(03)00194-5
21 Gamelin L, Boisdron-Celle M, Delva R, Guérin-Meyer V, Ifrah N, Morel A, Gamelin E: Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium in fusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res 10(12 Pt 1): 4055-4061, 2004. DOI: 10.1158/1078-0432.CCR-03-0666
22 Mogyoros I, Kiernan MC, Burke D: Strength-duration properties of human peripheral nerve. Brain 119(2): 439-447, 1996. DOI: 10.1093/brain/119.2.439
23 Bostock H, Rothwell JC: Latent addition in motor and sensory fibres of human peripheral nerve. J Physiol 498 (Pt 1)(Pt 1): 277-294, 1997. DOI: 10.1113/jphysiol.1997.sp021857
24 Kiernan MC, Cikurel K, Bostock H: Effects of temperature on the excitability properties of human motor axons. Brain 124(4): 816-825, 2001. DOI: 10.1093/brain/124.4.816
25 Kovalchuk MO, Franssen H, Van Schelven LJ, Sleutjes BTHM: Comparing excitability at 37˚C *versus* at 20˚C: Differences between motor and sensory axons. Muscle Nerve 57(4): 574-580, 2018. DOI: 10.1002/mus.25960
26 Schwarz JR: The effect of temperature on Na currents in rat myelinated nerve fibres. Pflugers Arch 406(4): 397-404, 1986. DOI: 10.1007/BF00590943
27 Heide R, Bostock H, Ventzel L, Grafe P, Bergmans J, Fuglsang-Frederiksen A, Finnerup NB, Tankisi H: Axonal excitability changes and acute symptoms of oxaliplatin treatment: *in vivo* evidence for slowed sodium channel inactivation. Clin Neurophysiol 129(3): 694-706, 2018. DOI: 10.1016/j.clinph.2017.11.015
28 Bennedsgaard K, Ventzel L, Grafe P, Tigerholm J, Themistocleous AC, Bennett DL, Tankisi H, Finnerup NB: Cold aggravates abnormal excitability of motor axons in oxaliplatin-treated patients. Muscle Nerve 61(6): 796-800, 2020. DOI: 10.1002/mus.26852
29 Kokotis P, Schmelz M, Kostouros E, Karandreas N, Dimopoulos MA: Oxaliplatin-induced neuropathy: a long-term clinical and neurophysiologic follow-up study. Clin Colorectal Cancer 15(3): e133-e140, 2016. DOI: 10.1016/j.clcc.2016.02.009
30 Pietrangeli A, Leandri M, Terzoli E, Jandolo B, Garufi C: Persistence of high-dose oxaliplatin-induced neuropathy at long-term follow-up. Eur Neurol 56(1): 13-16, 2006. DOI: 10.1159/000094376
31 Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC: Long-term neuropathy after oxaliplatin treatment: challenging the dictum of reversibility. Oncologist 16(5): 708-716, 2011. DOI: 10.1634/theoncologist.2010-0248
32 Burakgazi AZ, Messersmith W, Vaidya D, Hauer P, Hoke A, Polydefkis M: Longitudinal assessment of oxaliplatin-induced neuropathy. Neurology 77(10): 980-986, 2011. DOI: 10.1212/WNL.0b013e31822cfc59
33 Ballarini E, Malacrida A, Rodriguez-Menendez V, Pozzi E, Canta A, Chiorazzi A, Monza L, Semperboni S, Meregalli C, Carozzi VA, Hashemi M, Nicolini G, Scuteri A, Housley SN, Cavaletti G, Alberti P: Sodium-calcium exchanger 2: a pivotal role in oxaliplatin induced peripheral neurotoxicity and axonal damage? Int J Mol Sci 23(17): 10063, 2022. DOI: 10.3390/ijms231710063

Received January 7, 2024
Revised March 1, 2024
Accepted March 4, 2024