REVIEW ARTICLE

Drug Safety 2006; 29 (1): 23-30
0114-5916/06/0001-0023/$39.95/0

Advances in Understanding Drug-Induced Neuropathies

Amanda C. Peltier[1] and *James W. Russell*[1,2]

1 Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA
2 Department of Neurology, Veterans Affairs Medical Center, Ann Arbor, Michigan, USA

Contents

Abstract

Many commonly used medications have neurotoxic adverse effects; the most common of these is peripheral neuropathy. Neuropathy can be a dose-limiting adverse effect for many medications used in life-threatening conditions, such as malignancy and HIV-related disease. Epidemiological evidence supports previous case reports of HMG-CoA reductase inhibitors (or 'statins') causing an axonal sensorimotor neuropathy or a purely small-fibre neuropathy in some patients. The neuropathy improves when the medication is withdrawn. Despite the association between HMG-CoA reductase inhibitors and neuropathy, the risk is low compared with the significant vascular protective benefits. Oxaliplatin, a new platinum chemotherapy agent designed to have fewer adverse effects than other such agents, has been shown to cause a transient initial dysaesthesia in addition to an axonal polyneuropathy. Thalidomide, an old therapy currently being utilised for new therapeutic indications (e.g. treatment of haematological malignancies), is associated with a painful, axonal sensorimotor neuropathy that does not improve on withdrawal of the drug. Nucleoside reverse transcriptase inhibitors are important components of highly active antiretroviral therapy, but are associated with a sensory neuropathy that is likely to be due to a direct effect of these drugs on mitochondrial DNA replication. New research demonstrates that lactate levels may help discriminate between neuropathy caused by nucleoside analogues and HIV-induced neuropathy. Understanding the mechanism of drug-induced neuropathy has led to advances in preventing this disabling condition.

Peripheral neuropathy is a common neurotoxic adverse effect of medications. Clinically, this becomes important as a significant limitation to medical therapies for serious illnesses, such as neoplasms and HIV infections. Drug-induced neuropathy can be difficult to recognise if it is a rare complication of a commonly used medication, especially as the neuropathy can develop years after the initiation of treatment and may not resolve immediately following cessation of the drug. Medications can also exacerbate underlying neuropathies, such as hereditary neuropathies, even at non-toxic doses. This has been reported in children receiving vincristine for leukaemia, but can occur in any patient.[1] The exact mechanism of neuronal toxicity is not known for the majority of drugs, but is inferred from the known mechanisms of action of the drug.

There are three general types of peripheral neuropathy, all of which can be drug induced. Axonal degeneration is the most common type of medication-induced neuropathy (table I). Commonly this occurs over weeks to months after exposure to the medication. Often electrophysiological testing will detect changes prior to the development of clinical symptoms. Because the damage is only to the axon, the neuropathy will resolve completely with cessation of the medication in many cases. Examples of medications causing a distal axonal degeneration include paclitaxel- and vincristine-induced neuropathy.[2,3]

Table I. Drugs associated with sensorimotor axonal degeneration

Colchicine
Dapsone[a]
Disulfiram
Gangliosides
Gold salts
HMG-CoA reductase inhibitors
Hydralazine
Isoniazid
Metronidazole
Misonidazole
Nitrofurantoin
Non-depolarising neuromuscular blocking drugs
Nucleoside analogues
Penicillamine
Phenytoin
Pyridoxine
Sulfasalazine
Suramin sodium
Tacrolimus[a]
Taxanes (paclitaxel)
Thalidomide
Vidarabine
Vinca alkaloids (vincristine)

a Predominantly affects motor nerves.

The second type of neuronal damage is cell death, usually of dorsal root ganglion cells. These cells are vulnerable as they are not protected by the blood-brain barrier. This causes a sensory predominant, irreversible neuropathy that is more physically debilitating than axonal degeneration. Cisplatin, carboplatin, oxaliplatin, suramin sodium (occasionally) and thalidomide (less common presentation) are the most frequently used medications that cause neuronal cell death. A newer alternative to cisplatin, oxaliplatin, can cause early and frequent dysaesthesias that correlate with electrophysiological evidence of nerve excitation in addition to the later developing sensory predominant neuropathy typical for this group of medications.[4] Another agent that can cause a sensory ganglionopathy is thalidomide, which was reintroduced as a potential therapy for multiple myeloma and certain rheumatological disorders.[5]

Demyelinating neuropathies secondary to medications are far less common and occur with specific agents, such as amiodarone, interferon-α, suramin sodium, perhexiline, chloroquine and tacrolimus. An acute onset of polyneuropathy can mimic Guillain-Barré syndrome and may not be recognised as a medication effect.

Much of the research into drug-induced neuropathies has been focused on the goal of ameliorating or preventing neuropathy without altering the effectiveness of the medication. This is especially important with antineoplastic agents and antiretroviral medications for the treatment of life-threatening illnesses, which necessitate the use of these medications. Advances in the understanding of the mechanism, diagnosis or prevention of neuropathy associated with medications, such as the HMG-CoA

reductase inhibitors, oxaliplatin, thalidomide, paclitaxel and the nucleoside reverse transcriptase inhibitors, will now be discussed. This review will illustrate recent understanding of the pathogenesis of drug-induced neuropathies.

1. HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors (or 'statins'), have become increasingly popular as more literature emerges about their benefits in the treatment of hyperlipidaemia in patients with cardiovascular disease, stroke and dysmetabolic syndrome in diabetes mellitus. Peripheral neuropathy has only recently been associated with HMG-CoA reductase inhibitors.[6,7] Previous case reports in the literature have suggested a link between HMG-CoA reductase inhibitors and neuropathy.[8-11] Most of the reports indicate that HMG-CoA reductase inhibitors are associated with a sensorimotor axonal neuropathy that is reversible after stopping treatment; however, persistent small-fibre neuropathy has been described.[8,9]

The exact cause of the neuropathy associated with HMG-CoA reductase inhibitors is unknown. However, several hypotheses have been proposed to explain both the myopathic and neuropathic complications of these medications.

One of the statin medications, atorvastatin, has been shown to rapidly and significantly decrease coenzyme Q_{10} levels in the blood of patients at risk for cardiovascular disease and stroke,[12] but these have not been reported to change in healthy volunteers.[13] Coenzyme Q_{10} is a potent antioxidant that is necessary for the coupling of oxidative phosphorylation in the mitochondrion and reduces the formation of reactive oxygen species.[14] In human and rodent myotube cultures, HMG-CoA reductase inhibitors induce apoptosis that is more dependent on aberrant geranylgeranylation of proteins than on the ubiquinone-coenzyme Q_{10} pathway.[15] The myopathic effects of HMG-CoA reductase inhibitors may be also be mediated through their inhibition of guanosine triphosphate signaling-related binding proteins; this may affect neurons as well.[16] Finally, HMG-CoA reductase inhibitors may inhibit the formation of selenoproteins through inhibitory effects on the mevalonate : transfer RNA isopentenyl transferase pathway.[17] This, in turn, would reduce the formation of specific selenoproteins required for structural integrity of the nerve, as well as reducing antioxidant defence pathways (e.g. glutathione peroxidase and thioredoxin reductase critical to nerve biochemical homeostasis). It must be stressed that, at present, these mechanisms of HMG-CoA reductase-induced nerve injury remain hypothetical.

It appears that clinically significant HMG-CoA reductase inhibitor-induced neuropathy is a rare phenomenon, given the small number of cases reported in the literature[7] compared with the large numbers of patients receiving this therapy. Cases have been reported with all of the available HMG-CoA reductase inhibitors on the market: atorvastatin, lovastatin, pravastatin, simvastatin, fluvastatin and rosuvastatin. Gaist et al.[18] found a 3.7 odds ratio for a patient developing neuropathy while being treated with HMG-CoA reductase inhibitors. Using a population-based case-control study, the odds ratios linking idiopathic polyneuropathy with current HMG-CoA reductase inhibitor use are 4.6 (95% CI 2.1, 10.0) for all cases and 16.1 (95% CI 5.7, 45.4) for definite cases of polyneuropathy.[18] Other case-control studies have shown similar but weaker associations between neuropathy and the use of HMG-CoA reductase inhibitors.[19] Thus, the true risk of developing neuropathy during HMG-CoA reductase inhibitor treatment is unknown because determination of the risk depends on the methodology used. On balance, the cardio- and cerebrovascular benefits of HMG-CoA reductase inhibitors outweigh the risk of neuropathy. However, alternative lipid lowering medications should be considered in subjects where neuropathy symptoms are severe and are linked temporally to HMG-CoA reductase inhibitor use. Alternative approaches include dietary and exercise interventions or the use of other lipid lowering medications, such as niacin, ezetimibe and colesevelam. However, other lipid-lowering drugs may also be associated with neuropathy, for example fibric acid derivatives are associated with a similar odds ratio to HMG-CoA reductase inhibitors

for the development of neuropathy.[19] Although coenzyme Q_{10} levels are reduced with HMG-CoA reductase inhibitor use, this may not be related to clinical disease and, based on the most recent literature, coenzyme Q_{10} supplements are not recommended at this time.[20,21]

2. Chemotherapeutic Agents

Three chemotherapeutic agents, oxaliplatin, paclitaxel and thalidomide that are associated with neuropathy are considered in the following sections. In addition, some newer agents used for the treatment of cancer may be associated with neuropathy. For example, bortezomib is a dipeptide boronic acid analogue that acts as a chemotherapeutic agent by selective inhibition of the proteasome. The common adverse effects of bortezomib include paresthesias and a painful peripheral neuropathy.[22] Initial experience with bortezomib suggests that the widespread chemotherapeutic potential of the drug is not limited by these adverse effects.[23]

2.1 Oxaliplatin

Oxaliplatin is a novel platinum agent that differs from carboplatin and cisplatin by a diaminocyclohexane group, which may enable it to confer greater resistance to DNA repair and prevent DNA replication. Platinum agents bind to DNA and prevent the DNA replication required for mitosis. Oxaliplatin is the only platinum compound to show clinical activity in colorectal cancer and has also been shown to be effective in gastric, ovarian, breast and lung cancers.[24] Although oxaliplatin has only mild haematological and gastrointestinal adverse effects, its dose-limiting toxicity is a cumulative sensory neurotoxicity (evident when the cumulative dose is ≥800 mg/m^2) that resembles that of cisplatin but is more rapidly reversible.

Oxaliplatin causes two types of neurotoxicity. One form is an early acute reaction that manifests as dysaesthesias and that occurs within hours or days of the first treatment in 85–95% of all patients.[25] The acute symptoms are paraesthesias and calf cramps, and a few patients complain of paresthesias of the throat, difficulty swallowing and jaw pain. Examination shows normal sensation and strength. Percussion over the posterior interosseous nerve can provoke delayed relaxation of the finger extensors.[4] The symptoms resolve completely within a few hours or days. Exposure to cold is a common trigger for the sensations. Delaying administration of further doses until the symptoms have resolved allows continued higher cumulative doses to be used in treatment. Although several neuromodulatory agents including antiepileptic medications (phenytoin or gabapentin), amifostine, thioctic acid (α-lipoic acid), glutathione and calcium-magnesium infusions have been used in neuro-prophylaxis, confirmatory clinical trials are lacking and make it unclear if any prophylactic agents have short- or long-term benefits.[25] Because of the reversible nature of these symptoms, most oncologists do not alter treatment but educate patients on what to expect, in order to alleviate anxiety.

Nerve conduction studies demonstrate repetitive discharges similar to neuromyotonia in the first 24–48 hours after infusion of oxaliplatin.[26] These discharges are caused by the blockade of potassium ion channels, which suggests interference with ion channels as a potential mechanism. This acute effect resolves by week 3. Oxaliplatin may also chelate calcium and its depletion could mediate the initial effects of oxaliplatin.[4,25] Calcium and magnesium supplementation have been effective in minimising symptoms.[27]

The second type of neurotoxicity manifests as a chronic sensory neuropathy with ataxia that is similar to that seen with cisplatin. This form of neurotoxicity is dose limiting, develops after 8–9 treatment cycles and is not associated with a slowing of the conduction velocity or neuromyotonic discharges.[26] Patients taking oxaliplatin should be carefully followed for development of sensory neuropathy. The exact mechanism of neuropathy is unknown for platinum compounds, but cisplatin *in vitro* interferes with axonal transport and induces apoptosis in dorsal root ganglion cells.[28] Another possible mechanism is accumulation of platinum in dorsal root ganglion cells (similar to mercury, lead

and other heavy metals), but this has been shown to not correlate well with neurotoxicity in rats.[28]

Recombinant human glial growth factor 2,[29] nerve growth factor[30] and tocopherol (vitamin E)[31] have been shown to reduce cisplatin-induced neuropathy *in vitro* and in animal models, but no trials in humans have been reported. Other efforts to reduce toxicity related to oxaliplatin have focused on altering the chemotherapy regimen by using nerve conduction or other physiological tests to identify preclinical nerve damage. To prevent neurotoxicity, administration of oxaliplatin is limited to a specific cumulative dose of <800 mg/m^2. An alternative strategy is to continue therapy until symptoms develop, discontinue oxaliplatin for 6 months and reintroduce if required.[25]

2.2 Paclitaxel

Paclitaxel is a common adjunctive therapy in women with node-positive breast cancer. It is also used for the treatment of other solid tumours, such as ovarian and non-small cell lung cancer.[2] Paclitaxel is derived from the Pacific yew tree *Taxus brevifolia* and binds to tubulin, stabilising microtubules, thus promoting the assembly and reducing the disassembly of microtubules. These changes reduce normal axonal transport.[32] A length-dependent sensorimotor axonal neuropathy is a common dose-dependent adverse effect of paclitaxel treatment.[2,33] It can also rarely cause cranial neuropathies, motor involvement and autonomic dysfunction.[34] The focus of current research is the prevention of the development of neuropathy, as this limits the clinical effectiveness of paclitaxel.

Several open trials of glutamine in human subjects have shown reduced clinical symptoms of paraesthesias and clinical development of neuropathy in patients receiving paclitaxel; however, results of nerve conduction studies were not significantly changed.[35] Amifostine, an organic thiophosphate that is converted to an active thiol metabolite that selectively binds to reactive species of cisplatin in normal tissues, has been shown to have a protective effect in platinum-induced renal toxicity, without diminishing drug activity.[25,36] However, amifostine has been shown to be ineffective in preventing peripheral neuropathy in clinical trials in patients receiving paclitaxel and cisplatin.[37,38]

In contrast, inhibition of calpains can reduce both the clinical and pathological effects of paclitaxel in rodent models of paclitaxel-induced neuropathy.[39] The ability of CX-295 (AK-295) to reduce paclitaxel-induced neurotoxicity is related to the inhibition of calpains and is not due to an effect on microtubule aggregation or programmed cell death.[39] Docetaxel also causes a dose-dependent neuropathy, but this occurs less often than with paclitaxel (30% vs 11%), and docetaxel has been substituted for paclitaxel in patients who have dose-limiting neuropathy. However, docetaxel causes more severe myelosuppression.[40]

2.3 Thalidomide

Thalidomide was originally marketed in the 1950s as a sedative agent, but because of teratogenicity was not approved by the US FDA as a therapy for erythema nodosum leprosum until 1998. Thalidomide has multiple effects on immune function including inhibition of tumour necrosis factor (TNF)-α, increasing T suppressor cell counts and reducing phagocytosis by polymorphonuclear leucocytes.[5,41,42] It has also been shown to have anti-angiogenic activity that has led to trials of thalidomide for the treatment of haematological malignancies (e.g. myeloma and other myelodysplastic syndromes).[5,43-46] Thalidomide and thalidomide analogues usually cause an axonopathy,[5] although dorsal root ganglion degeneration has been described in phycomyelic rabbits[47] and humans.[41] The neuropathy may be cumulative and dose dependent, but only with high doses (>20g).[42] The risk of neuropathy increases >10% with a 20g dose.

The sensory axonal polyneuropathy may be reversible in its early stages. Symptoms include numbness, paraesthesias, cramps and burning pain. Typical electrophysiology studies in humans suggest an axonal sensorimotor neuropathy. The prevalence of neuropathy is variable, with literature reports ranging from 1% to 70%.[41] There is some evidence that older age and a higher daily dose of

thalidomide are linked to an increased frequency of neuropathy,[42,48] regardless of duration.[49,50] Reduction in the sural nerve amplitude is sometimes seen prior to the clinical development of neuropathy.[48]

At this time, there is no definite evidence that therapy can be restarted if the neuropathy improves, but electrophysiological testing (nerve conductions using sural sensory nerve action potential and peroneal F-waves) may detect the presence of neuropathy before symptoms are evident.[51]

3. Nucleoside Reverse Transcriptase Inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs) are an important component of highly active antiretroviral therapy (HAART), which is the most commonly prescribed treatment for HIV-infected patients. HAART traditionally incorporates two nucleoside analogues with at least one protease inhibitor. In addition to myopathy, one of the common potential complications with zalcitabine, didanosine, stavudine and lamivudine is a painful distal symmetric polyneuropathy. Use of skin biopsies with intraepidermal nerve fibre measurements[52,53] may be useful in determining the severity and progression of HIV- or NRTI induced-neuropathy.

The sensory axonal neuropathy observed with NRTIs is likely to be related to mitochondrial injury.[2] The mechanism behind the neurotoxicity of NRTIs has recently been elucidated. Decreased mitochondrial DNA in PC-12 cells and decreased levels of acetyl carnitine in patients with didanosine neuropathy are consistent with mitochondrial toxicity.[54,55] A small open-label study using l-acetyl carnitine demonstrated improvement in the symptoms of neuropathy induced by NRTIs, supporting this concept.[55,56] Dideoxynucleoside analogues are phosphorylated by thymidine kinase isoforms. They then compete with natural substrates for the HIV reverse transcriptase, thus terminating the DNA chain. The NRTIs also selectively affect γ-DNA polymerase, which is the enzyme required for mitochondrial DNA replication. Mitochondrial DNA is reduced along with mitochondrial DNA-encoded enzymes. Other evidence of mitochondrial toxicity associated with NRTI therapy includes lactic acidosis, peripheral neuropathy and lipoatrophy.[57,58] Fialuridine causes a more permanent neuropathy and profound liver toxicity that is thought to be secondary to irreversible mitochondrial DNA damage.[55] Because HIV and associated conditions, such as hepatitis C, can also cause a painful peripheral neuropathy, it is often difficult to distinguish whether nerve damage is drug induced or secondary to HIV infection. The peripheral neuropathy associated with NRTIs tends to be more abrupt in onset and more painful than the neuropathy associated with HIV. Neuropathy onset is usually related temporally to the start of NRTI therapy and there is amelioration after cessation of treatment.

Like most drug-induced neuropathies, the chance of developing neuropathy is dose related and is higher with combination therapy, particularly with hydroxycarbamide (hydroxyurea). Lactic acidosis is a recognised complication of nucleoside therapy. This has been attributed to mitochondrial specific toxicity.[59,60] Recently, serum lactate levels have been found to help distinguish between nucleoside-induced neuropathy and HIV neuropathy with a specificity and sensitivity of 90%. Lactate levels were drawn after 10 minutes of rest, without a tourniquet or fist clenching.[61] Mean lactate levels from HIV-positive subjects in each of the following groups were: stavudine recipients with neuropathy, 3.16 ± 0.81 mmol/L; HIV with neuropathy, 1.8 ± 0.67 mmol/L; stavudine recipients without neuropathy, 1.68 ± 0.4 mmol/L; and individuals with HIV who were not receiving stavudine and did not have neuropathy, 1.54 ± 0.36 mmol/L.[61] It is not known whether lactate levels would be useful in distinguishing between drug-induced and HIV-induced neuropathy with other NRTIs. Another potential technique to predict treatment toxicity is to use the single-tube duplex real-time DNA-nucleic acid sequence-based amplification assay. This assay quantifies mitochondrial DNA in peripheral blood mononuclear cells and may predict the degree of mitochondrial toxicity due to zalcitabine or didanosine.[58]

Zalcitabine is more neurotoxic than didanosine or stavudine, but didanosine and stavudine together are more potent neurotoxins than stavudine alone.[52] It is not clear why zalcitabine, didanosine and stavudine seem to have specificity for axons and Schwann cells in contrast to the effect of zidovudine, which primarily occurs in skeletal muscle mitochondria.[55,56] All NRTIs require phosphorylation by thymidine kinase to be recognised by DNA polymerase. Differential toxicity for axons of certain NRTIs may be secondary to their affinity for specific thymidine kinase isoforms.[55,56]

4. Conclusion

Awareness of the potential of medications to cause peripheral neuropathy is key to preventing significant nerve damage in treated patients. Currently available research has focused on ways to prevent neurotoxicity without affecting the main mechanism of action of the drug. This is especially important in HIV and cancer therapy where treatment options can be limited by disabling peripheral neuropathies. The recognition of neuropathy as a rare effect of HMG-CoA reductase inhibitors is important for potential reversal of symptoms in these patients.

Acknowledgements

The authors would like to thank Ms Denice Janus for secretarial assistance. The authors were supported in part by NIH NS42056, The Juvenile Diabetes Research Foundation Center for the Study of Complications in Diabetes (JDRF), Office of Research Development (Medical Research Service), Department of Veterans Affairs (JWR) and NIH T32 NS07222 (ACP). The authors have no conflicts of interest that are directly relevant to the content of this review.

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Correspondence and offprints: Dr *James W. Russell*, Department of Neurology, University of Michigan, 200 Zina Pitcher Place, 4410 Kresge III, Ann Arbor, MI 48109-0585, USA.