**Side Effects of Drugs**

**Drug-induced peripheral neuropathies**

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**Summary and conclusions**

Review of the various drugs in current clinical use showed that over 50 of them may cause a purely sensory or mixed sensorimotor neuropathy. These include antimicrobials, such as isoniazid, ethambutol, ethionamide, nitrofurantoin, and metronidazole; antineoplastic agents, particularly vinca alkaloids; cardiovascular drugs, such as perhexiline and hydralazine; hypnotics and psychotropics, notably methaqualone; antirheumatics, such as gold, indomethacin, and chloroquine; anticonvulsants, particularly phenytoin; and other drugs, including disulfiram, calcium carbimide, and dapsone.

Patients receiving drug treatment who complain of paraesthesiae, pain, muscle cramps, or other abnormal sensations and those without symptoms who are receiving drugs that are known or suspected to be neurotoxic should undergo neurological examination and studies of motor and sensory nerve conduction. This will allow the incidence of drug-induced peripheral neuropathy to be determined more precisely.

**Introduction**

Various drugs may cause peripheral nerve damage when used therapeutically.1, 4 Some, such as thalidomide and clioquinol, have been withdrawn from clinical use, while others are still freely prescribed. In this review we deal only with the second group of drugs, particularly those that have recently been recognised or suspected to be neurotoxic. We consider only those forms of neuropathy resulting from the therapeutic use of such drugs, and do not discuss the complications of drug addiction.3

Awareness of the possibility of drug-induced peripheral nerve damage is important because of the ever-increasing number of therapeutic agents being introduced into clinical practice, and prompt recognition of this complication is imperative if severe neurological deficits are to be avoided. The incidence of drug-induced peripheral neuropathy is difficult to establish, since the association with drug treatment is not always recognised, mild forms are easily overlooked, and subclinical disorders are probably more frequent than is generally appreciated.4, 5

**Pathogenesis**

Experimental studies have clarified the pathogenesis of certain drug-induced neuropathies,6, 7 but the basic mechanisms are generally still poorly understood. Because these disorders are potentially reversible the opportunities for histological and other studies of peripheral nerve in man are limited. Nevertheless, with some exceptions, such as perhexiline neuropathy, in which segmental demyelination is prominent,9 axonal degeneration is the major pathological process in most drug-induced neuropathies.

The mechanism of action of some drugs is relatively well understood. Vincristine and colchicine have a specific effect on neurotubules.9, 10 Isoniazid interferes with pyridoxine metabolism,11 thalidomide inhibits riboflavin,12 prolonged administration of chloramphenicol may lead to vitamin B12 deficiency,13 and the nitrofurans interfere with pyruvate oxidation by competing with thiamine pyrophosphate.14 Perhexiline may interfere with lipid metabolism.15 Other drugs may cause ischaemic nerve damage by inducing arteritis16 or severe vasospasm, as in chronic ergotism.17

Several factors may predispose to the neurotoxic effects of drugs. The best-known genetic predisposition is the striking susceptibility of the Japanese to develop subacute myelo-opticneuropathy as a complication of clioquinol treatment.1 Variations in drug pharmaco-
kinetics are also important. Slow acetylators of isoniazid are more likely to develop peripheral neuropathy,13 as are patients with impaired renal function, who may develop toxic blood concentrations of drugs such as nitrofurantoin.14 Strained exercise was thought to predispose to the development of neuropathy in patients treated with the older sulphonamides.15 The underlying disease may itself modify the susceptibility to neuropathy—for example, patients with lymphoma developing vincristine neuropathy more often than those with other malignancies.21 Others who may be predisposed include patients with cancer, diabetes, alcoholism, or vitamin deficiency, conditions in which the peripheral nerves may already be affected.

Clinical presentations

Most of the drugs we considered cause either a purely sensory neuropathy or a mixed sensorimotor neuropathy. Sensory manifestations usually precede motor disorders, and neurological deficits usually develop first and are most severe distally in the legs. Paraesthesiae alone are difficult to evaluate,28 but suggest that sensory nerve function may be disturbed. Some drugs, such as capsaicin,29 cause an almost exclusively motor neuropathy. Symptoms of autonomic dysfunction may be prominent, particularly in patients with vincristine neuropathy.30 Localised damage to peripheral nerves or a nerve plexus may result from intramuscular injections, intra-articular infusions of cytotoxic agents,23 or haemorrhage in patients in whom anticoagulant treatment is poorly controlled.27 Brachial plexus neuropathy may occasionally develop after intramuscular injections of penicillin, presumably on an "allergic" basis.28 Certain cranial nerves may also be affected, either selectively or as part of a more generalised neuropathy, the optic,39 trigeminal,40 and eighth cranial39 nerves being most often affected.

Specific drugs

The drugs that have been implicated and the clinical syndromes they produce are listed in the table.

**ANTIMICROBIAL AGENTS**

Some of the antituberculosis agents in use may cause peripheral or optic neuropathy. Isoniazid produces a mixed sensorimotor peripheral neuropathy that may be prevented by giving vitamin B12 supplements.33 The condition has been reviewed in detail by Le Queus.31 Ethambutol is less neurotoxic but may cause optic neuropathy,27 a mixed sensorimotor neuropathy, or a predominantly sensory neuropathy.29 Ethionamide, which is structurally related to isoniazid, may rarely cause peripheral neuropathy, as may streptomycin after prolonged administration, although this is less frequent than the ototoxic effects of the drug.

Sensorimotor neuropathy of variable severity in patients treated with nitrofurantoin is well recognised.24 Symptoms may develop during or after a course of treatment, particularly in patients with renal insufficiency. Electrophysiological studies have shown a high incidence of subclinical neuropathy, even in non-urinary patients,17 and in healthy volunteers taking therapeutic doses of the drug.4 Histological studies have shown axonal degeneration in peripheral nerves and associated spinal cord damage in a postmortem study.1 Long-term experimental studies have shown evidence of a "dying-back" neuropathy.

There are several reports of sensory neuropathy developing in patients treated with conventional doses of metronidazole for 6–24 weeks.29–31 Electrophysiological studies have shown that both sensory and motor nerve fibres may be affected.46 A sural-nerve biopsy specimen from one patient showed axonal degeneration affecting both small- and large-diameter fibres.46 The neuropathy is reversible after withdrawal of the drug but recovery may be protracted. The incidence of this complication is not known, and further clinical and electro-physiological studies of patients receiving short- and long-term treatment are required.

**ANTINEOPLASTIC AGENTS**

The vinca alkaloids, which have been used in treating various forms of malignancy, are particularly neurotoxic. Most patients receiving long-term vincristine treatment develop a peripheral neuropathy that may be associated with a painful proximal myopathy.4 The clinical features of vincristine neuropathy are well documented.41–42 Both sensory and motor nerves may be severely affected, and the tendon reflexes are lost at an early stage. Postural hypotension and constipation due to autonomic disorders may be early symptoms.43 Electro-physiological studies have shown evidence of severe axonal damage affecting motor and sensory fibres,4 the reflex loss probably being due to damage to afferent fibres from the muscle spindles.45 Histological studies have shown severe axonal degeneration with only minor segmental demyelination.46 Several other cytotoxic drugs may cause peripheral nerve damage but are less neurotoxic than vincristine (table).

**CARDIOVASCULAR DRUGS**

Peripheral neuropathy has been recognised only relatively recently in patients treated with the coronary vasodilator perchloriline, but is now well documented.44–45 Symptomatic neuropathy occurs in about 0·1% of treated patients, but subclinical disorders have been found in as many as two-thirds of patients studied electrophysiologically.46 Sensory symptoms, including muscle pain and tenderness, are usually prominent, appearing as early as three weeks after treatment begins, and may be followed by severe weakness of distal and even of proximal muscle groups. In most cases symptoms have occurred only after several months of treatment with daily doses of 200–300 mg of the drug. Papilloedema, dysgeusia, deafness, cerebellar signs, autonomic disorders, and raised concentrations of protein in cerebrospinal fluid have been reported.46–47 Histological studies of peripheral-nerve biopsy specimens have shown prominent segmental demyelination.

Clinical syndromes of drug-induced neuropathy and drugs implicated

<table>
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<th>Clinical presentation</th>
<th>Antimicrobial drugs</th>
<th>Antineoplastic drugs</th>
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<tr>
<td>Sensory neuropathy</td>
<td>ethionamide</td>
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<td>phenelzine</td>
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<td>cetylarbin</td>
<td>propranolol</td>
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<td>phenelzine</td>
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<td>Sensornotor neuropathy</td>
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<td>vincristine</td>
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*References are given only for drugs not discussed in the text.
with associated axonal degeneration, and membranous and para-
crystalline inclusions in Schwann cells and endothelial cells.1 4
Biochemical studies have shown an increased ganglioside content in
peripheral nerve.5 Complete recovery usually occurs within several
months of stopping treatment.

A predominantly sensory neuropathy may occur in patients treated
with hydralazine.4 10 Mild or subclinical neuropathy may occur in as
many as 15% of patients taking the drug.1 11 This seems to be unrelated
to the systemic lupus erythematosus-like syndrome induced by the
drug, and may be due to a disturbance of pyridoxine metabolism,
since hydralazine is structurally related to isoniazid.12 Peripheral
neuropathy may occasionally develop in patients receiving
amiodarone13 or disopyramide.14 The evidence suggests that amiodarone
causes demyelinating neuropathy. Few cases of peripheral
nerve damage have been reported in patients in the typical painful myopathy
caused by clofibrate.15 16

**HYPNOTIC AND PSYCHOTROPIC DRUGS**

Several reports have raised suspicion that methaqualone may be
neurotoxic. Some patients have transient acropaesthesiae or numbness shortly after taking the drug before the onset of sleep.7
At least 11 cases of a sensorimotor neuropathy have been reported in
patients taking 200-600 mg of methaqualone nightly for a few days to
two years, either alone or with diphenhydramine, diazepam,
meprobamate, or promazine.14 16 17 Symptoms improved in most
patients after methaqualone was withdrawn, improving being rapid and
complete in those whose symptoms were of recent onset. In a
German study of 232 patients taking the drug, 44 of whom had
undergone electromyographic studies, only a single case of peripheral
neuropathy was found.18 Few cases of neuropathy have been reported
in Great Britain, and further clinical and electromyographic studies of
regular consumers of the drug are required to determine the incidence of
this complication.

A predominantly motor neuropathy may occasionally develop in
patients treated with imipramine19 20 and amitriptyline,21 but such
cases have not been studied fully. Reports of "neuritis" developing in
patients receiving chlorpromazine and of acropaesthesiae in
those receiving phenelzine are difficult to evaluate.22 Sensory
neuropathy has been described in patients addicted to glutethimide
but is not a complication of conventional use of the drug.23 24

**ANTINEUROTIC DRUGS**

Peripheral neuropathy occurs in 0.5-1%, of patients with rheumatoid
arthritis who have gold treatment.77 25 Motor disorders are prominent
and sensory symptoms may be inconspicuous. An abrupt onset and
rapid progression in some cases, and associated facial diplegia and
raised protein concentration in cerebrospinal fluid may mimic acute
postinfective polyneuropathy. Few cases have been studied electro-
physiologically or pathologically but axonal degeneration appears to
be the main process.26 Indomethacin has also been implicated in
causing a neuropathy. A report on four patients with a sensorimotor
neuropathy and two with sensory symptoms only suggested that the
drug was responsible.27 Electromyographic studies showed con-
siderable slowing of motor conduction velocities in one case. Further
studies are needed to determine the incidence of this complication.

Chloroquine may cause a mild sensorimotor neuropathy as well as a
severe vacuolar myopathy.71 28 Histological studies have shown both
axonal degeneration and damage to Schwann cells.29 Peripheral
neuropathy has been reported in patients treated with penicillamine,30
but less often than the myasthenic syndrome that develops in some
patients treated with the drug. The mechanism of the neuropathy may
be related to that caused by isoniazid, since penicillamine has an
anti(pyridoxine effect.31 Paraesthesiae and muscle weakness have been
reported in some patients treated with phenylbutazone but are
difficult to evaluate.32

**ANTICONVULSANTS**

Patients receiving long-term phenytoin treatment may develop a
predominantly sensory polyneuropathy that is usually mild and rarely
causes symptoms. The incidence of this complication is uncertain,
but signs of peripheral nerve disorders, such as depression of tendon
reflexes, are found increasingly often in patients receiving prolonged
treatment.33 Electrophysiological studies have shown that subclinical
lesions are common and that the neuropathy is of the "dying-back"
axonal degeneration type.34 The drug also has acute, reversible effects,
particularly on slow-conducting motor nerve fibres.35 36 There is no convincing evidence to show that any of the other
commonly used anticonvulsants cause peripheral nerve damage.

**OTHER DRUGS**

Disulfiram and citrated calcium carbimide,43 which are used in treating
alcoholism, may both cause peripheral neuropathy. Disulfiram
causes a sensorimotor neuropathy with axonal degeneration and may
also cause optic-nerve damage.34 45 These effects may be due to its
neurotoxic metabolite carbon disulphide.46 A number of the sulphones
may also cause neuropathy. Dapsone, which has been used in treating
leprosy and several dermatological conditions, may cause a subacute,
amost purely motor neuropathy, particularly after prolonged high-
dose treatment.47 48 Sulfoxide sodium, on the other hand, may
cause a purely sensory neuropathy.39

**Conclusions**

Drugs used in treating various conditions may cause peripheral
nerve damage. This may be clinically manifest, but in many
instances is asymptomatic. We suggest that a careful neurological
examination and studies of motor and sensory nerve conduction
should be performed in patients who complain of paraesthesiae,
pain, muscle cramps, weakness, or other abnormal sensations
during drug treatment. Investigation of such patients and of
patients without symptoms who are being treated with drugs
that are known or suspected to be neurotoxic will allow the
incidence of drug-induced peripheral nerve damage to be
determined more precisely.

We thank Professor Sir John Walton, who kindly reviewed the
manuscript, and Mrs I Gibbs, who provided secretarial help.

**References**

1 Le Quesne, P M, in Peripheral Neuropathy, ed P J Dyck, P K Thomas,

2 Cohen, M M, in Handbook of Clinical Neurology, ed P J Vinken and G W

3 Challenor, Y B, Richter, R W, and Pearson, J, Annals of Internal Medicine,
1971, 74, 838.


9 Schochet, S, Usar, M C, and Lampt, P W, Journal of Neuropathology
and Experimental Neurology, 1968, 27, 645.


11 McCormick, D B, and Sheib, E E, Proceedings of the National Academy of
Sciences of the United States of America, 1959, 45, 1371.


13 Satoyoshi, E, and Wakata, N, paper presented at 4th International
Congress on Neuromuscular Diseases, Montreal, abstract 89. Amster-


24 Varot, P, Goudemand, M, and Habay, D, Revue Neurologique, 1965,
113, 464.


26 Bond, M R, Clark, S D, and Neal, P E, British Medical Journal, 1964,
1, 951.

27 Dhalwahl, G S, Schlagenhauff, R E, and Megahed, S M, Diseases of the
Nervous System, 1976, 37, 239.

28 Keith, L C, and Gray, S J, Journal of the American Medical Association,
1946, 132, 212.
Is there now a method by which people on continuous corticosteroids—for instance, for Addison's disease—can be vaccinated against smallpox. Also, may they have infections against yellow fever?

Apart from the recent Birmingham outbreak, no cases of smallpox have occurred anywhere in the world for nearly one year. It would therefore seem an unwarrantable risk to vaccinate any person taking continuous corticosteroids who has not been in actual contact with a smallpox case. In such circumstances vaccination could be carried out under cover of vaccinal globulin, which is distributed by the Public Health Laboratory Service and is administered by intramuscular injection in a dose that is dependent on body weight. For an average adult this is 0.5 g.

As yellow fever vaccine is also made up of live virus, theoretically it would seem prudent to avoid this vaccination in patients taking steroids.

Will there be any harmful effect in the recipient if the blood from a donor who takes diuretic or iron tablets is used for transfusion?

This is unlikely since patients requiring either iron or diuretic treatment should not at the same time be donating blood for transfusion. Iron entering blood after oral treatment or even if given parenterally is unlikely to produce symptoms in a recipient. Only free iron is toxic. Iron absorbed by mouth would be bound to transferrin in plasma, and parenteral iron would remain as part of a larger organic complex. Similarly, the dose of diuretic in, say, 200 ml of plasma in a unit of blood will be too small to produce an effect in most recipients. An extensive review of untoward effects of transfusion does not record any reported examples of recipients affected by such preparations.1

Is dried yeast of value in the treatment of multiple sclerosis?

I have not only never used dried yeast to treat multiple sclerosis but I have never seen any results from a controlled study. I would doubt very much whether it had any useful part to play in treating the disease. One could only presume by its contents that it might be a form of immunotherapy such as giving Corynebacterium parvum. Until I know more about the aetiology of the disease I do not think I would recommend it.

Reference