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Drug-Induced Myoclonus
Frequency, Mechanisms and Management

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Abstract

Myoclonus is a sudden, abrupt, brief, 'shock-like' involuntary movement caused by muscular contractions ('positive myoclonus') or a sudden brief lapse of muscle contraction in active postural muscles ('negative myoclonus' or 'asterixis'). Various disorders can cause myoclonus including neurodegenerative and systemic metabolic disorders and CNS infections. In addition, myoclonus has been described as an adverse effect of some drugs. Level II evidence is available to indicate that levodopa, cyclic antidepressants and bismuth salts can cause myoclonus, while there is less robust evidence to associate numerous other drugs with the induction of myoclonus.

The pharmacological mechanisms responsible for this adverse effect are not well established, although increased serotonergic transmission may be involved in the induction of myoclonus by several drugs. Drug-induced myoclonus usually resolves after withdrawal of the offending drug, but in some cases specific treatments are needed.

The term 'myoclonus' describes sudden, abrupt, brief, 'shock-like' involuntary movements caused by muscular contractions ('positive myoclonus') or sudden brief lapses of muscle contraction in active postural muscles ('negative myoclonus' or 'asterixis').[1,2] The aetiology of symptomatic myoclonus includes a number of neurodegenerative disorders, infections of the CNS, systemic metabolic disorders, physical agents, focal brain lesions and spinal cord injury, as well as a number of toxins including drugs.[3] Drug-induced myoclonus can be considered one of the most common causes of 'curable' myoclonus, and clinicians should have a high level of suspicion about the sudden appearance of myoclonus in patients being treated with drugs.[4] The drugs that have been reported as possibly inducing myoclonus, according to a Medline search using the terms 'myoclonus' and 'drug-induced', are summarised in table I.[5,6] The drugs most commonly associated with causing myoclonus are levodopa, cyclic antidepressants, serotonin reuptake inhibitors, bismuth salts and antiepileptic drugs (AEDs).

1. Clinical Features and Frequency

1.1 Antiparkinsonian Drugs

The first mention of levodopa-induced myoclonus was made by Cotzias et al.[8] in 1969 who observed myoclonus in a small number of patients treated with levodopa. Klawans et al.,[9] in 1975, described 12 patients who developed myoclonus after taking levodopa for at least 1 year. The myoclonic jerks were usually bilateral and symmetric and occurred during sleep (awakening the patient at some times), during periods of drowsiness and, less frequently, in the awake patient at rest. Seven patients also had choreiform dyskinesias.

Vardi et al.[10] reported six additional cases and showed that the dopamine agonist bromocriptine also induced myoclonus in these patients when this drug was substituted for levodopa. Other early reports of levodopa-induced myoclonus were single cases.[11,12]

Nausieda et al.[13] carried out a survey of levodopa-induced myoclonus and its relationship to sleep disruptions and hallucinations caused by levodopa in 100 patients with parkinsonism. They found a positive correlation between the prevalence and severity of myoclonus and the duration of levodopa therapy. Levodopa-induced myoclonus was a relatively late complaint (this complication was present in 50% of patients after 10 years of levodopa use) and preceded the presence of waking hallucinosis in many instances. Sleep studies showed that levodopa-induced myoclonus was usually not associated with spontaneous awakening.

Tandberg et al.[14] reported on a community-based survey of sleep disorders in 245 patients with Parkinson's disease (some recently diagnosed and, therefore, not receiving levodopa therapy) and two control groups (100 healthy persons and 100 patients with diabetes mellitus). Although the frequency of patients with nocturnal myoclonus was significantly higher in the Parkinson's disease group than in the control groups (24.3% vs 11%), the frequency of this symptom in the control groups was also relatively high.

Luquin et al.[15] reported levodopa-induced myoclonus in 6 of 168 patients with levodopa-induced dyskinesias. Marconi et al.[16] described myoclonus in 10 of 15 patients with advanced Parkinson's disease (most of them had been receiving levodopa therapy for at least 10 years) and dyskinesias.

In addition to the 'typical' levodopa-induced myoclonus described by Klawans et al.,[9] case reports of small numbers of patients (five or less) have indicated that levodopa can induce asterixis,[17] an acute encephalopathy with myoclonus and periodic triphasic waves on the EEG[18] or seizures, myoclonus and giant somatosensory-evoked potentials.[19]

Besides levodopa, other antiparkinsonian drugs have been reported to induce or elicit myoclonus, including bromocriptine,[10,20] amantadine[21] and entacapone used as an adjunct to levodopa.[22] However, the robustness of the evidence for causality is less than with levodopa (see table I).

1.2 Antidepressants and Lithium

Cyclic antidepressant drugs (e.g. imipramine, maprotiline, clomipramine, desipramine, doxepin), alone or in combination with lithium, can induce reversible action myoclonus, even when used at nontoxic doses.[23-47] Garvey and Tollefson[32] re-

Table I. Drugs reported to induce myoclonus; the class of evidence has been determined using the American Academy of Neurology 1993 levels of evidence[7][a]

Drug	Level of evidence
Antiparkinsonian drugs	
Levodopa[8-19]	II
Bromocriptine,[10,20] amantadine,[21] entacapone[22]	III
Antidepressant drugs	
Cyclic antidepressants[23-47]	II
Serotonin reuptake inhibitors,[48-56] monoamine oxidase inhibitors,[49,57-63] lithium[34,64-68]	III
Dopamine-blocking agents	
Antipsychotic drugs[39,44,69-73] including clozapine,[38,74-78] metoclopramide,[79,80] sulpiride[81]	III
Bismuth salts[70-73,82-97]	II
Antiepileptic drugs[b]	
Valproic acid (sodium valproate),[98,99] carbamazepine,[100-103] phenytoin,[104,105] gabapentin,[106] lamotrigine[107]	III
Opiate drugs	
Morphine and its derivatives (administered intravenously or intrathecally),[108-120] fentanyl,[121-125] methadone,[126,127] pethidine (meperidine),[128] norpethidine,[129] hydrocodone[130]	III
Antineoplastic drugs	
Chlorambucil,[131-134] prednimustine,[135-137] busulfan plus cyclophosphamide,[138] ifosfamide[139]	III
Anti-infective drugs	
Penicillin [140-147]	III
Carbenicillin,[145] ticarcillin,[148] cephalosporins,[149-153] imipenem,[154,155] piperacillin[156] quinolones,[157,158] piperazine,[159] isoniazid[160] aciclovir (acyclovir)[161]	III
Anxiolytics	
Buspirone,[162,163] lorazepam,[164] midazolam,[165] carisoprodol,[166] benzodiazepine withdrawal[167,168]	III
Cardiovascular drugs	
Propafenone,[169-171] flecainide,[172] diltiazem,[173] nifedipine,[174] buflomedil,[175] veratramine[176]	III
General anaesthetic drugs	
Propofol,[177,178] etomidate,[179-182] enflurane,[183,184] choralose[185,186]	III
Other drugs	
Drugs used in spinal anaesthesia,[187] antihistamines,[188-190] physostigmine,[191] tryptophan,[192,193] diclofenac,[194,195] cobalamine supplementation after cobalamine deficiency,[196] cimetidine[197]	III

a Class I: evidence provided by one or more well-designed, randomised, controlled trials; class II: evidence provided by one or more well-designed clinical studies such as case control, cohort studies, etc.; class III: evidence provided by expert opinion, nonrandomised historical controls or case reports of one or more patients.

b Although more frequent with supra-therapeutic doses, myoclonus has also been reported when these drugs are taken at therapeutic doses.

ported that 30% of 98 patients treated with cyclic antidepressants experienced myoclonus, although in only 9% was this adverse effect clinically significant. Cyclic antidepressant-induced myoclonus may be associated with EEG abnormalities[26] and enlarged cortical somatosensory evoked potentials,[36,38,39] although these abnormalities have not been found by other researchers in a single-patient study.[35] More recently, Evidente and Caviness[47] reported the presence of a focal cortical transient myoclonus in a patient receiving doxepin and lithium.

Level III evidence indicates that serotonin reuptake inhibitors can induce myoclonus,[48-56] although this movement disorder is most frequently associated with the so-called 'serotonin syndrome'. According to the first review by Sternbach,[198] the serotonin syndrome was most commonly the result

of the interaction between serotonergic agents and monoamine oxidase inhibitors; the most frequent clinical features are changes in mental status, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor. Apnoea and coma[199] and EEG abnormalities such as triphasic waves have also been reported in patients experiencing the syndrome.[200] The serotonin syndrome has been also reported with nonselective serotonin reuptake inhibitors[201,202] or SSRIs administered alone[199,203-209] or in combination with buspirone,[162,210] isocarboxazid and methylphenidate,[211] lithium,[212] lithium and amitriptyline,[213,214] and pethidine.[57]

Monoamine oxidase inhibitors, mainly phenelzine,[49,57-63] and lithium[34,64-68] can also induce myoclonus, according to level III evidence.

1.3 Dopamine Antagonists

Various types of dopamine antagonists, such as antipsychotics[39,44,69] (including the atypical antipsychotic clozapine[64,74-78]), metoclopramide,[79,80] clebopride and sulpiride[81]have been reported to induce myoclonus (see table I).

The reports of antipsychotic-induced myoclonus are related to typical antipsychotics. Tominaga et al.[70] described 'tardive myoclonus' as persistent postural myoclonus that was a late complication of antipsychotic treatment. Later on, the same group reported that 38% of 60 patients receiving long-term antipsychotic therapy showed postural myoclonus, which was more frequent in male patients. The patients with myoclonus had been given significantly higher doses of antipsychotics than those without myoclonus.[71] Little and Jankovic[72] reported a case of tardive myoclonus within 5 months of antipsychotic withdrawal. Tardive myoclonus was present in 1 in 100 patients with tardive syndromes who were taking sulpiride and clebopride followed up in five movement disorders units.[81]

Interestingly, Staedt et al.[73] have recently reported the presence of nocturnal myoclonus syndrome-related insomnia in the all-night polysomnography of ten schizophrenic patients receiving long-term antipsychotic therapy.

1.4 Bismuth

Abuse of bismuth can induce a toxic encephalopathy with generalised, asymmetric, action induced and stimulus-sensitive myoclonus, ataxia, confusion and, in severe cases, convulsions, coma and death.[82-97] EEGs usually show, as a nonspecific finding, frontotemporal slow waves and sometimes spike-and-wave activity. Although this encephalopathy improves after drug withdrawal, a 10% risk of mortality and/or tardive neuropsychiatric sequelae has been reported.[85] Neurochemical findings include increased CSF 5-hydroxy-indoleacetic acid levels.[92] The metal chelator dimercaprol increases the renal clearance of and improves the clinical signs of encephalopathy associated with bismuth.[88,92,93]

1.5 Other Drugs

1.5.1 Antiepileptic Drugs

Although some AEDs are used in the treatment of some types of myoclonus, not all AEDs are antimyoclonic;[4] moreover, some AEDs can induce or aggravate myoclonus. Overdoses of valproic acid,[98,99] carbamazepine[100-103] and phenytoin[104,105] have been associated with myoclonic encephalopathy. Supra-therapeutic doses of gabapentin[106] and lamotrigine[107] can also induce reversible myoclonus (see table I for level of evidence).

1.5.2 Opiate Drugs

Morphine administered either intravenously or intrathecally can induce myoclonus (see table I for level of evidence).[108-120] In single case reports, morphine-induced myoclonus has been reported to improve in patients treated with clonazepam,[215] midazolam infusion[216] and dantrolene[217] and in experimental models with ketamine.[218]

Myoclonus has also been reported to be induced by other opiate derivatives, such as fentanyl or its withdrawal,[121-125] methadone,[126,127] pethidine (meperidine),[128] norpethidine[129] and hydrocodone (see table I for level of evidence).[130]

1.5.3 Antineoplastic Drugs

The nitrogen mustard chlorambucil can induce myoclonus, both in overdose situations and at therapeutic doses (see table I for level of evi-

dence).[131-134] EEG abnormalities seen in patients with chlorambucil-induced myoclonus include generalised slowing or paroxysms of high-amplitude spike-wave activity. Both the myoclonus and EEG abnormalities resolve after withdrawal of the treatment.

Other antineoplastic drugs that have been reported to induce myoclonus include prednimustine,[135-137] busulfan plus cyclophosphamide[138] and ifosfamide (see table I for level of evidence).[139]

1.5.4 Anti-Infectives

Penicillin,[140-147,219,220] carbenicillin,[145] ticarcillin,[148] some cephalosporins,[149-153] imipenem,[154,155] piperacillin,[156] and quinolones[157,158] can induce a neurotoxic syndrome with encephalopathy and nonrhythmic, asymmetric and stimulus-sensitive myoclonus. This adverse effect is most common in patients with renal dysfunction.

Piperazine drugs, used as antihelmintic agents,[159] and the antituberculous drug isoniazid[160] have also been reported to induce myoclonus (see table I for level of evidence).

Aciclovir (acyclovir), a synthetic purine nucleoside analogue, is used in the treatment of herpes simplex and varicella zoster virus infections. This drug blocks replication by inhibiting viral DNA synthesis and is eliminated by the kidneys. A rare reversible encephalopathy occurs in <1% of patients treated with conventional doses. Disorientation and confusion develop initially, followed by a florid delirium with hallucinations, dysarthria, restlessness and tremor and, in severe cases, myoclonus and seizures. Patients with renal insufficiency and bone marrow transplantation recipients are predisposed to this encephalopathy. Symptoms usually improve upon discontinuation of the drug.[161]

1.5.5 Anxiolytics

Induction of myoclonus has been reported with some anxiolytic drugs including buspirone,[162,163] lorazepam,[164] midazolam[165] and carisoprodol (see table I for level of evidence).[166] Withdrawal from benzodiazepine treatment can also induce myoclonus.[167,168]

1.5.6 Miscellaneous

Other drugs that have been reported to induce myoclonus (level III evidence) are: some drugs used to treat cardiovascular diseases;[169-176] general anaesthetic drugs such as propofol,[177,178] etomidate,[179-182] enflurane[183,184] and choralose;[185,186] drugs used in spinal anaesthesia[187] antihistamines;[188-190] physostigmine;[191] tryptophan;[192,193] diclofenac[194,195] and cobalamine used as a supplement in cobalamine deficiency.[196]

The histamine H_2 receptor antagonist cimetidine can cause a dose-related acute encephalopathy, especially in patients with hepatic or renal dysfunction or in the elderly. The encephalopathy includes confusion and mild disorientation, occasional progressive cognitive impairment and rarely toxic psychosis with hallucinations, myoclonus and abnormal EEGs. The encephalopathy gradually abates after drug withdrawal.[197]

2. Mechanisms

The two neurotransmitter systems most frequently implicated in the pathophysiology of different causes of myoclonus are the serotonergic and GABAergic systems. The contribution of other neurotransmitters such as glycine, dopamine, excitatory amino acids and acetylcholine has also been shown in experimental models and humans.[4] Pharmacological mechanisms of drug-induced myoclonus have not been completely elucidated. The most extensively studied examples have been myoclonus induced by levodopa, cyclic antidepressants, serotonergic drugs and benzodiazepines.

2.1 Levodopa

Klawans et al.[221] attempted to elucidate the pharmacology of levodopa-induced myoclonus in an open-label study using selected drugs and monitoring the response to their withdrawal or addition. They demonstrated that the withdrawal or addition of anticholinergics, withdrawal of amantadine or addition of propranolol did not induce any change in the severity of myoclonus. As expected, increasing the dose of levodopa worsened the severity of the myoclonus, whereas decreasing the dose improved it. The serotonin antagonist methysergide improved myoclonus in all 12 patients (and stopped it completely in seven of the patients). For this reason, the authors suggested that a serotonergic mechanism may contribute to the aetiology of levodopa-induced myoclonus.

In addition, these investigators described an improvement in 5-hydroxytryptophan (5-HTP)-induced myoclonus in guinea pigs with long-term pretreatment with levodopa or dopamine receptor agonists; in contrast, they reported a worsening with long-term pretreatment with haloperidol.[221,222] These data suggest a role of dopaminergic mechanisms in myoclonic disorders.

Levodopa elicits myoclonus in rats pretreated with nialamide and pimozide, which is blocked by the α_1-adreneoceptor antagonist prazosin, suggesting a role of the adrenergic system.[223]

2.2 Cyclic Antidepressants

Klawans et al.[221] performed an experiment in guinea pigs to assess the behavioural effect of subthreshold doses of the serotonin precursor 5-HTP given alone and in conjunction with the tricyclic antidepressant imipramine. Although neither imipramine nor 5-HTP given alone induced myoclonus, the combination of these two drugs led to myoclonus. In addition, antagonists of noradrenaline (norepinephrine), dopamine and acetylcholine receptors failed to block the potentiation of myoclonus with imipramine. These data suggest that imipramine acts as a direct or indirect serotonin agonist.

2.3 Serotonergic Drugs

The implication of the serotonergic system in some forms of myoclonus was first demonstrated in 1971 by Lhermitte et al.[224] These investigators described a marked improvement of posthypoxic action myoclonus with 5-HTP in an open-label study of patients following cardiorespiratory arrest. This model of myoclonus has been connected with a serotonergic deficiency disorder and usually improves not only with treatment with 5-HTP but also with other drugs promoting serotonergic activity such as paroxetine[225] and fluoxetine combined with 5-HTP.[226]

Paradoxically, myoclonus can also be associated with increased serotonergic transmission. Giménez-Roldán et al.[225] reported a patient with persistent action myoclonus after an episode of asphyxia, which was aggravated by 5-HTP and sodium valproate and improved dramatically with the serotonin antagonist methysergide. In addition, serotonin reuptake inhibitors can induced isolated myoclonus[48-56] or myoclonus as a part of the serotonin syndrome.[198-209]

The best known model of myoclonus induced by increased serotonergic transmission is 5-HTP-induced myoclonus in guinea pigs.[227-234] In this model, myoclonus can also be induced by the administration of 5-HTP plus a monoamine oxidase inhibitor or agents acting as serotonin receptor agonists; it is abolished by treatment with central decarboxylase inhibitors and agents that block serotonin receptors such as methysergide and cyproheptadine.[228] The interaction between serotonin 5-HT_{1A} and 5-HT_2 receptors seems to be necessary to induce myoclonus, since selective agonists for 5-HT_{1A} and 5-HT_2 receptors do not induce myoclonus when given individually.[232,234]

2.4 Benzodiazepines

The primate *Papio papio* shows two different types of myoclonus. One type, induced by fotic stimulation (intermintent luminous stimulation) preceded by paroxysmal discharges, is blocked by lorazepam and other benzodiazepines. In contrast, the other type of myoclonus may be induced or facilitated by lorazepam and, to a lesser extent, diazepam. This type of benzodiazepine-induced myoclonus is blocked by drugs that increase brain GABA levels.[235,236] These findings suggest that benzodiazepine-induced myoclonus is caused by antagonism of the GABAergic system.

3. Management

Because the list of drugs that can induce myoclonus is long and growing (table I), and many descriptions arise from single-patient case reports, the management of drug-induced myoclonus is not well established in most instances. Withdrawal of the offending drug usually leads to the gradual resolution of myoclonus. Therefore, it seems reasonable to withdraw the offending drug whenever possible.

Regarding specific treatments, levodopa-induced myoclonus improves with reduction of the levodopa dose and with the administration of the serotonin receptor antagonist methysergide.[191] In a single case report of tricyclic antidepressant-induced encephalopathy with myoclonus, an improvement

occurred with the administration of the anticholinesterase physostigmine.[26] The serotonin antagonists methysergide and cyproheptadine also improve myoclonus or the serotonin syndrome induced by serotonin reuptake inhibitors.[228] Recovery from myoclonic encephalopathy due to bismuth salts may be accelerated by increasing renal clearance with the metal chelator dimercaprol.[88,92,93] Finally, as discussed in section 1.5.2, improvement of morphine-induced myoclonus has been reported with clonazepam,[215] midazolam infusion[216] and dantrolene.[217]

To our knowledge, the potential usefulness of the main drugs used in the treatment of other causes of myoclonus, such as valproic acid, clonazepam, piracetam, 5-HTP (paradoxically this drug can also induce myoclonus) and primidone, has not been proven, with the exception of the improvement of morphine-induced myoclonus with clonazepam.[215]

4. Conclusions

Many drugs that have been reported to induce myoclonus. However, the exact frequency of this drug-induced effect is not well known because for many of these drugs, experience is limited to case reports or short series. There are diagnostic difficulties and methodological problems in studies of drugs and myoclonus, such as the experience for many drugs being limited to case reports or short series. Moreover, according to the American Academy of Neurology levels of evidence,[7] there is only class III evidence of this adverse effect for most of the offending drugs (table I).

The drugs that have been reported most frequently as a cause of myoclonus are levodopa, cyclic antidepressants, serotonin reuptake inhibitors, bismuth salts and AEDs. The pharmacological mechanisms of drug-induced myoclonus are not well established, but the contribution of effects on the serotonergic system in myoclonus induced by levodopa, cyclic antidepressants and serotonin reuptake inhibitors has been suggested. The potential role of other neurotransmitter systems such as dopamine and GABA is not well established. In most cases, withdrawal of the offending drug leads to the resolution of myoclonus, although specific treatments may be life saving in some situations, such as myoclonic encephalopathy associated with bismuth abuse.

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