

Neurological Effect of Drugs: An Overview

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Abstract

Each drug shows two types of effects, one is useful or wanted therapeutic effect and other is harmful or unwanted secondary effect. One of the common and known effects of drug is on the central nervous system (CNS) or peripheral nerves which results into disturbances in patient's memory, sleeping habit and daily biological rhythms. The outcome of this review appraised herein will help the workers of this field to understand the drug-induced iatrogenic neurological disorders, neurotoxicity, drug reactions and drug-disease interactions.

Keywords: Drug; Central Nervous System (CNS); Neurotoxicity; Drug Reactions

Introduction

A drug is a chemical compound used for the diagnosis, treatment and prevention of diseases. Even if any drug is tested and approved for the treatment of any disease usually comes with adverse reactions or side effects [1]. Adverse drug reactions can also be one of the possible causes of injury or death of patients undergoing medical treatments [2]. Side effects of any drug may vary from simple, such as headaches to serious, such as carcinoma [3]. Side effects are usually harmful to humans, but sometimes can also be an alternative for other uses [3]. Viagra is one example of such types of drugs [3]. Therefore, it is highly desirable to automatically discover new targets for known drugs and to understand the mechanisms that cause side effects for target-specific treatments [3]. This article includes discussion of drug-induced neurological disorders, adverse drug reactions, drug-disease interactions, iatrogenic neurological disorders, and neurotoxicity caused by various drugs. We have focused on the most famous drugs like Glucocorticoids which may cause myopathy, visual blurring, tremor and psychosis [4]. Anticholinergics are the possible cause of confusion, memory problems, incoherent speech and disorientation [5]. Contraceptive drugs show side effects like headaches, mood changes and visual changes with contact lenses [6]. Neurological effects of Antiepileptic, Antipsychotic, Antimalarial, Anti-tuberculosis, Methotrexate, Monoclonal Antibody, Nonsteroidal anti-inflammatory drug (NSAID), Antibiotics, Antihistamines, theophylline and Amphetamine have also been discussed.

Neurological effect of drugs

Anticholinergic drugs

Anticholinergic therapy is a muscarinic receptor antagonist. Muscarinic receptors in the brain play a significant role in cognitive function. There is growing awareness that antimuscarinic drugs could have adverse effects on central nervous system (CNS) that may vary

from headache to cognitive impairment and episodes of psychosis. But that are recorded only in 10% of the total patients. Highest ratios of adverse CNS events were recorded in patients receiving oral oxybutynin, which would be expected from its propensity to cross the BBB. Few CNS adverse events were observed for trospium chloride, the transdermal delivery forms of oxybutynin (patch and gel) and fesoterodine. In patients taking overactive bladder (OAB) drugs; headache, somnolence, and dizziness are the common side effects. However, the other effects may also be associated are cognitive impairment, confusion, fatigue, psychotic behavior, and insomnia. The side effects may range from mild symptoms such as drowsiness to severe intoxication (manifested by hallucinations), severe cognitive impairment, and even coma. Hallucinations and episodes of psychosis following the use of oral oxybutynin or tolterodine have also been reported [5].

Methotrexate (MTX)

Methotrexate has its role for prophylaxis and treatment of CNS and in systemic control of leukaemia. MTX can cause neurotoxicities leading to leukoencephalopathy that can be seen as white matter hyperintensities on Magnetic Resonance Imaging (MRI). The clinical significance of these white matter changes is unknown [7].

Anti-tuberculosis drugs

Isoniazid

The mechanism of action of first-line anti-tuberculosis therapeutic agent isoniazid (INH) is still unclear [8]. Isoniazid-related toxicities are uncommon. The most common adverse effects of these drugs are on liver, manifested most often by enzyme elevation, followed by the effects on nervous system. Both the peripheral and central nervous systems are susceptible to the effects of isoniazid. These effects on nervous system includes restlessness, insomnia, headaches, muscle twitching, psychiatric symptoms, seizures, peripheral neuropathy, optic neuropathy and, less commonly cognitive impairment. Patients with isoniazid-induced peripheral neuropathy report symptoms such as lower extremity burning and paraesthesias. Weakness or upper extremity involvements are less common symptoms associated with this drug therapy [9].

Rifampicin

Rifampicin is an inhibitor of the beta-subunit of the ribonucleic acid (RNA) polymerase of prokaryotes, including *Mycobacterium tuberculosis*. Peripheral nervous system and CNS side effects are rare but could include a headache, drowsiness, ataxia and dizziness. Also, since rifampicin is known to cause an orange discoloration of body fluids, it may not be surprising that xanthochromia of the Cerebrospinal fluid (CSF) has been connected to rifampicin therapy. Rifampicin was found associated with a proximal myopathy reported in one patient [10].

Ethambutol (EMB)

This drug targets the biosynthesis of the cell wall [11]. There are only few reports of a sensory peripheral neuropathy with EMB. The most common and serious nervous system complication of EMB is a retro-bulbar optic neuropathy that is characterized by decreased visual acuity, defective colour discrimination and a normal fundoscopic examination. EMB toxicity depends on dose and duration of therapy. Patients receiving more than 2 months of EMB in the treatment of tuberculosis have been reported incidence of retrobulbar optic neuropathy. Patients taking EMB should undergo a baseline assessment of visual acuity and colour discrimination testing. They should be asked about vision changes at each visit while receiving therapy [9].

Non-steroidal anti-inflammatory drug (NSAID)

NSAID drugs reduce inflammation and relieve fever and pain by inhibiting the cyclooxygenase pathway [12]. Aseptic meningitis one of important neurological side effect that referred to the use of NSAID [13]. One study found that rats (systemic lupus erythematosus (SLE)-susceptible mice) developed meningitis when exposed to ibuprofen for a longer period of time. The mice developed meningitis, only if exposed to ibuprofen and not to ketoprofen, explaining that not all the NSAID are responsible for meningitis [12]. Available data

and reports suggest that NSAID drugs develop meningitis in people with autoimmune diseases and in those who have a natural immunity to the drug [12]. Overuse of the drug during medication could result in a refractory daily chronic headache. That can be resolved by stopping the use of analgesic [13].

Glucocorticoids

Glucocorticoids are the steroid hormone released by the adrenal gland under control of hypothalamic-pituitary-adrenal axis. Steroid receptors are expressed in many locations of the brain for regulation of various neurotransmission including serotonin and dopamine. The use of corticosteroids is strongly associated with the development of psychiatric/neurological side effects. These effects are due to the high expression of glucocorticoid receptor in the brain, and their long-term modulation. These neurological complications include myopathy, mood disturbance, anxiety and insomnia. Seizures can be seen at higher doses but it is an unusual side effect. Brain atrophy and decreasing volume of hippocampal due to reduced blood flow to the brain area are responsible for cognitive functions [14].

Antiepileptic drugs (AED)

Epilepsy requires long-term (AED) therapy [15]. AEDs exert their effects principally on one or more of the major classes of molecular targets on neuronal cell membranes which are voltage-gated sodium and calcium channels, ionotropic glutamate receptors, and gamma-aminobutyric acid (GABA) receptors [16]. There are significant differences in adult between the newer AEDs in terms of their Psychiatric and behavioural side effects (PBSEs) profiles. Patients taking gabapentin and lamotrigine experience significantly fewer PBSEs as compared to those who are taking levetiracetam. Patient with a psychiatric history doubles the chances of experiencing PBSEs [17]. All AEDs may impair cognition in children, but the side effects are usually modest for monotherapy when anticonvulsant blood levels are within the standard therapeutic ranges [18].

Antimalarial drugs

Till now, malaria control has relied upon the traditional quinolone and its related agent. The most common of them with neurotoxic effect is the Mefloquine [19]. Mefloquine interferes in digestion of haemoglobin in the blood at different stages of malaria life cycle. As a result, the haem which is released during haemoglobin breakdown develops toxicity thereby killing the parasite with its own toxic waste. Some particularly neuropsychiatric reactions have been reported as a result of this process [20]. In 40% of the total patients some neuropsychiatric adverse effects can appear. Among those sleep disturbances, dizziness, anorexia, ataxia, and fatigue are common. More serious adverse effects like panic attacks, paranoid delusions, convulsions, acute psychosis, suicidal ideation, disorders of mood are rarely noticed. The precise mechanism of serious neurologic and psychiatric reactions is still unknown. The possible mechanisms may include binding to neuroreceptors, cholinesterases, inhibition of sarcoendoplasmic reticulum ATPase (SERCA), and interference with the cellular Ca^{+2} homeostasis. Accumulation in the CNS and reductions in CNS efflux in individuals possessing certain multidrug resistance protein 1 (MDR1) polymorphisms has also been reported [21].

Amphetamines

Amphetamines are a group of drugs that increase the activity of the certain chemical compounds in the brain (stimulant drugs). This group include methamphetamine (Meth) and its derivative, 3,4-methylenedioxymethamphetamine (MDMA). Their potential for abuse and dependency is high and they are often for their euphoric and energy-producing effects. Some serious health effects of using amphetamine like anxiety, depression and memory disturbance has also been seen in patients. Amphetamines have a long-term outcome that includes brain injury and neurotoxicity, Paranoia, Hallucinations, Cravings for the drug, Convulsions, Respiratory problems, Loss of coordination, Obsessive behaviour and development of Parkinson's disease. Acute effect of high dose is Gliosis [22], it also may cause Chorea, Gray and White matter abnormalities [23]. Methamphetamine action on the brain is to elevate the levels of extracellular monoamine neurotransmitters (dopamine, serotonin, norepinephrine) by enhancing their release from the nerve endings [22].

Antibiotics**Penicillins**

Penicillin can cause a wide spectrum of neurotoxic manifestations including encephalopathy, behavioural adjustments, seizures, myoclonus as well as non-convulsive states epileptics (NCSE). A group of CNS disease has been described as a risk for encephalopathy associated with beta-lactam use. Penicillin has an inhibitory effect on GABA transmission because of their beta-lactam ring structure, which has comparable structural functions to those of GABA neurotransmitters. Piperacillin has been implicated in cases of tardive seizures. Benzylpenicillin has the most epileptogenic capacity, independent of CSF concentrations of the antibiotic. Flucloxacillin induces irritable patterns on electroencephalogram (EEG) such as bursts of spikes and polyspikes [24].

Cephalosporins

First generation cephalosporins can result in neurological disorders such as myoclonus, non-convulsive status epilepticus (NCSE), tardive seizures, encephalopathy, truncal-asterixis, seizures and coma. EEGs of patients showed diffused slowing with triphasic waves indicate toxic-metabolic encephalopathy. Second, third and fourth generation neurological effects range from encephalopathy to non-convulsive status epilepticus. This also happens in the cases of renal impairment in those with normal creatinine clearance. Decreased creatinine clearance, impaired renal characteristics and extra dosage of medication have been defined as impartial risk factors for neurotoxic outcomes [24].

Aminoglycosides

Aminoglycosides cause ototoxicity, peripheral neuropathy, encephalopathy and neuromuscular blockade. Gentamicin cause peripheral neuropathy and encephalopathy. Some other studies have described brain lesions after intrathecal gentamicin administration. The patient develops multiple small separated lesions in mesencephalon and pons that are characterized by axonal loss, oligodendroglial, astrocytic, as well as an inflammatory response [24].

Antihistamines

There is a high risk of adverse effects in the CNS associated with an antihistamine. The effects are more significant with first-generation. The lipophilic molecules that can cross the blood-brain barrier easily affect dopaminergic, alpha-adrenergic, serotonergic and muscarinic-cholinergic pathways. Most of the adverse effects of the use of first-generation appear as drowsiness, difficulty in concentration of mind, fatigue, sedation and reduced learning performance in children [25]. But the second-generation are lipophobic and shows mild neurologic side effects as there is less crossing of the blood-brain barrier. So, it provides a good alternative for the first generation [26].

Theophylline

Theophylline is used for the treatment of lung diseases such as asthma, also benefit in patients with nocturnal asthma or steroid-dependent asthma [27]. It may cause caffeine-like side effects as insomnia, anxiety and headache. These side effects are relieved as the person stops using the drug. These effects can be avoided by having low doses in the beginning and then increasing the doses slowly until a therapeutic blood level is reached. The toxic effect appears if the blood level exceeds 20 micrograms/mL [27].

Antipsychotic

Conventional antipsychotics, especially haloperidol and the second generation antipsychotic “risperidone” in higher doses are more likely to be associated with reports of extrapyramidal symptoms. They are less prevalent and more benign course with other second-generation antipsychotics, extrapyramidal symptoms may occur with higher doses. Young patients may be at high risk of extrapyramidal symptoms with the antipsychotic agent used. In a clinical trial, it was revealed that over 50% of the children and teenagers had extrapy-

ramidal symptoms and many required anticholinergic medication. Tremors and other “abnormal movements”, and headaches were also noted in some studies, especially in patients with pervasive developmental disorders. Seizure thresholds may be decreased by all antipsychotics, especially in combination. Only clozapine which is a second-generation antipsychotic associated with high risk of seizures [28].

Contraceptives

Oral contraceptives (OC) are a prescribed pills used for birth control. It is a combination of estrogen and progesterone. Nowadays there are three common types of contraceptives are in use combined estrogen-progesterone progesterone only and extended or continuous pills [29]. Among them combined types are very common where progesterone is the one that prevents the pregnancy and estrogen to control menstrual bleeding. These OC is a very effective contraceptive method, but on the other side it can shows some side effects [29].

A study showed a slight increase risk of developing multiple sclerosis (MS) in women using combined oral contraceptives (COC), even with adjusting other known confounders [30]. Exogenous estrogens like COCs could decrease the risk of MS, with anti-inflammatory properties [30]. However, contemporary COCs that contain low doses of estrogen in combination with one of a variety of progestin could increase the risk of MS or other autoimmune diseases [30]. Another study showed an affection in olfactory performance in women used OC with high doses of ethinyl estradiol (EE), which may has a negative effect on the natural endogenous estrogen production [31]. With the long-term uses it may results in a decreased olfactory performance. Even the cerebral venous sinus thrombosis (CVST) in other study has shown a sevenfold higher in productive women age with the use of OC as compared to those who are not using it [31].

Monoclonal antibody (mAbs)

Several neurological diseases have been associated with the use of (mAbs) including Progressive Multifocal Leukoencephalopathy (PML) that associated with Natalizumab, Rituximab, Alemtuzumab and Efalizumab. In addition, some patients with metastatic kidney or colon cancers presented with symptoms of posterior leukoencephalopathy such as cortical blindness, seizures, decreased mental status and MRI findings after infusion of bevacizumab. All existing forms of demyelinating neuropathies like Guillain-Barré syndrome GBS and Miller–Fisher syndrome, Lewis Sumner syndrome, multifocal motor neuropathy with conduction blocks, and chronic polyradiculoneuritis have been reported in patients receiving anti-tumour necrosis factor therapy, especially infliximab which is particularly immunogenic. The part played by anti-tumour necrosis factor therapy in the pathogenesis of demyelinating neurological disease yet to be elucidated. As reported, tumor necrosis factor is important in the inflammatory immune response and may have a role in the pathogenesis and evolution of multiple sclerosis [32].

Drugs used to treat tremor

Beta blocker

There is only one approved Beta blocker by United States Food and Drug Administration (FDA) that is considered as first line of treatment for essential tremor (level A) is propranolol. It acts by blocking effect of peripheral beta-2 receptors which is located in muscle spindles [33]. The side effect can categorize as acute, that occur in 8% of patients and chronic which occur in 17% of the total patients [34]. Propranolol showed many side effects such as lightheadedness, sleep disturbance, fatigability, bradycardia and headache. Though, the non-selective beta blocker are contraindicated, Atenolol, Sotalol and Metoprolol can be used for essential tremor (level B), however, their efficacy are lower [35].

Primidone

Primidone is an anticonvulsant drug that reduces high-frequency repetitive firing of neurons and acts as anti-tremor by alternation of trans-membranous sodium and calcium ion channel movement [36]. It is considered for essential tremor (level A) when there are contraindication for propranolol [37]. Primidone cause side effects that are commonly noticed during the course of treatment such as

drowsiness, nausea, vomiting, fatigue, and bone marrow suppression. It also has a chance to develop suicidal thoughts, so should be tapered after 6 month of use [33].

Benzodiazepines

Benzodiazepines are known for anxiolytic, anticonvulsant, sedative, muscle relaxant and anti-tremorgenic effects. Its activity appears by potentiate GABAergic neurotransmission which result in inhibition of action potential firing and thus, hyperpolarization of the cell membrane [33]. It is considered when the patient does not respond to propranolol and primidone as a first line of treatment for essential tremor (level C) [38]. Common side effects of benzodiazepine are cognitive impairment, drowsiness and drug dependence [33].

Pregabalin

Pregabalin act on the alpha 2-delta protein, an auxiliary subunit of voltage-gated calcium channel which reduces the synaptic release of several neurotransmitters thus the neuronal excitability [39]. It has a tremor-lytic action, although the effect on essential tremor is uncertain due to less authentic evidences [40]. Common side effects of pregabalin are peripheral edema, fatigue, asthenia, euphoria, thinking abnormal, disturbance in attention, confusional state, somnolence, tremor, amblyopia, blurred vision, diplopia, ataxia, balance disorder, incoordination, vertigo and dizziness [41].

Gabapentin

Gabapentin action is to reduce neuronal excitation and on an auxiliary subunit of voltage-sensitive calcium channel [42]. It is considered when the first line of treatment for essential tremor was failed [43] and can use as monotherapy when there is contraindication to use propranolol [33]. Common side effects of Gabapentin are dizziness, sedation and dry mouth [33].

Topiramate

Topiramate is known for its multifactorial action at Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid (AMPA) receptor sites and involves in potentiation of GABAergic transmission, blockade of voltage-dependent sodium channels and inhibition of excitatory pathways [44]. It is considered for the treatment of moderate to severe essential tremor (level B) [33]. The most common treatment-limiting adverse events in topiramate are concentration/attention difficulty, paresthesia, somnolence and nausea [33].

Immunoglobulin

The clinical use of intravenous immunoglobulin is common for the treatment of patients with primary immunodeficiencies [45]. Although a large number of clinical trials have explained that immunoglobulins are effective and shows a remarkable tolerance by the patients. Several adverse effects have been reported are the neurological disorders which include headache, aseptic meningitis, posterior reversible encephalopathy syndrome (PRES), seizure, abducens nerve palsy [46].

A case study presented a 35 years old Syrian male with history of Behçet's disease (BD) with its complexities of clinical symptomatology. He was on gamma globulin and triamcinolone (2.0 mg. daily), when he noted a tingling sensation of his fingers and complained of loss of balance and vertigo which had been present for nine months. However after neurologic consultation, this was attributed to the central nervous system manifestation of BD and then vitamin-B12 therapy was recommended [47].

Conclusions

In conclusion, adverse neurological side effects are not uncommon. Up to 40% of patients who are treated by anti-malarial drug experience neuropsychiatric disorder. Almost all antiepileptic drugs can impair cognitive function in children. However, the risk increases in polytherapy and history of psychiatric disorders. Moreover, clinical trials have found that 50% of children experience extra pyramidal

symptoms after use of antipsychotic medication. However, more benign and less prevalent symptoms in 2nd generation other than risperidone have been reported. Oral contraceptives have showed a sevenfold higher risk of developing cerebral venous sinus thrombosis (CVST) in productive women age with the use of OC as compared to those who are not taking it.

Adverse effects of drugs are rarely found in a case study report and often physician are not familiar with it. Recognition of patient at risk and identification of the serious adverse effect are the most important steps toward management. Less than 10% of patients receiving Anticholinergic drugs (mainly oral forms) exhibit multiple forms of CNS complications.

In order to anticipate the adverse effects, physicians should be encouraged to deep understanding of the mechanism of drug action. The use of monoclonal antibody, exhibiting the potentiality to counteract tumor necrosis would explain the pathogenesis of demyelinating neuropathy in patients who are receiving anti-tumour necrosis factor therapy, especially infliximab.

In some cases we can avoid the neurological side effect by minimizing the dose in the beginning or by stopping the medication like in the case of theophylline. Drugs used to treat headaches may end up by causing headaches that can be reversed only when the patient stop using the drugs. In some instances clinical monitoring of adverse effect is mandatory, especially when the drug course is long term. Using ethambutol for the treatment of Tuberculosis (TB) has to be in conjunction with visual acuity assessment due to retrograde -bulbar optic neuropathy. Long term use of the Glucocorticoids is strongly associated with the development of psychiatric and neurological side effects.

Patients with essential tremors who are medically treated should be aware of common side effects which varied from simple headache and drowsiness to a suicidal thoughts, drug dependence and cognitive impairment. Some antibiotics like penicillin and cephalosporins can cause a wide spectrum of neurotoxic manifestations ranging from seizures, encephalopathy, non-convulsive status epilepticus to tardive seizures in piperacillin. First generation cephalosporin making the severity of neurotoxic side effect differs from one type to another. There are some EEG changes recorded in Flucloxacillin and first generation cephalosporin that is why we recommend EEG to any patients on antibiotics having seizure. Second, third and fourth generation cephalosporin can be neurotoxic only in case of renal impairment so measuring the creatinine levels before giving these types of antibiotics is highly recommended. Amphetamine abuser may experience chronic side effects including brain injury, hallucinations and convulsions. They also have acute side effect like Gliosis with high doses. Aseptic meningitis is known to be one of the serious neurological side effects that referred to the use of NSAID. Ibuprofen is the NSAID that is mostly responsible to cause Aseptic meningitis, Aseptic meningitis are not seen in patients using ketoprofen.

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