

DRUG INDUCED DISORDERS SEEN IN THE ICU

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Drug induced neurologic disorders which are fairly routinely encountered in the intensive care unit (ICU) are reviewed below. Illustrative cases will be presented in an interactive manner in the accompanying course.

Drug Related Hyperthermic Syndromes

Drugs induce hyperthermia either through increased heat production or impaired heat dissipation. Increased motor activity, uncoupling of oxidative phosphorylation and impaired dissipation through vasoconstriction of cutaneous blood vessels lead to hyperthermia in both serotonin and sympathomimetic syndromes. Withdrawal of GABA agonists such as ethanol, benzodiazepines, baclofen and barbiturates result in hyperthermia through autonomic overstimulation.

Various drugs of abuse can produce a sympathetic toxidrome caused by modulation of central and peripheral catecholamine neurotransmitter function. These drugs include, but are not limited to cocaine, amphetamines and related substances including methamphetamine, "bath salts," methylphenidate, cathinone ("khat"), and MDMA ("ecstasy"). The typical clinical picture is one of adrenergic overdrive with increased sympathetic activity manifesting as tachycardia, tachypnea, diaphoresis, hypertension, hyperthermia, mydriasis, hyperreflexia, and tremor. Medical sequelae include acute coronary syndrome, heart failure, renal failure, and hepatotoxicity and electrolyte abnormalities. Rhabdomyolysis has been reported. Neurologic sequelae include acute encephalopathy, seizures, stroke (discussed further below) and coma.

Antipsychotics (neuroleptics) are commonly used in the inpatient setting for management of symptoms resulting from the development of hospital acquired delirium, decompensated dementia, and acute psychosis. Antidepressants are sometimes initiated during prolonged hospitalizations for situational depression and perhaps more commonly following acute ischemic stroke where there is evidence for their early initiation. Both antidepressants and antipsychotic agents are also frequently continued as part of an outpatient regimen for treatment of primary psychiatric disorders upon admission to the hospital. Neurologic complications relating to these drugs primarily arise when doses are increased or when other dopaminergic or serotonergic agents are added to the medication regimen in hospital.

A well-recognized complication of antipsychotic use is the neuroleptic malignant syndrome (NMS). NMS is typically characterized by a tetrad of mental status changes, fever, rigidity, and autonomic instability. As no specific diagnostic test exists, diagnosis is purely clinical. NMS must be recognized because of its potential to result in death. Published cases of NMS have suggested mortality rates as high as 25%, but with timely diagnosis and appropriate treatment survival rates can exceed 90%. Monitoring the serum creatine kinase may provide supportive evidence of the diagnosis and assess the risk of renal injury and response to therapy. Myoglobinemia and renal failure have been reported as strong predictors of mortality. Treatment involves discontinuation of anti-dopaminergic medications, IV hydration to protect against rhabdomyolysis, maintenance of normothermia, administration of dantrolene and/or bromocriptine, and supportive care. NMS is widely attributed to the overuse of certain medications however; an NMS-like syndrome (parkinsonism-hyperpyrexia syndrome) can also develop after abrupt discontinuation of medications with dopamine agonist activity. Reported cases have involved patients previously treated for idiopathic Parkinson's Disease whose medications were abruptly stopped or reduced. The approach to treatment is similar to NMS with immediate reintroduction of the patient's dopaminergic medications. This phenomenon highlights the importance of medication reconciliation at the time admission. A study performed at a large institution in the US reported that greater than one-third of patient admissions had medication errors, nearly half of errors were admission errors, and antidepressants and neurological agents were two classes among the top five most common classes involved in errors.

The serotonin syndrome is a potentially life-threatening drug reaction that results from therapeutic drug use, intentional self-poisoning, or inadvertent interactions between drugs. Excessive stimulation of serotonin-5-hydroxytryptamine (5HT)-1a or 5HT-2 receptors in the central nervous system is hypothesized to mediate these

reactions, which may be mild to severe. A number of medication classes including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, and herbal products can cause serotonin syndrome. The syndrome is a constellation of symptoms including encephalopathy, mydriasis, clonus, tremor, hypertonicity (legs>arms), fever and hyperactive bowel sounds. Often, only a few of the features are present. In the hospital, serotonin syndrome is most likely to occur when an opiate (most commonly fentanyl) or antiemetic is initiated in the setting of SSRI or SNRI use. Antidepressants taken in the outpatient setting are often overlooked when they are not continued in hospital. The majority of these agents have long half-lives, and continue to be biologically active for days to weeks. It is being increasingly recognized after cardiac arrest, when patients undergoing therapeutic hypothermia are treated with fentanyl infusions. Treatment is primarily supportive and involves removal of any potential triggers, aggressive control of hyperthermia, maintenance of adequate hydration, and control of blood pressure and tachycardia. Cyproheptadine, a 5-HT_{2a} antagonist, is recommended for moderate to severe serotonin syndrome.

Antimicrobial Induced Neurotoxicity

Innumerable neurologic sequelae of antimicrobial drugs have been reported in the literature however they rarely require attention in the ICU. Two that do deserve mention here.

Cefepime, a beta lactam antibiotic, is commonly prescribed in ICUs. Neurotoxicity may develop in some patients and is more likely to occur when critically ill patients with chronic kidney disease receive cefepime in doses that are not adjusted for renal function. Cefepime neurotoxicity typically manifests as encephalopathy with or without myoclonus, seizures or NCSE and is likely an overlooked cause of encephalopathy in the ICU. There is typically a delay of 3 to 5 days between the initiation of cefepime and onset of symptoms. The typical clinical scenario is a patient who develops a depressed level of consciousness and disorientation on average, 3 to 5 days after initiation of cefepime. The presence of myoclonus and kidney injury in this setting is suggestive of the diagnosis. Coma, leading to death has been observed in some cases and thus, a therapeutic trial of discontinuing cefepime in favor of an alternative antibiotic is justified. Discontinuation results in reversal of symptoms within several days. Since more widespread recognition of this syndrome began approximately 5-6 years ago, the frequency with which we are encountering this syndrome is declining.

The literature on fluoroquinolone induced seizures is not strong primarily because patients frequently have other comorbid factors which could potentially be responsible for the seizure (such as sepsis itself). In our experience of all the antimicrobials, fluoroquinolones are the most prone to triggering breakthrough seizures in epileptic patients, and can even cause de novo seizures in patients with no history of epilepsy. Levofloxacin is the biggest culprit but it is not clear if this is because of more frequent use in the hospital compared with the other fluoroquinolones.

Chemotherapy and Immunosuppressant Induced Neurologic Dysfunction

Posterior reversible encephalopathy syndrome (PRES) is a syndrome variably manifesting as acute onset of headache, encephalopathy, focal neurologic deficits and seizures. Characteristic MRI findings include bilateral asymmetric predominantly subcortical vasogenic edema, classically in the parietal and occipital lobes. PRES is typically reversible but can result in permanent morbidity when hemorrhages or infarcts occur and it has rarely been associated with a rare fatal phenomenon known as subacute diencephalic angioencephalopathy (SDAE). Any cytotoxic drug may be associated with PRES, most commonly cyclosporine, and less frequently, tacrolimus and rituximab. When PRES develops in a patient taking either tacrolimus or cyclosporine, the drug should, in most cases, be held at least temporarily. This often requires an increase or addition of alternative immunosuppressant agents, in order to reduce the risk of transplant rejection. Cases of PRES associated with sirolimus are rare and neurologic disease is rarely associated with everolimus. These decisions should be made in conjunction with a transplant specialist.

Corticosteroids can produce a myopathy resulting in variable degrees of weakness. The presentation is typically proximal muscle weakness and atrophy. Significant myopathy has been demonstrated at doses of 40 mg/day with prednisone. This problem is encountered by neurologists in the intensive care unit when they are consulted for failure to wean from mechanical ventilation or alternatively, when they have recurrent hypercapnic respiratory failure and cannot be liberated from noninvasive mechanical ventilation. Steroids may also cause psychosis which may require transfer to the intensive care unit for control, particularly upon initiation of steroids or administration of high doses.

Drug-Induced Cerebrovascular Disorders

Drug-induced stroke is uncommon; however, abuse of recreational drugs is a risk factor for stroke and is a fairly common cause of stroke among adolescents and young adults. Over-the-counter ephedra-like compounds (phenylpropanolamine, ephedrine, pseudoephedrine) have all been linked to stroke as well. Mechanisms of drug-induced ischemic stroke seen in the ICU include (1) sympathomimetic vasoconstriction (cocaine, amphetamines, lysergic acid diethylamide, phencyclidine), (2) vasculitis (amphetamines, cocaine, heroin), (3) cardioembolism due to endocarditis (IV drug injection), (4) enhancement of coagulation (cocaine), and (5) reversible cerebral vasoconstriction syndrome (RCVS) (cocaine, amphetamines, marijuana, etc). Mechanisms of drug-induced hemorrhagic stroke include (1) hypertension-induced arterial rupture with or without underlying vascular malformation (cocaine, amphetamines, and phencyclidine), (2) vasculitis (amphetamines, cocaine, heroin), and (3) rupture of septic aneurysm (any intravenous drug use).

In young adults (aged 15–44 years) with ischemic stroke, 12 have a history of recent illicit drug use and drug use is the probable cause of stroke in 5%. The etiologic evaluation of stroke is beyond the scope of this discussion. However, it is reasonable to obtain urine cocaine, PCP, and amphetamine screens in addition to the usual laboratory evaluation of stroke in young adults. Some substances can produce false-positive results on urine PCP and amphetamine screens, and the presence of a drug or its metabolite does not prove causality. Management of acute ischemic or hemorrhagic stroke should be performed according to usual standards of care, independent of drug use.

Drug Withdrawal

Agitated delirium and seizures suggests the possibility of a withdrawal syndrome. Withdrawal from alcohol or other GABA agonists such as barbiturates, baclofen and benzodiazepines can cause a life threatening withdrawal syndrome characterized by agitated delirium, tremor, autonomic instability, hallucinations and seizures. Alcohol withdrawal seizures are usually brief in duration and easily controlled by benzodiazepines (although high doses may be required) while baclofen and barbiturate withdrawal are more likely to result in refractory status epilepticus. If status epilepticus results from withdrawal of barbiturates, barbiturates will almost certainly be required to stop the seizures. Similarly, baclofen should be restarted, in addition to benzodiazepines, for seizures related to baclofen withdrawal.

Other

Neurologists are occasionally consulted urgently for evaluation of a 'blown pupil' and on examination the patient is found to be otherwise normal. A cursory discussion with the patient will often disclose a long-standing history of benign anisocoria, prior cataract surgery, or a poorly tolerated facemask used to deliver recent aerosolized anticholinergics (i.e. ipratropium).

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