Extrapyramidal Side Effects in the Psychiatric Emergency Service

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The benefits that neuroleptic medications provide in treating psychotic symptomatology in schizophrenia are well established (1). In addition, neuroleptic medications are often used to treat acute, psychotic episodes not related to schizophrenia, such as micropsychotic episodes among patients with personality disorders or posttraumatic stress disorder; acute psychosis from LSD, PCP, or cocaine intoxication; or psychotic states related to dementias and other neurological conditions. Neuroleptic medications are also often used for their acute sedative properties in treating agitated patients, both in psychiatric and nonpsychiatric settings.

In tandem with the benefits of neuroleptic medications are significant risks associated with their use. These risks are primarily acute and chronic neurological adverse effects involving voluntary and involuntary musculature.

This column focuses primarily on the acute side effects of neuroleptics, generally referred to as extrapyramidal side effects. These side effects are often seen as sequelae of acute neuroleptic treatment, often resulting in presentation to a psychiatric emergency service, such as an emergency room, a psychiatric emergency clinic in an emergency room, or a psychiatric consultation service in a general hospital. We discuss diagnosis, proposed etiology, and treatment of extrapyramidal side effects in the acute clinical setting.

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Extrapyramidal side effects

The most common extrapyramidal side effects are dystonias, parkinsonism, and akathisia (2). Dystonias are prolonged and unintentional muscular contractions of voluntary or involuntary muscles. Neuroleptic-induced parkinsonism is characterized by the triad of tremor, rigidity, and bradykinesia; it can closely resemble idiopathic Parkinson's disease caused by nigrostriatal degeneration. Akathisia is characterized by a patient's subjective sense of restlessness, along with such objective evidence of restlessness as pacing or rocking.

Extrapyramidal side effects are often quite uncomfortable for patients and may compromise compliance with an otherwise beneficial neuroleptic medication regimen. In addition, extrapyramidal side effects can be frightening to patients. They can also manifest, albeit rarely, as a life-threatening condition, such as laryngeal dystonia or dystonias of other musculature related to breathing. These rare side effects may be associated with withdrawal when a regimen of neuroleptic medication is discontinued, a condition known as withdrawal dyskinesia.

Another major acute side effect of neuroleptics is more ominous, neuroleptic malignant syndrome. Severe muscular rigidity, fever, an altered level of consciousness, and autonomic instability characterize neuroleptic malignant syndrome. It is a condition with significant mortality, although detection and treatment have greatly improved outcomes.

Tardive dyskinesia is a serious condition resulting in abnormal, unintentional choreoathetoid movements of the head, limbs, and trunk. It has a delayed onset associated with long-term treatment with neuroleptics. Because tardive dyskinesia does not occur in acute neuroleptic treatment, it is not discussed this column.

Neurobiology

The mechanisms by which neuroleptic medications exert antipsychotic effects is not precisely known. It is generally believed that antagonistic binding of dopaminergic D_2 receptors in the mesolimbic and mesocortical regions of the brain plays a major role. Unfortunately, neuroleptics are unable to bind dopaminergic neurons in these brain regions selectively; they bind to other regions of the brain that also have high dopaminergic activity. It is this antidopaminergic effect in the caudate nucleus and other basal ganglia nuclei that is thought to produce most of the neurological side effects of neuroleptic medications.

The basal ganglia are subcortical structures that mediate involuntary and voluntary muscular movements. The basal ganglia belong to the extrapyramidal system of the brain, so named because they are located separately from the axons of the pyramidal cells, large motor cortical neurons that send motor signals directly to the spinal cord.

Diagnosis

Clinically, disruption of basal ganglia neuronal circuits are most often exhibited as dystonic posturing, parkinsonism, and akathisia, but choreiform (dancing) or athetoid (writhing) move-

ments may occur as well. Symptoms generally occur within the first few days of treatment; parkinsonian symptoms generally appear between three and nine days after initiation of treatment. Dystonias frequently occur on the first day—usually within one to two hours after the first dose of neuroleptic is administered (3). Acute dystonias are characterized by brief or prolonged contractions of muscles, resulting in abnormal or unintentional movements and postures.

Several types of dystonia exist, each affecting a different muscular region. Torticollis involves spasms of cervical muscles, resulting in a contorted, twisted posturing of the neck. Trismus involves contraction of the jaw musculature and can result in lockjaw. In opisthotonus, arched posturing of the head, trunk, and extremities occurs. Laryngeal dystonia may cause difficulty in breathing. Oculogyric crises result from involuntary contraction of one or more of the extraocular muscles, which may result in a fixed gaze with diplopia.

The symptomatic triad of resting tremor, muscular rigidity, and bradykinesia characterizes neuroleptic-induced parkinsonism. The tremor is often described as a "pill-rolling tremor" of the fingers, with three to six oscillations per second and suppression of the tremor with intentional movement. The tremor may also affect other parts of the body, such as the lips and perioral muscles, resulting in a rabbit-like movement of the face. The muscular rigidity may be either the lead-pipe type or the cogwheel type, in which a tremor is superimposed on rigidity. Cogwheel rigidity may be revealed when an examiner attempts to passively flex the forearm of the patient at the elbow. A rhythmic, intermittent resistance may be encountered, as opposed to constant resistance, as in lead-pipe rigidity. Bradykinesia may be manifested as a mask-like facial expression or reduction of accessory limb movement or as a problem in initiating movements. Parkinsonian side effects may also include slowed cognition, worsening of negative symptoms, shuffling gait, and excessive salivation.

As mentioned previously, akathisia is characterized by subjective feelings of restlessness and often by objective signs of restlessness. Patients often report sensations of muscular discomfort, dysphoria, and agitation. This discomfort often causes patients to pace relentlessly, alternate between sitting and standing, or rock back and forth in a chair. Akathisia may appear at any time in a patient's treatment and is often underdiagnosed because it may be mistaken for anxiety or symptoms related to the primary psychosis.

This difficulty in diagnosis may be more pronounced in an emergency situation when an agitated patient is given neuroleptics acutely for sedation. The patient may develop akathisia and appear more agitated and activated after the first dose of neuroleptic. With such a presentation, administration of additional neuroleptic medication may appear to be the best treatment option, but it may make the patient even more restless and agitated.

With conventional neuroleptics such as haloperidol, the prevalence of akathisia is about 20 percent within the first three months of treatment (2). Akathisia is often the most treatment-resistant extrapyramidal symptom (5).

Newer, atypical neuroleptics appear to be associated with a reduced risk of acute extrapyramidal signs and symptoms (2), which may be related to their higher affinity for the 5-HT2A serotonergic receptor than for the D_2 receptor. Clozapine appears to have the lowest risk of causing extrapyramidal side effects, which may be related to its low affinity for D_2 receptors, a higher affinity for 5-HT2A serotonergic receptors, or an inherent protective anticholinergic effect (2). However, clozapine is associated with other serious risks, most notably agranulocytosis, an uncommon but potentially fatal suppression of bone marrow, as well as seizures and marked sedation. Patients on clozapine must have a white blood cell count every week for the first six months of treatment and biweekly thereafter for early detection of bone marrow suppression.

Risperidone, olanzapine, and other new neuroleptics also seem to be associated with fewer extrapyramidal side effects. The risks of risperidone in causing extrapyramidal side effects appear to be about halfway between those of conventional neuroleptics and clozapine (2). More data on olanzapine and other new, atypical neuroleptics need to be collected to gain an accurate assessment of their propensity to cause extrapyramidal side effects (9).

A few important patient- and treatment-related risk factors are associated with a higher incidence of extrapyramidal side effects. Young males have an increased susceptibility to develop extrapyramidal side effects, although the effects can and do occur in both sexes (1). The reasons for increased risk in males are not fully known but may be related to increased muscle mass in men. The incidence of extrapyramidal side effects also appears to be dose dependent. In addition, intramuscular dosing of neuroleptics may increase the chances of causing extrapyramidal side effects.

Treatment

The two basic principles of treating extrapyramidal side effects are withholding subsequent doses of the causative neuroleptic and starting pharmacological treatments. Often this step can be followed by switching to a neuroleptic with a lower incidence of associated extrapyramidal side effects, an atypical neuroleptic, if further treatment is needed.

Pharmacological treatments most commonly consist of anticholinergic and antihistaminergic medications. Benzodiazepines, beta-adrenergic antagonists (propranolol), beta-adrenergic agonists (clonidine), or dopamine agonists (amantadine) may also be used. Anticholinergics can be given either orally or intramuscularly for more severe forms of extrapyramidal side effects, such as acute oculogyric crises or dystonias impairing a patient's breathing. Trihexyphenidyl 2 to 8 mg per day and benztropine 2 to 8 mg per day are the most common anticholinergics given. Benztropine comes in an intramuscular form (usual doses are .5 to 2 mg) and generally reduces symptoms within one to two hours.

Benzodiazepines, beta-adrenergic antagonists, and beta-adrenergic agonists are usually used for akathisia; anticholinergics are usually not effective for akathisia. The dopamine reuptake inhibitor amantadine can also be used for symptoms related to parkinsonism. Acute extrapyramidal side effects tend

to resolve quite rapidly and without serious sequelae with dose reduction, withdrawal of the offending neuroleptic, or pharmacological treatment. Akathisia may be both difficult to detect and difficult to treat. It may take trials of benzodiazepines, beta-adrenergic antagonists, or beta-adrenergic antagonists to treat akathisia.

Conclusions

Extrapyramidal side effects are frequently encountered adverse consequences of acute neuroleptic treatment that are usually easily diagnosed and treated. Dystonias are the most common type of extrapyramidal side effects. Parkinsonism and akathisia are less common but are often more difficult to diagnose and to treat. Treatment for all types of extrapyramidal side effects is based on discontinuation of the neuroleptic medication, or switching to an atypical neuroleptic, and pharmacologic treatments.

It appears that the more that new neuroleptics incorporate nondopaminergic neurotransmitter systems, such as the serotonergic system, the less that risk exists for causing extrapyramidal side effects. Thus most research on extrapyramidal side effects is focusing on the atypical neuroleptics and on developing new medications based on a similar chemistry.

Clozapine has the lowest risk for causing extrapyramidal side effects. In the United States, clozapine is not used for acute treatment because of its adverse side effect profile; it is used as a treatment for refractory psychosis. In Europe clozapine is often used for a short time (one week) to stabilize a manic patient until a mood-stabilizing medication can take effect. Clozapine is then discontinued so that hematological side effects are not an issue. In the future, new medications based on the pharmacologic profile of clozapine may continue to pave the way for a decreased incidence of extrapyramidal side effects. ♦

References

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