Fortnightly review: Acute dystonia induced by drug treatment

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BMJ 1999;319;623-626

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Acute dystonia induced by drug treatment can be a side effect of treatment with antipsychotic drugs and other drugs, and it may occur at an early stage of treatment.[1 2] Acute dystonia is often frightening and may seriously disturb the relationship between the doctor and the patient. Therefore, every doctor who prescribes dopamine blocking agents should be familiar with the prevalence of and the risk factors for acute dystonia and should know how to prevent and treat the condition.

Summary points

- Acute dystonia induced by drug treatment can be caused by antipsychotic, antiemetic, and antidepressant drugs
- Acute dystonia caused by drug treatment can seriously disturb the relationship between doctor and patient and should be prevented
- Patients who develop abnormal positioning or muscle spasms within seven days of starting drug treatment or of a rapid increase in the dose of a drug may be diagnosed with acute, drug induced dystonia
- Biperiden 5 mg should be administered intramuscularly to treat the condition; this is nearly always effective within 20 minutes
- Risk factors for acute, drug induced dystonia include young age, male sex, use of cocaine, and a history of acute dystonia
- Drug induced dystonia can be prevented either by adding, during the first four to seven days of treatment, anticholinergic drugs to treatment with antipsychotic drugs or by starting treatment with atypical antipsychotics

Methods

We searched Medline and Embase for the period 1980-98 using the key terms extrapyramidal syndromes, dyskinesia, dystonia, movement disorders, side effects, and antipsychotics, and we checked the reference lists of the articles that we identified. This information supplemented our own research into extrapyramidal side effects induced by antipsychotic drugs.[3–5]

Prevalence and risk factors

Acute dystonia induced by antipsychotic drugs is described as "sustained abnormal postures or muscle spasms that develop within seven days of starting or rapidly raising the dose of the antipsychotic medication, or of reducing the medication used to treat (or prevent) acute extrapyramidal symptoms (eg anticholinergic agents)."[6] Whether acute dystonia occurs as a result of the use of antipsychotic drugs depends mainly on the presence of risk factors. Therefore, the prevalence varies widely—from 2% to 90%.[1 2] Patient related risk factors for acute dystonia are presented in the table. In patients aged 10-19 years the risk of acute dystonia is high but it decreases linearly with age; in patients over 45 years of age acute dystonia is rare.[7–12] Most studies have found that men are more likely to develop acute dystonia than women.[8–11] A history of acute dystonia has been identified as the most powerful predictor of the likelihood of a patient developing the condition.[8] Cocaine use was found to be a risk factor in a prospective study.[4] High potency antipsychotic drugs such as haloperidol, fluphenazine, and pimozide cause dystonia more frequently than do low potency drugs such as chlorpromazine and thioridazine.

The differential rates of dystonia which occur with different antipsychotic drugs might be explained by the receptor blocking ratio between dopamine and acetylcholine in the basal ganglia. The higher the ratio of dopamine-acetylcholine antagonism, the higher the risk of acute dystonia.[1] In fact, the intrinsic anticholinergic effect of low potency antipsychotic drugs decreases the risk of acute dystonia. When a patient is treated with high potency antipsychotic drugs a low starting dose is recommended because this reduces the risk of acute dystonia compared with a standard dose.[1 10] Atypical antipsychotic drugs such as olanzapine, sertindole, quetiapine, and a low dose of risperidone (<4 mg) are associated with a low incidence of acute dystonia.[13] Clozapine is the only known atypical antipsychotic drug that does not induce acute dystonia[13]; other atypical antipsychotic drugs all have the potential to induce acute dystonia at certain specific doses.[13] The mechanism underlying the reduced risk of atypical antipsychotics is not known.[13] Anticholinergic properties may reduce the risk of acute

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BMJ 1999;319:623–6

dystonia but are only present in olanzapine and clozapine. The balance between serotonin and dopamine blockade may also play a role in reducing risk.[13]

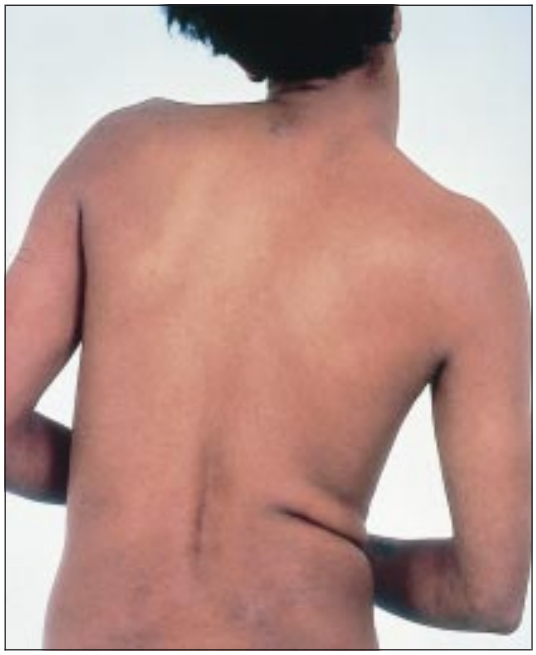
Pathophysiology

The pathogenesis of acute dystonia is still unclear. Since all antipsychotics bind to D_2 receptors, it has been suggested that blockage of these receptors in the caudate, putamen, and globus pallidus is partly responsible for causing acute dystonia.[14] This would also explain the diminished propensity of these drugs to cause acute dystonia in elderly patients, since D_2 activity decreases with age.[15]

Clinical features

In 95% of all cases, acute dystonia appears within 96 hours of starting treatment with antipsychotic drugs or after a large increase in the dose.[1 2 6] The dystonia may appear in all muscle groups but is observed mainly in the head and neck area. This may lead to a variety of forms of dystonia, such as torticollis, trismus, "mouth opening" dystonia, grimacing, dysarthria, oculogyric crisis, blepharospasm, and swallowing difficulties.[1 2 6] A tense tongue or throat may indicate a moderate form of acute dystonia. Sometimes only the hands or just a few fingers may be affected. Frequently, however, acute dystonia worsens when one or more muscle groups are activated, such as while walking. Sometimes, the dystonia is only visible during activity but not at rest. Acute dystonia may occur in a generalised form and may lead to the distressing state of a patient in opisthotonos. Acute dystonia often causes anxiety or pain, or both. Only rarely do life threatening dystonias occur; stridor caused by laryngospasm is an example of a life threatening dystonia.[1 2]

Acute dystonias seem to occur more frequently between 12 00 and 23 00.[16] Sometimes, acute dystonia is diagnosed during maintenance treatment with a depot antipsychotic within a few days after the depot has been administered.[17] The oculogyric crisis is the only form of acute dystonia that may occur while the patient is receiving a stable dose of an antipsychotic drug; it may be provoked by alcohol, emotional stress, fatigue, or suggestion.[18]



Dystonic gait

Differential diagnosis

The diagnosis of acute dystonia caused by antipsychotic drugs can only be made if a patient has been treated with antipsychotics within the past few days. However, the patient may be too psychotic to give reliable information, or may have received a depot antipsychotic injection but has not interpreted it as drug treatment. Sometimes doctors prescribe dopamine blocking antiemetics (for example, metoclopramide) without being aware that such agents can cause acute dystonia. Occasionally, antipsychotics are misused as drugs or children may take them unwittingly.[1 2]

Simulation and conversion

Simulation and conversion are clinically important in the differential diagnosis of acute drug induced dystonia. Psychogenic dystonia may be suspected in cases in which the dystonia has a static form, in which it is absent when patients think that they are not being observed, when other psychogenic movement disorders or non-organic neurological features are present, when several symptoms of somatisation disorder are present, or when the patient will clearly obtain a secondary (for example, financial) gain from the disorder.[19] However, no symptom unambiguously allows for a distinction to be made between psychogenic and organic dystonia. Simulation or conversion are often overdiagnosed.[19] It is a common misconception to consider that there is a psychological cause when the dystonic features are exacerbated by fear and alleviated by relaxation. However, a fixed form of dystonia suggests a psychological cause. Some patients misuse anticholinergic drugs for their euphoric effect and therefore their symptoms may simulate dystonia.[20]

Catatonia

Catatonia may resemble dystonia. Catatonia is often accompanied by symptoms such as rigidity, akinesis, cerea flexibilitas, and mutism, which are not seen in acute dystonia. In contrast to acute dystonia, catatonia is not related to starting or raising a dose of antipsychotic drugs, and the administration of anticholinergic drugs does not promote a quick recovery.[2 6]

Tardive dystonia

The symptoms of tardive dystonia and acute dystonia are practically identical.[1–3] However, tardive dystonia occurs only after months or years of treatment with antipsychotic drugs and does not improve rapidly after the administration of anticholinergics.

Other causes

Temporal epilepsy may cause bizarre behaviour and bizarre movements and can therefore be confused with dystonia.[2] Hypocalcaemia may cause features resembling those of acute dystonia. If treatment for acute dystonia is not successful, serum calcium concentrations should be measured.[2]

Patient related risk factors for acute dystonia caused by treatment with antipsychotic drugs

Risk factor	Estimated relative risk
Younger age[7-12]	2-3*
Male sex[8-11]	2
Previous instance of acute dystonia[8]	6
Recent cocaine use[4]	3-4
Race (white *v* Asian)[32]	Conflicting results
Presence of affective disorders[33 34]	Conflicting results
Hypocalcaemia, dehydration, or hypoparathyroidism[2]	Increased risk

*Patients aged 10-19 years compared with patients aged 30-39.

Drugs that may cause acute dystonia

Antipsychotic drugs are the most common cause of dystonia that has been induced by drug treatment. These agents are indispensable for the treatment of psychotic disorders but they are also widely used to treat anxiety, behavioural disorders, and hypochondriasis.[1 2]

Antiemetic drugs, which are used frequently, may also induce dystonia. The prevalence of acute dystonia caused by treatment with metoclopramide has been estimated to be 28.6/1 000 000 prescriptions.[21] Patients aged 12 to 19 years are affected significantly more often than other patients.[21]

Antidepressant drugs may also cause acute dystonia, and a number of case reports suggest that the risk of acute dystonia is higher when selective serotonin reuptake inhibitors are used than when other types of antidepressants are used.[22] Furthermore, the concentration of antipsychotic drugs in the blood may increase substantially when antidepressants such as paroxetine are added to treatment, and this may induce acute dystonia.[23]

There have been several case reports of acute dystonia in patients being treated with other drugs such as antivertigo agents (cinnarizine, flunarizine), anticonvulsant drugs (carbamazepine, phenytoin), antimalaria agents (chloroquine, hydroxychloroquine, amodiaquine), and cocaine.[24 25] Anecdotal case reports of acute dystonia have been reported during the use of buspirone,[24] diazepam,[24] sumatriptan,[26] phenylpropanolamine,[27] and ecstasy (3,4 methylenedioxymethamphetamine).[28]

Treatment

The treatment of acute dystonia is usually straightforward and nearly always effective. Intramuscular administration of anticholinergic drugs (for example, biperiden 5 mg or procyclidine 5 mg) or antihistamines (for example, promethazine 50 mg) is usually effective within 20 minutes.[1 2] Occasionally, second or third injections are necessary; they should be administered at half hour intervals. If the dystonia persists, a search for other underlying illnesses should be made.[1 2] If the patient has an oculogyric crisis that does not respond to anticholinergic drugs, treatment with clonazepam 0.5 to 4 mg may be beneficial.[29]

After the dystonia has resolved, treatment with anticholinergics should be continued in addition to the treatment with antipsychotic drugs for at least 24 to 48 hours to prevent a recurrence. In practice, treatment with the anticholinergic drug is usually continued for four to seven days.[1 2] Intravenous administration of an anticholinergic is only necessary in cases of highly dangerous forms of acute dystonia such as stridor.[1 2]

Prophylaxis

A prophylactic drug is usually given by adding an anticholinergic (for example, benztropine 2 mg, two to three times daily) to treatment with the antipsychotic drug. The use of the anticholinergic orphenadrine is not recommended because of its narrow therapeutic index and because an overdose has a rapid toxic effect on several organ systems.[30] With biperiden, benzhexol, procyclidine, or benztropine, toxicity is mainly connected to their anticholinergic properties. Anticholinergic side effects include dry mouth, constipation, blurred vision, memory impairment, urinary retention (particularly among older men), and confusion or delirium. Therefore, no strict rule about prophylactic treatment can be given. A useful strategy is probably to estimate the risk of acute dystonia by investigating the patient's risk factors (table) and the antipsychotic drug being used (including dose, potency, and intrinsic anticholinergic activity).[4 7–12 31–33] The higher the risk of acute dystonia, the more reason there is to give prophylactic treatment and the more effective the prophylaxis.[34] If the patient is intolerant of anticholinergic drugs, a possible alternative is amantadine 100 mg given one to three times daily.

Acute dystonia occurs regularly in patients during treatment of their first psychotic episode since these patients are usually young; if this occurs it may lead to non-compliance with treatment. Non-compliance greatly enhances the risk of a psychotic relapse.

The decision to add anticholinergic drugs to treatment with antipsychotics should take into account whether the patient is being treated in an inpatient or an outpatient setting, although this factor is hardly ever mentioned in treatment guidelines. In inpatient settings greater risks can be taken because aid is directly available. Thus, anticholinergic drugs may be prescribed more frequently for outpatients. In patients addicted to other drugs the risk of misuse of the prescribed anticholinergics may be a problem.[20] Prophylaxis is usually continued for about seven days. After that, the dose of the anticholinergic should be reduced gradually; stopping the drug suddenly may again induce acute dystonia. The occurrence of other acute extrapyramidal side effects, such as parkinsonism, is usually a reason to continue the anticholinergic agent for longer than seven days. The idea that the addition of anticholinergic drugs may increase the risk of tardive dyskinesia is probably incorrect.[5] Anticholinergics may aggravate an existing dyskinesia but are not causally related to tardive dyskinesia.[5]

Treating acute dystonia

- Administer intramuscularly anticholinergic drugs (for example, biperiden 5 mg or procyclidine 5 mg) or antihistamines (for example, promethazine 50 mg). Intravenous administration is necessary only if acute dystonia is life threatening
- Intramuscular administration is usually effective within 20 minutes. If it is not effective, second or third injections may be necessary; these should be administered at half hour intervals
- After the dystonia has resolved, anticholinergic drugs should be used prophylactically for four to seven days; the dose should be reduced gradually

Conclusion

Acute dystonia is a common side effect of antipsychotic drugs. Its occurrence can disturb the relationship between the doctor and the patient. Patients at high risk of developing acute dystonia should receive prophylactic treatment with anticholinergic drugs.

Competing interests: None declared.

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(Accepted 28 April 1999)

Correction

Evidence based cardiology: Prevention of ischaemic stroke

Some values in the table in this article by Henry J M Barnett et al (5 June, pp 1539-43) were incorrect, due to an editorial error. The corrected version is given below. The revised values are those from the North American symptomatic carotid endarterectomy trial (NASCET).

Number needed to treat by endarterectomy to prevent one stroke in 2 years in patients with carotid stenosis

	No of patients in specified trial	Medical risk (%) at 2 years	Surgical risk (%) at 2 years	Risk difference (%)	Relative risk reduction (%)	No needed to treat*	Perioperative stroke and death rate (%)
Symptomatic patients:							
70-99% (NASCET)[33]	659	24.5	8.6	15.9	65	6	5.8
70-99% (ECST)[31]**	501	19.9	7.0	12.9	65	8	5.6
50-69% (NASCET)[32]	858	14.6	9.3	5.3	36	19	6.9
50-69% (ECST)[31]**	684	9.7	11.1	–1.4	–14	—	9.8
<50% (NASCET)[32]	1368	11.7	10.2	1.5	13	67	6.5
<50% (ECST)[31]**	1822	4.3	9.5	–5.2	–109	—	6.1
Asymptomatic patients:							
⩾50% VA, men only[45]	444	7.7†	5.6†	2.1	27	48	4.4
ACAS[35]	1662	5.0	3.8‡ (actual)	1.2	24	83	2.6
ACE[43]	1521	5.0§ (assumed)	5.8	–0.8	-	-	4.6

NASCET=North American symptomatic carotid endarterectomy trial; ECST=European carotid surgery trial; ACAS=asymptomatic carotid atherosclerosis study; ACE=aspirin and carotid endarterectomy trial.
*Number of patients needed to treat by endarterectomy to prevent one stroke in 2 years after the procedure, compared with medical treatment alone.
**By NASCET measurement. Additional data supplied by Dr P Rothwell.
†Extrapolated from results.
‡Assigning a perioperative risk of 2.6% based on 724 of 825 patients who actually received endarterectomy in the surgical arm of ACAS, and utilizing the 0.6% risk of stroke in each of the two years after endarterectomy. The same 1.2% risk is assumed for the ACE patients and VA patients.
§No medical arm—assumed from ACAS data.