Acute Dystonic Reactions Case 2: Drug-Drug Interaction 2-12-16

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Information on Diagnosis and Treatment of Acute Dystonic Reaction is described in another presentation, “Death by Antipsychotics Case 1: Laryngeal Acute Dystonic Reaction”, which is considered Acute Dystonic Reaction Case 1.

2. Acute Dystonic Reaction
Case 2:
Drug-Drug Interaction

J Neuropsychiatry Clin Neurosci 1999;11:518-9

http://www.ncbi.nlm.nih.gov/pubmed/10570771

Educational Objectives

At the conclusion of this presentation, the participant should be able to:

1. Consider pharmacological principles in the context of polypharmacy
2. Appreciate the potential for lithium drug-drug interactions
3. Show familiarity with the antipsychotic pharmacological mechanisms associated with acute dystonic reactions

Abbreviations

- ADR: adverse drug reaction
- AP: antipsychotic
- D_2: dopamine 2 receptor
- EPS: extrapyramidal symptoms

2. Acute Dystonic Reaction: Case 2

2.1. Case Description
2.2. Case Interpretation
2.3. Review of Involved Drugs
- 2.3.1. Valproate and Acute Dystonic Reactions
- 2.3.2. Benztropine and Acute Dystonic Reactions
- 2.3.3. Risperidone and Acute Dystonic Reactions
- 2.3.4. Lithium and Acute Dystonic Reactions

2.1. Case Description

2.1. Acute Dystonic Reaction Case 2: Description

- 81 yo Caucasian ♂ with bipolar disorder
- Treated with:
  - risperidone: 1 mg/d
  - valproic acid liquid: 2,250 mg/d
  - benztropine: 4 mg/d

2.1. Acute Dystonic Reaction Case 2: Description

- Lithium treatment:
  - Lithium carbonate 600 mg/d was started.
  - A switch to lithium citrate 600 mg/d was made; the staff was concerned with compliance.
  - After 4 days, a possible ADR occurred.

2.1. Acute Dystonic Reaction Case 2: Description

- In the evening of that day:
  - His trunk leaned to the left.
  - His speech was slurred.
  - He used a shuffling gait.
- He got worse the next day.
- All medications were held.
  Lithium level 0.5 mEq/l.

2.2. Case Interpretation

2.2. Acute Dystonic Reaction Case 2: Interpretation

So, what is your diagnosis?

2.2. Acute Dystonic Reaction Case 2: Interpretation

So, what is your diagnosis?

Acute dystonic reaction with some associated parkinsonian symptoms.

2.2. Acute Dystonic Reaction Case 2: Interpretation

So, what is your treatment?

2.2. Acute Dystonic Reaction Case 2: Interpretation

So, what is your treatment?

An anticholinergic drug.

2.2. Acute Dystonic Reaction Case 2: Interpretation

- The patient:
  - refused an IM anticholinergic.
  - agreed to take extra oral benztropine 2 mg.
- After 3 hours of lack of response, he agreed to take 1mg IM benztropine; it provided mild improvement.
- Medication changes:
  - Risperidone was stopped.
  - Lithium and valproate were continued.
- Dystonia resolved completely in days.

2.2. Acute Dystonic Reaction Case 2: Interpretation

- Unstable courses and slow resolutions of dystonia are not unusual.
- Please see the presentation “Death by Antipsychotics Case 1”. It explains that after an acute dystonic reaction responds to an IM anticholinergic:
  - it is important to prescribe oral anticholinergics to avoid relapses.
- Anticholinergics:
  - have shorter half-lives than APs and
  - are cleared faster from the body.

2.2. Acute Dystonic Reaction Case 2: Interpretation

- Several months later, the patient:
  - had 2 similar episodes of trunk dystonia.
  - was diagnosed with end-dose dystonia during levo-dopa treatment for Parkinson disease.

http://www.ncbi.nlm.nih.gov/pubmed/8413978

2.2. Acute Dystonic Reaction Case 2: Interpretation

So, is it relevant that the patient had dystonia with levo-dopa?

2.2. Acute Dystonic Reaction Case 2: Interpretation

So, is it relevant that the patient had dystonia with levo-dopa?

Possibly, it indicates individual vulnerability.

2.3. Review of Involved Drugs

2.3. Acute Dystonic Reaction Case 2: Drug Review

- Polypharmacy:
  - valproic acid liquid 2,250 mg/d
  - benztropine 4 mg/d
  - risperidone 1 mg/d
  - after 4 days of lithium 600 mg/d

2.3. Drug Review

2.3.1. Valproate and Acute Dystonic Reactions
2.3.2. Benztropine and Acute Dystonic Reactions
2.3.3. Risperidone and Acute Dystonic Reactions
2.3.4. Lithium and Acute Dystonic Reactions

2.3.1. Valproate and Acute Dystonic Reactions

2.3.1. Acute Dystonic Reaction Case 2: Valproate

- Valproate:
  - is not associated with dystonic reactions.
  - dose was not changed.

2.3.1. Acute Dystonic Reaction Case 2: Valproate

So, valproate explained the acute dystonic reaction ?

2.3.1. Acute Dystonic Reaction Case 2: Valproate

So, valproate explained the acute dystonic reaction ?

Probably not.

2.3.1. Acute Dystonic Reaction Case 2: Valproate

- Some contribution from valproate may be possible through:
  - a DDI with risperidone:
    - pharmacokinetic DDI: probably not important
    - pharmacodynamic DDI: possible
  - a DDI with lithium:
    - pharmacokinetic DDI: no
    - pharmacodynamic DDI: likely

2.3.2. Benztropine and Acute Dystonic Reactions

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

So, benztropine explained the acute dystonic reaction ?

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

So, benztropine explained the acute dystonic reaction ?

No.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

- Benztropine:
  - does not cause dystonias.
  - is used to treat and prevent dystonias.
  - should have prevented the dystonia in this patient.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

- Oral anticholinergic prophylaxis for high haloperidol oral doses:
  - ↓ risk for acute dystonic reactions
  - but did not completely eliminate it.
- This is supported by a:
  - naturalistic study

http://www.ncbi.nlm.nih.gov/pubmed/8097213

  - a RCT http://www.ncbi.nlm.nih.gov/pubmed/2056136

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

Is benztropine treatment relevant in any way in this case?

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

Is benztropine treatment relevant in any way in this case?

Probably, yes.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

In which way was benztropine treatment relevant?

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

In which way was benztropine treatment relevant?

Lack of prevention of dystonias by benztropine indicates that the patient probably had a peculiar vulnerability to dystonias.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

- The patient refusal of more aggressive anticholinergic treatment surely contributed to slow recovery.
- The patient was taking 4 mg/day of oral benztropine.
  He only allowed:
  - 2 mg of additional oral and
  - 1 mg IM.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

The 81 yo patient was taking 4 mg/d benztropine; what does this tell you?

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

The 81 yo patient was taking 4 mg/d benztropine, what does this tell you?

First thought:

Dr. de Leon did not know what he was doing.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

Giving 4 mg/d benztropine to an 81-year-old patient is risky. Antimuscarinic ADRs are likely in geriatric patients.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

Let's assume that Dr. de Leon knew what he was doing by prescribing 4 mg/d benztropine; what does this tell you?

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

Let's assume that Dr. de Leon knew what he was doing by prescribing 4 mg/d benztropine, what does this tell you?

The patient was particularly vulnerable to EPS.

2.3.2. Acute Dystonic Reaction Case 2: Benztropine

Giving 4 mg/d benztropine can help if the patient has Parkinson disease.

The patient was diagnosed with Parkinson disease after risperidone discontinuation.

2.3.3. Risperidone and Acute Dystonic Reactions

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

So, did
risperidone contribute to
the acute dystonic reaction?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

So, did
risperidone contribute to
the acute dystonic reaction?

Definitively.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

So, did
risperidone by itself explain
the acute dystonic reaction?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

So, did
risperidone by itself explain
the acute dystonic reaction?

Probably not.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- APs usually cause acute dystonic reactions:
  - at the onset of treatment, or
  - with dose ↑,
  - more rarely after anticholinergic discontinuation
- The patient was on a stable risperidone dose.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

What do we know about the pharmacology mechanism behind acute dystonic reactions?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

What do we know about the pharmacology mechanism behind acute dystonic reactions?

Not much.

It is described in the Presentation “Death by Antipsychotics Case 1”.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

We know a little more about dystonic reactions on first-generation antipsychotics. What do we know about their pharmacokinetic mechanisms?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- Acute dystonic reactions are possibly dose-related:
  - No studies designed to prove it.
  - Experienced clinicians described that if a large initial AP dose is given, 50% of patients will have acute dystonic reactions. http://www.ncbi.nlm.nih.gov/pubmed/4387257
  - Haloperidol IM is particularly prone to cause acute dystonic reactions. The IM route provides higher serum peaks than the oral route.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

What do we know about the pharmacodynamic mechanisms behind acute dystonic reactions induced by first-generation APs?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- Acute dystonic reactions were mainly caused by high potency APs:
  - haloperidol
  - fluphenazine

  They are very potent D_2 blockers with very high affinity.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

What do we know about the pharmacokinetic mechanisms behind acute dystonic reactions induced by second-generation APs?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- If acute dystonic reactions are dose-related in first-generation APs:
  - It is reasonable to think that they are dose-related on second-generation APs.
  - Moreover, in overdoses acute dystonic reactions happen even with quetiapine, an AP with very low risk for acute dystonic reactions.

http://www.ncbi.nlm.nih.gov/pubmed/19192473

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

What do we know about the pharmacodynamic mechanisms behind acute dystonic reactions induced by second-generation APs?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- There are no good prevalence studies but the limited literature suggests that:
  - Second-generation APs have less risk than haloperidol.
  - Among them, risperidone may be more likely to cause acute dystonic reactions.

http://www.ncbi.nlm.nih.gov/pubmed/18801830

- Risperidone has very high affinity to D_2 receptors. As a matter of fact, risperidone may be more potent than haloperidol.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

So, how do we compare the potency of risperidone and haloperidol in the real world?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

So, how do we compare the potency of risperidone and haloperidol in the real world?

Use a table for dose equivalency, such as Gardner's table.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- Equivalence Ratio by Gartner et al.

http://www.ncbi.nlm.nih.gov/pubmed/20360319 Table 1 (page 687)

	Versus	
	Olanzapine	Chlorpromazine
Haloperidol	2	60
Risperidone	3.33	100

- Comparison according to equivalents
  - 1 mg risperidone = 1.7 haloperidol (3.33/2=1.7) or (100/60=1.7), Risperidone is more potent. Doses are lower than haloperidol.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

The greater clinical potency of risperidone versus haloperidol indicates greater blocking potency at D_2 receptors, correct?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

The greater clinical potency of risperidone versus haloperidol indicates greater blocking potency at D_2 receptors, correct?

Not necessarily.

The greater potency can be explained by pharmacokinetics and/or pharmacodynamics.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

Can pharmacokinetics (e.g., a greater bioavailability of risperidone) contribute to a greater clinical potency of risperidone versus haloperidol?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

Can pharmacokinetics (e.g., a greater bioavailability of risperidone) contribute to a greater clinical potency of risperidone versus haloperidol?

Yes,

but there are no good studies comparing their bioavailability.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

Can pharmacodynamics (greater affinity for D_2 receptors by risperidone) contribute to a greater clinical potency of risperidone versus haloperidol ?

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

Can pharmacodynamics (greater affinity for D_2 receptors by risperidone) contribute to a greater clinical potency of risperidone versus haloperidol ?

Yes,
but data do not appear to support that.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- In vitro study by Richelson and Souder:

http://www.ncbi.nlm.nih.gov/pubmed/11132243

Table 2 describes "Equilibrium dissociation constants for antipsychotic drugs at human brain"

The lower the value of the dissociation constant, the higher the receptor affinity:

	D_2 receptors
haloperidol	2.6±0.5
risperidone	3.77±0.04

Haloperidol appears slightly more potent but these are molar concentrations measured in nM; as we prescribe them in mg, we need to adjust by molecular weight.

2.3.3. Acute Dystonic Reaction Case 2: Risperidone

- In summary, risperidone appears to be a very potent AP similar to haloperidol; thus, it is likely that risperidone acute dystonic reactions may be also dose-related.
  - However, in this patient the risperidone dose was NOT ↑.
  - It is likely that the personal vulnerability of this patient may also have contributed to the acute dystonic reaction.

2.3.4. Lithium and Acute Dystonic Reaction

2.3.3. Acute Dystonic Reaction Case 2: Lithium

So, did the addition of lithium contribute to the acute dystonic reaction ?

2.3.3. Acute Dystonic Reaction Case 2: Lithium

So, did the addition of lithium contribute to the acute dystonic reaction ?
Definitively. It happened after adding lithium and getting steady state.

2.3.3. Acute Dystonic Reaction Case 2: Lithium

You are proposing that the acute dystonic reaction was caused by a lithium-risperidone DDI?

2.3.3. Acute Dystonic Reaction Case 2: Lithium

You are proposing that the acute dystonic reaction was caused by a lithium-risperidone DDI?

Yes, by a pharmacokinetic and/or a pharmacodynamic DDI.

2.3.3. Acute Dystonic Reaction Case 2: Lithium

Does adding lithium cause a pharmacokinetic DDI with risperidone?

2.3.3. Acute Dystonic Reaction Case 2: Lithium

Does adding lithium cause a pharmacokinetic DDI with risperidone?

No. Lithium

is eliminated by the kidney, is not metabolized by CYP, and is not a CYP inducer or inhibitor.

2.3.3. Acute Dystonic Reaction Case 2: Lithium

Does adding lithium cause a pharmacodynamic DDI with risperidone?

2.3.3. Acute Dystonic Reaction Case 2: Lithium

Does adding lithium cause a pharmacodynamic DDI with risperidone?

Possibly.

Data support the possibility of a pharmacodynamic DDI between lithium and APs.

2.3.3. Acute Dystonic Reaction Case 2: Lithium

- Animal studies suggest lithium:
  - ↓ dopamine release in the accumbens

    http://www.ncbi.nlm.nih.gov/pubmed/15888507
  - ↓ dopamine-associated behaviors

    http://www.ncbi.nlm.nih.gov/pubmed/15044694
  - interferes with striatal dopaminergic neurotransmission

    http://www.ncbi.nlm.nih.gov/pubmed/2865683
  - prolongs haloperidol-induced catalepsy

    http://www.ncbi.nlm.nih.gov/pubmed/7200429

2.3.3. Acute Dystonic Reaction Case 2: Lithium

- It has not been well studied, but lithium may exacerbate EPS caused by first-generation APs. http://www.ncbi.nlm.nih.gov/pubmed/6126349
- In a prospective study in 10 patients with first-generation APs and single-blindly rated:
  - An EPS scale showed
    ↑ scores in all 10 patients, but the
    EPS were distressing only to 3 patients.

    http://www.ncbi.nlm.nih.gov/pubmed/2903220
- Many cases of neuroleptic malignant syndrome on second-generation APs are associated with lithium treatment. http://www.ncbi.nlm.nih.gov/pubmed/15119907

2.3.3. Acute Dystonic Reaction Case 2: Lithium

- This case is probably explained by a pharmacodynamic DDI:
  - Lithium ↑ the effects of risperidone.
    It was equivalent to ↑ the risperidone dose.
- Personal vulnerability probably contributed, too.
  The patient's vulnerability was suggested by two occurrences of dystonia with levo-dopa.

Questions

- Please review the 10 questions on the pdf “Questions on the Presentation Acute Dystonic Reactions Case 2 Drug Drug Interaction”.
- You will find the answers on the last slide after the “Thank you” slide. No peeking until you have answered all the questions.
- If you did not answer all the questions correctly, please review the PowerPoint presentation again to reinforce the pharmacological concepts.

Thank you

Answers

1. D
2. D
3. B
4. A
5. B
6. D
7. D
8. D
9. C
10. B