Death by Antipsychotics: Case 1 2-12-16

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Based on a case published by Yagmur et al., 2009

Death by Antipsychotics: Case 1

Yagmur et al. described this clinical presentation in *Pharmacopsychiatry 2009;43:118-9*

http://www.ncbi.nlm.nih.gov/pubmed/20446229

Dr. de Leon added all comments and interpretations. He is fortunate never to have encountered such a case when working as a clinician or consultant. Since he has no personal experience with this, he is using this published case as an example.

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 lethality of an adverse drug reaction associated with antipsychotics.
3. Show familiarity with the treatment and prophylaxis of an adverse drug reaction associated with antipsychotics.

Abbreviations

- ADR: adverse drug reaction
- AEP: antiepileptic drug
- AP: antipsychotic
- D_2: dopamine 2 receptor
- EPS: extrapyramidal symptoms
- IM: intramuscular
- RCT: randomized clinical trial

1.0. Death by APs: Case

1.0.1. Case Description
1.0.2. Interpretation
1.0.3. Outcome in Real Life
1.0.4. Adding AP Doses
1.0.5. High Chlorpromazine Doses
1.0.6. High Olanzapine Doses
1.0.7. Conclusion

After establishing the ADR diagnosis:

- Another section (1.1.) describing this ADR will be presented.
- The presentation will be retitled at the end in the Final Conclusion section.

1.0.1. Case Description

1.0.1. Death by Antipsychotics Case 1: Description

- 36-yo Turkish ♂ with schizophrenia
- Treated with risperidone for a long time
- Acute psychotic exacerbation led to a psychiatric hospital admission

1.0.1. Death by Antipsychotics Case 1: Description

- Excited, aggressive and agitated
- Formal thought disorder, delusions and hallucinations
- Medications: 4 mg/d risperidone
- Routine labs and EKG: normal

1.0.1. Death by Antipsychotics Case 1: Description

- Acute treatment was added:
  - haloperidol 15 mg IM and
  - chlorpromazine 25 mg IM
- The psychotic exacerbation was controlled.
- Then:
  - 5 mg/day of oral olanzapine was administered by mistake,
  - instead of administering risperidone.

1.0.1. Death by Antipsychotics Case 1: Description

- 5 hours later:
  - acute breathing difficulty
  - inspiratory laryngeal stridor, suggesting upper airway obstruction
  - no signs of aspiration

1.0.2. Case Interpretation

1.0.2. Death by Antipsychotics Case 1: Interpretation

So, what is your diagnosis?

1.0.2. Death by Antipsychotics Case 1: Interpretation

So, what is your diagnosis?

Acute dystonic reaction: laryngeal dystonia.

1.0.2. Death by Antipsychotics Case 1: Interpretation

So, what do you do?

1.0.2. Death by Antipsychotics Case 1: Interpretation

So, what do you do?

Urgently administer parenteral anticholinergics.

1.0.3. Outcome in Real Life

1.0.3. Death by Antipsychotics Case 1: Outcome

So, what happened?

1.0.3. Death by Antipsychotics Case 1: Outcome

So, what happened?

The patient finally died.

1.0.3. Death by Antipsychotics Case 1: Outcome

- Vital signs were measured:
  - tachycardia
  - blood pressure: 120/80 mm Hg
  - temperature: 37^0 C
- Evolution:
  - he became unconscious, and
  - his lips were cyanotic
- Actions:
  - endotracheal intubation and
  - transfer to emergency room

1.0.3. Death by Antipsychotics Case 1: Outcome

- Could not breathe unassisted
- EKG: sinus tachycardia and non-specific ST abnormalities in leads V_{1-4}
- Blood pressure: 120/80 mm Hg
- Ventilated using an ambu bag
- Soon the EKG showed asystolia and the patient died.

1.0.3. Death by Antipsychotics Case 1: Outcome

- Autopsy:
  - organ examination: no cause for death
  - no secretions suggesting aspiration in the lungs

1.0.3. Death by Antipsychotics Case 1: Outcome

- Antipsychotic blood analysis:
  - haloperidol: 17 ng/ml
  - chlorpromazine: 42 ng/ml
  - risperidone: 16 ng/ml
  - olanzapine: 4 ng/ml

All were within the therapeutic range.

- No other chemicals were detected in the toxicological blood analysis

1.0.3. Death by Antipsychotics Case 1: Outcome

- The final diagnosis, according to the authors:
  - acute laryngeal dystonia
  - caused by the additive effects of 4 APs

1.0.3. Death by Antipsychotics Case 1: Outcome

- Dr. de Leon's comments on AP therapy:
  - Prescribing 4 APs at the same time is somewhat messy and makes it complicated to grasp the total dose.
  - Individual AP daily doses were not out of the ordinary.
  - Giving 15 mg of haloperidol by IM route is not a good idea: high peak serum concentrations.
  - All 4 APs block D_2 receptors.

1.0.3. Death by Antipsychotics Case 1: Outcome

Can you add the AP doses in this patient?

1.0.3. Death by Antipsychotics Case 1: Outcome

Can you add the AP doses in this patient?

Yes.

1.0.4. Adding AP Doses

1.0.4. Death by Antipsychotics Case 1: AP Doses

How do you add AP doses?

1.0.4. Death by Antipsychotics Case 1: AP Doses

How do you add AP doses?

Traditionally,
by calculating
chlorpromazine equivalents.

1.0.4. Death by Antipsychotics Case 1: AP Doses

- Chlorpromazine (the first AP) was introduced by Delay & Deniker in 1952. http://www.ncbi.nlm.nih.gov/pubmed/14756121
- Chlorpromazine, a phenothiazine, was considered a low-potency first-generation AP.
- Haloperidol, a butirophenone, was considered a high-potency first-generation AP.

1.0.4. Death by Antipsychotics Case 1: AP Doses

- Chlorpromazine equivalents were used to compare doses.

  http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1 Page 11.

- 2 mg of haloperidol = 100 mg of chlorpromazine.
  - haloperidol is 50 x more potent
  - chlorpromazine is less potent (0.02 x potency of haloperidol).

1.0.4. Death by Antipsychotics Case 1: AP Doses

A patient is taking haloperidol 10 mg/d.
What is the equivalent dose of chlorpromazine?

1.0.4. Death by Antipsychotics Case 1: AP Doses

A patient is taking haloperidol 10 mg/d.
What is the equivalent dose of chlorpromazine?

500 mg/day chlorpromazine is the equivalent (10 x 50=500).

1.0.4. Death by Antipsychotics Case 1: AP Doses

A patient is taking haloperidol 3 mg/d.

What is the equivalent dose of chlorpromazine?

1.0.4. Death by Antipsychotics Case 1: AP Doses

A patient is taking haloperidol 3 mg/d.
What is the equivalent dose of chlorpromazine?

150 mg/d of chlorpromazine is the equivalent (3 x 50=150).

1.0.4. Death by Antipsychotics Case 1: AP Doses

What happened after the introduction of second-generation APs?

1.0.4. Death by Antipsychotics Case 1: AP Doses

- Chlorpromazine equivalents are no longer used.
- Doses are harder to compare since they have different EPS profiles.
- A good article that you need to download and keep in your files:

Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. Am J Psychiatry. 2010 Jun;167(6):686-93. doi: 10.1176/appi.ajp.2009.09060802. Epub 2010 Apr 1. PubMed PMID: 20360319. http://www.ncbi.nlm.nih.gov/pubmed/20360319

1.0.4. Death by Antipsychotics Case 1: AP Doses

- Assuming the patient's daily doses:
  - chlorpromazine 25 mg
  - haloperidol 15 mg
  - olanzapine 5 mg
  - risperidone 4 mg
- Gardner et al. provide in Table 1 the "Equivalence Ratio" by using
  - chlorpromazine and
  - olanzapine equivalents.

1.0.4. Death by Antipsychotics Case 1: AP Doses

- Equivalence Ratio

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

	Versus	
	Olanzapine	Chlorpromazine
Chlorpromazine	0.033	1
Haloperidol	2	60*
Olanzapine	1	30
Risperidone	3.33	100

*Another reference (http://www.amazon.com/Handbook-Psychiatric-Therapy-HymanArana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1 Page 11) estimated 50 instead of 60. Most textbooks propose 50.

1.0.4. Death by Antipsychotics Case 1: AP Doses

Use Gardner's table.

How many daily chlorpromazine equivalents did the patient take?

1.0.4. Death by Antipsychotics Case 1: AP Doses

Use Gardner's table.

How many daily chlorpromazine equivalents did the patient take?

1475.

1.0.4. Death by Antipsychotics Case 1: AP Doses

- Calculating chlorpromazine equivalents

	Dose	Factor	Total
Chlorpromazine	25	x 1	25
Haloperidol	15	x 60	900
Olanzapine	5	x 30	150
Risperidone	4	x100	400
			1475

1.0.5. High Chlorpromazine Doses

1.0.5. Death by Antipsychotics Case 1: Chlorpromazine Dose

Is 1475 mg/d a high chlorpromazine dose?

1.0.5. Death by Antipsychotics Case 1: Chlorpromazine Dose

Is 1475 mg/d a high chlorpromazine dose?

Yes.

1.0.5. Death by Antipsychotics Case 1: Chlorpromazine Dose

How do I know 1475 mg/d is a high chlorpromazine dose?

1.0.5. Death by Antipsychotics Case 1: Chlorpromazine Dose

How do I know 1475 mg/d is a high chlorpromazine dose?

By going to DailyMed.

1.0.5. Death by Antipsychotics Case 1: Chlorpromazine Dose

- Go to DailyMed. http://dailymed.nlm.nih.gov
- All the prescribing information is from generic products. Select the first one.

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=298de270-99a5-47cc-9116-a91fd6099385

- Click on “Dosage & Administration”.
- Read *“Hospitalized Patients*

Acute Schizophrenic or Manic States

It is recommended that initial treatment be with chlorpromazine injection until patient is controlled. Usually patient becomes quiet and cooperative within 24 to 48 hours and oral doses may be substituted and increased until the patient is calm. **500** mg a day is generally sufficient. While gradual increases to **2000** mg a day or more may be necessary, there is usually little therapeutic gain to be achieved by exceeding **1000** mg a day for extended periods. In general, dosage levels should be lower in the elderly, the emaciated and the debilitated. ”

1.0.5. Death by Antipsychotics Case 1: Chlorpromazine Dose

- Remember the statement on a chlorpromazine dose of 1000 mg/d:

"there is usually little therapeutic gain to be achieved by exceeding **1000** mg a day for extended periods."

1.0.6. High Olanzapine Doses

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Use Gardner's table.
How many
daily olanzapine equivalents
did the patient take?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Use Gardner's table.
How many
daily olanzapine equivalents
did the patient take?

49.1.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

- Calculating olanzapine equivalents

	Dose	Factor	Total
Chlorpromazine	25	x 0.033	0.8
Haloperidol	15	x 2	30
Olanzapine	5	x 1	5
Risperidone	4	x 3.33	13.3
			49.1

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

How do I know 49.1 mg/d is a high olanzapine dose?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

How do I know 49.1 mg/d is a high olanzapine dose?

By going to DailyMed.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

- Go to DailyMed. http://dailymed.nlm.nih.gov
- Select Eli Lilly prescribing information.

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d5051fbc-846b-4946-82df341fb1216341

- Click on “Dosage & Administration”.
- Read the last sentence of the paragraph:

“**2.1 Schizophrenia**
Adults
Dose Selection — Oral olanzapine …”

- Read the last sentence of the paragraph:

“Olanzapine is not indicated for use in doses above 20 mg/day.”

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Do clinicians use olanzapine doses > 20 mg/d?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Do clinicians use olanzapine doses > 20 mg/d?

Of course they do. Olanzapine has a wide therapeutic window.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

- The AGNP http://www.ncbi.nlm.nih.gov/pubmed/22053351 defines
  Therapeutic Reference Ranges = ranges of medication Cs:
  - OLA: 20-80 ng/mL

More details about therapeutic range and window are provided in the presentation “Pharmacokinetics of Oral Second-Generation Antipsychotics”.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What is the therapeutic window/index for olanzapine?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What is the therapeutic window/index for olanzapine?

80/20=4.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

How does
Dr. de Leon refer to a therapeutic window/index of 4?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

How does
Dr. de Leon refer to a therapeutic window/index of 4?

Wide,

because is > 3.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

- In a study at Eastern State Hospital:

Botts S, Littrell R, de Leon J. Variables associated with high olanzapine dosing in a state hospital. J Clin Psychiatry. 2004 Aug;65(8):1138-43. PubMed PMID: 15323601.
http://www.ncbi.nlm.nih.gov/pubmed/15323601

- The Methods section in the Abstract states that:
  "Olanzapine doses of > 20 mg/day were considered high doses."
- The Results section in the Abstract says:
  "RESULTS: Nine percent (48/522) of olanzapine patients were prescribed high doses."

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

- In fact, Dr. de Leon was one of the prescribers.
- On page 1141, a statement at the end of fourth paragraph, left column, states: “The long-term units have 3 physicians with prescription rates of high doses ranging from 17-33%. One was an outlier with 0%.”
- Dr. de Leon was the outlier. None of his patients had an olanzapine dose > 20 mg/d.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

In summary, can we conclude that Dr. de Leon never prescribed olanzapine doses > 20 mg/d?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

In summary, can we conclude that Dr. de Leon never prescribed olanzapine doses > 20 mg/d?

This conclusion is completely wrong.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

In fact,
Dr. de Leon
routinely prescribed
olanzapine doses > 20 mg/d
for difficult patients
in one situation.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

In what situation does Dr. de Leon routinely prescribe olanzapine doses > 20 mg/d for difficult patients?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

In what situation does Dr. de Leon routinely prescribe olanzapine doses > 20 mg/d for difficult patients?

Patients taking potent inducers.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What are the potent AED inducers?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What are
the potent AED inducers?

Carbamazepine, phenytoin and phenobarbital.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Are olanzapine doses > 20 mg/d recommended by the prescribing information in patients with inducers?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Are olanzapine doses > 20 mg/d recommended by the prescribing information in patients with inducers?

No.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Is there any statement related to induction in the olanzapine prescribing information?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

Is there any statement related to induction in the olanzapine prescribing information?

Yes,
but it is hidden.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

- Go to DailyMed. http://dailymed.nlm.nih.gov
- Select Eli Lilly prescribing information.

http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d5051fbc-846b-4946-82df341fb1216341

- Look for Section 7:

“7. DRUG INTERACTIONS”

Subsection 7:

“7.1 Potential for Other Drugs to Affect Olanzapine“

- Read the paragraph on inducers:

“:Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.“

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What does "carbamazepine (400 mg/d) causes an approximately 50% increase in the clearance of olanzapine" mean?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What does "carbamazepine (400 mg/d) causes an approximately 50% increase in the clearance of olanzapine" mean?

Metabolism increases by 1.5.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What are the implications of multiplying metabolism by 1.5 for olanzapine dosing?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What are the implications of multiplying metabolism by 1.5 for olanzapine dosing?

You need to multiply the olanzapine dose by 1.5 when co-prescribing carbamazepine, 400 mg/d, a subtherapeutic carbamazepine dose.

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What are Dr. de Leon's recommendations when adding an AED inducer to olanzapine?

1.0.6. Death by Antipsychotics Case 1: Olanzapine Dose

What are Dr. de Leon's recommendations when adding an AED inducer to olanzapine?

Dr. de Leon recommends multiplying the olanzapine dose by 2-3 times.

(see the presentation on Pharmacokinetics of Oral Second-Generation Antipsychotics).

1.0.7. Conclusion

1.0.7. Death by Antipsychotics Case 1: Conclusion

- The patient died because of an acute dystonic reaction.
- The acute dystonic reaction was associated with a very high AP dose. The combined daily dose of 4 APs was very high:
  - 1475 chlorpromazine equivalents, or
  - 49.1 olanzapine equivalents.
- This dose is very high in the absence of any inducer.
- 2 IM APs provided higher peaks.

NEW SECTION:

1.1. Acute Dystonic Reactions

1.1. Acute Dystonic Reactions

1.1.1. Description

1.1.2. Etiology

1.1.3. Prophylaxis

1.1.4. Treatment

1.1.5. Pharmacological Mechanism

1.1. Acute Dystonic Reactions

1.1.1. Description

1.1.2.1. Acute Dystonic Reactions

1.1.2.2. Other Reversible EPS

1.1.2. Etiology

1.1.2.1. First-Generation APs

1.1.2.2. Second-Generation APs

1.1.3. Prophylaxis

1.1.3.1. Oral Prophylaxis

1.1.3.2. IM Prophylaxis

1.1.4. Treatment

1.1.5. Pharmacological Mechanism

1.1.5.1. Pharmacokinetic Mechanisms

1.1.5.2. Pharmacodynamic Mechanisms

1.1.1. Description

1.1.1. Description

1.1.2.1. Acute Dystonic Reactions
1.1.2.2. Other Reversible EPS

1.1.1.1. Acute Dystonic Reaction

1.1.1.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction

What is dystonia?

1.1.1.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction

- Dystonia: intermittent or sustained muscular spasms and abnormal postures
- Acute dystonic reactions:
  - acute reactions associated with AP treatment
  - one of three forms of reversible EPS caused by APs

1.1.1.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction

- Most frequent muscles:
  - adults: head and neck
  - children <15 years: axial and limbs

http://www.ncbi.nlm.nih.gov/pubmed/1119613

- In 116 cases in 1152 patients:
  - torticollis (30%)
  - tongue (17%)
  - trismus (15%)
  - oculogyric crises (6%)
  - opisthotonos (3%)

http://www.ncbi.nlm.nih.gov/pubmed/1119613

1.1.1.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction

- Laryngeal dystonias:
  - are rare
  - can be lethal

http://www.ncbi.nlm.nih.gov/pubmed/2572029

1.1.1.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction

- Onset:
  - dramatic
  - usually occurs within the first 24-48 hours of starting the antipsychotic, or
  - less commonly occurs when the dose is increased

1.1.1.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction

- Course:
  - Often episodic and recurrent
  - May last from seconds to hours
  - May worsen with stress
  - Rapidly relieved by parenteral anticholinergics http://www.ncbi.nlm.nih.gov/pubmed/13685365
  - Do not confuse them with conversions. http://www.ncbi.nlm.nih.gov/pubmed/5272365

1.1.1.2. Other Reversible EPS

1.1.1.2. Death by Antipsychotics Case 1: Other Reversible EPS

What are the other two reversible EPS caused by APs?

1.1.1.2. Death by Antipsychotics Case 1: Other Reversible EPS

What are the other two reversible EPS caused by APs?

Akathisia and parkinsonism.

1.1.1.2. Death by Antipsychotics Case 1: Other Reversible EPS

- Be aware that there are some rare reversible EPS called acute or paradoxical dyskinesias:
  - Acute (not tardive) dyskinesias will respond to anticholinergics.
  - They were described by Gerlach.

Gerlach, J., & Korsgaard, S. (1983). Classification of abnormal involuntary movements in psychiatric patients. Neuropsychiatric Clinics, 2, 201-208.

And in other PubMed article:

http://www.ncbi.nlm.nih.gov/pubmed/19698387

1.1.1.2. Death by Antipsychotics Case 1: Other Reversible EPS

- Acute/paradoxical dyskinesias are:
  - not described in textbooks
  - ignored by most psychiatrists who do not know they exist
- Acute dyskinesias:
  - behave like acute dystonic reactions
  - are dyskinesias, not dystonias

1.1.1.2. Death by Antipsychotics Case 1: Other Reversible EPS

- Description of EPS (at the time when first-generation APs were used):
  de Leon J, Simpson GM. Assessment of neuroleptic-induced extrapyramidal symptoms. In Adverse Effects of Psychotropic Drugs. Kane JM, Lieberman JA (eds). Guilford Press: New York, 1992, pp 218-234”

http://www.amazon.com/Adverse-Effects-Psychotropic-Drugs Lieberman/dp/0898628857/ref=sr_1_1?s=books&ie=UTF8&qid=1361987352&sr=1-1&keywords=Adverse+Effects+of+Psychotropic+Drugs

In the future it will be available here:

http://uknowledge.uky.edu/do/search/?q=author_lname%3A%22de%20Leon%22%20AND%20author_fname%3A%22Jose%22&start=0&context=1674591&sort=date_desc

1.1.2. Acute Dystonic Reactions: Etiology

1.1.2.1. First-Generation APs
1.1.2.2. Second-Generation APs

1.1.2.1. Acute Dystonic Reaction Etiology: First-Generation APs

1.1.2.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction and First-Generation APs

- Mainly associated with high potency:
  - haloperidol
  - fluphenazine
- Possibly dose-related:
  - There are no good studies designed to prove it.
  - Experienced clinicians affirmed that 50% of patients would have acute dystonic reactions if a large initial dose was given. http://www.ncbi.nlm.nih.gov/pubmed/4387257

1.1.2.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction and First-Generation APs

- Most important risk factors:
  - young age
  - male gender

http://www.ncbi.nlm.nih.gov/pubmed/1119613

- Other factors described in the literature:
  - hypocalcemia
  - alcohol ingestion
  - personal history of previous episodes
  - family history of drug-induced dystonia

1.1.2.2. Acute Dystonic Reaction Etiology: Second-Generation APs

1.1.2.2. Death by Antipsychotics Case 1: Acute Dystonic Reaction and Second-Generation APs

- There are no good prevalence or treatment studies.
- There are many published case reports.
- According to a review, acute dystonic reactions on second-generation APs:
  - are rare
  - are short-lived
  - do not tend to recur

http://www.ncbi.nlm.nih.gov/pubmed/11806865

1.1.2.2. Death by Antipsychotics Case 1: Acute Dystonic Reaction and Second-Generation APs

- In a retrospective cohort of AP intoxications: quetiapine may be the least likely of second-generation APs to cause acute dystonic reactions http://www.ncbi.nlm.nih.gov/pubmed/19192473

1.3. Acute Dystonic Reactions: Prophylaxis

1.3. Acute Dystonic Reactions: Prophylaxis

1.3.1. Oral Prophylaxis
1.3.2. IM Prophylaxis

1.3. Death by Antipsychotics Case 1: Prophylaxis

- References for prophylaxis/treatment:
  - Chapter by Stanilla and Simpson

http://www.amazon.com/American-Psychiatric-Publishing-Psychopharmacology-Schatzberg/dp/1585623091/ref=sr_1_1?ie=UTF8&s=books&qid=1278966588&sr=1-1

  - Handbook by Labbate et al.

http://www.amazon.com/Handbook-Psychiatric-Therapy-Hyman-Arana/dp/0781774861/ref=sr_1_1?ie=UTF8&s=books&qid=1278707314&sr=1-1

  - Handbook by American Pharmacy Association (AmPhAs).

http://www.amazon.com/Drug-Information-Handbook-Comprehensive-Professionals/dp/1591953073/ref=sr_1_1?s=books&ie=UTF8&qid=1350489676&sr=1-1&keywords=drug+information+handbook+2012-2013

- Be aware that anticholinergic dosing varies for each individual (determined by trial and error; Stanilla & Simpson).

1.3.1. Acute Dystonic Reactions: Oral Prophylaxis

1.3.1. Acute Dystonic Reactions: Oral Prophylaxis

1.3.1.1 First-Generation APs
1.3.1.2. Second-Generation APs

1.3.1.1. Oral Prophylaxis: First-Generation APs

1.3.1.1. Death by Antipsychotics Case 1: Oral Prophylaxis in First-Generation APs

- When oral first-generation APs were the only AP drugs available, oral anticholinergics were used as prophylaxis in some patients:
  - with history of acute dystonic reactions
  - at high risk:
    such as young ♂ started on high doses of haloperidol

1.3.1.1. Death by Antipsychotics Case 1: Oral Prophylaxis in First-Generation APs

- Recommended oral anticholinergic doses:
  - benztropine:
    - 1-4 mg/day (Stanilla & Simpson)
    - 1-2 mg twice a day (Labbate et al.)
  - biperiden: 1-3 mg twice a day (Labbate et al.)
  - trihexyphenidyl:
    - 5-15 mg/day (Stanilla & Simpson)
    - 1-2 mg 3 times a day (Labbate et al.)
  - diphenhydramine:
    - 75-150 mg/day (Stanilla & Simpson)
    - 25 mg 2-4 times or 50 mg 2 times a day (Labbate et al.)

1.3.1.1. Death by Antipsychotics Case 1: Oral Prophylaxis in First-Generation APs

- Oral anticholinergic prophylaxis during treatment with oral haloperidol in the high doses used in the past:
  - ↓ acute dystonic reaction risk
  - 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

1.3.1.1. Death by Antipsychotics Case 1: Oral Prophylaxis in First-Generation APs

- When using anticholinergics to prevent acute dystonic reactions, Stanilla & Simpson recommend:
  - weaning the dose slowly
  - over 10 days
  - while watching for development of:
    - parkinsonism or
    - akathisia.

http://www.amazon.com/American-Psychiatric-Publishing-Psychopharmacology-Schatzberg/dp/1585623091/ref=sr_1_1?ie=UTF8&s=books&qid=1278966588&sr=1-1

1.3.1.2. Oral Prophylaxis: Second-Generation APs

1.3.1.2. Death by Antipsychotics Case 1: Oral Prophylaxis in Second-Generation APs

- Rarely needed in the average patient.
- Recent double-blind prospective RCT in patients with history of AP-induced acute dystonic reactions (or at least moderate parkinsonism) found the need for anticholinergics was present in:
  - 40% of risperidone patients
  - only 10% of olanzapine patients

  Patients with a history of acute dystonic reactions may need prophylactic anticholinergics, especially if on risperidone.

1.3.2. Acute Dystonic Reactions: IM Prophylaxis

1.1.3.2. Acute Dystonic Reactions: IM Prophylaxis

1.1.3.2.1. First-Generation APs
1.1.3.2.2. Second-Generation APs

1.3.2.1. IM Prophylaxis First-Generation APs

1.3.2.1. Death by Antipsychotics Case 1: IM Prophylaxis in First-Generation APs

- For prophylaxis of reversible EPS: administer IM anticholinergics with IM high potency first-generation AP:
  - IM haloperidol, and
  - IM long-acting formulations.
    - haloperidol decanoate
    - fluphenazine decanoate
- Prophylaxis is particularly important in highly vulnerable patients, especially for those with history of acute dystonic reactions.

1.3.2.1. Death by Antipsychotics Case 1: IM Prophylaxis in First-Generation APs

- Reasonable IM doses are:
  - 1-2 mg of benztropine, or
  - 50 mg of diphenhydramine

  but it is better to use prior history to guide dosing.

1.3.2.1. Death by Antipsychotics Case 1: IM Prophylaxis in First-Generation APs

- In the US, the parenteral formulations of two antihistamines:
  - diphenhydramine or
  - promethazine

  are much cheaper than the parenteral formulation of benztropine.

http://www.ncbi.nlm.nih.gov/pubmed/19192477

1.3.2.2. IM Prophylaxis Second-Generation APs

1.3.2.2. Death by Antipsychotics Case 1: IM Prophylaxis in Second-Generation APs

- A meta-analysis of second-generation IM RCTs:
  - IM haloperidol + IM anticholinergic-antihistaminic drug (promethazine)

  was not associated with acute dystonias, and its profile is as good as the IM second-generation APs. http://www.ncbi.nlm.nih.gov/pubmed/19192477
- In patients with a history of acute dystonic reactions requiring an IM AP, based on this meta-analysis:
  - IM haloperidol + IM anticholinergic is as safe as
  - IM second-generation APs.

1.3.2.2. Death by Antipsychotics Case 1: IM Prophylaxis in Second-Generation APs

- Currently, there is no information on whether acute dystonic reactions induced by second-generation APs may require oral anticholinergics to avoid relapses after IM anticholinergics.
- Dr. de Leon encourages clinicians:
  - to use oral anticholinergic prophylaxis after IM treatment, or
  - at least consider it and document the risk-benefit in the chart.

1.4. Acute Dystonic Reactions: Treatment

1.4. Death by Antipsychotics Case 1: Acute Dystonic Reaction Treatment

- Use the IM route most of the time.
- Recommended adult doses:
  - benztropine:1-2 mg(Stanilla & Simpson)

    2 mg (AmPhAs)
  - diphenhydramine: 50 mg(Labbate et al.)

1.4. Death by Antipsychotics Case 1: Acute Dystonic Reaction Treatment

- The dose can be repeated in 30 minutes if recovery is incomplete. (Stanilla & Simpson).
- Parenteral benztropine may take less time to resolve acute dystonic reactions than parenteral diphenhydramine.

http://www.ncbi.nlm.nih.gov/pubmed/502106

1.4. Death by Antipsychotics Case 1: Acute Dystonic Reaction Treatment

- It is important to consider oral anticholinergics to avoid relapses. Remember APs have longer half-lives than anticholinergics.
- If AP is continued, use:
  - benztropine: 2 mg twice a day for 2 weeks and slowly taper off
  - equivalent doses of another anticholinergic
- If AP is discontinued:
  - benztropine: 1-2 mg twice a day for 2-3 days

.

1.4. Death by Antipsychotics Case 1: Acute Dystonic Reaction Treatment

- **Laryngeal dystonias:**
  - use IV route
  - 4 mg benztropine dose repeated in 10 minutes
  - slow IV administration of lorazepam 1-2 mg can also be added (Labbate et al.).

1.5. Acute Dystonic Reactions: Pharmacological Mechanisms

1.5. Acute Dystonic Reactions: Pharmacological Mechanisms

1.5.1. Pharmacokinetic Mechanisms
1.5.2. Pharmacodynamic Mechanisms

1.5.1. Acute Dystonic Reactions: Pharmacokinetic Mechanisms

1.5.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction Pharmacokinetics

What do we know about the pharmacokinetics of acute dystonic reactions in first-generation APs?

1.5.1. Death by Antipsychotics Case 1: Acute Dystonic Reaction Pharmacokinetics

- Possibly dose-related:
  - There are no studies designed to prove it.
  - Experienced clinicians affirmed that 50% of patients would have acute dystonic reactions if a large initial dose was given. http://www.ncbi.nlm.nih.gov/pubmed/4387257

1.5.2. Acute Dystonic Reactions: Pharmacodynamic Mechanisms

1.5.2. Death by Antipsychotics Case 1: Acute Dystonic Reaction Pharmacodynamics

What do we know about the pharmacodynamics of acute dystonic reactions in first-generation APs?

1.5.2. Death by Antipsychotics Case 1: Acute Dystonic Reaction Pharmacodynamics

- Mainly associated with high potency APs:
  - haloperidol
  - fluphenazine

  They are very potent D_2 blockers with very high affinity.

1.2. Final Conclusion

RETITLING THE CASE:
Death by Antipsychotics:
Case 1:
Laryngeal Acute Dystonic Reaction

True 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 lethality of laryngeal acute dystonic reactions
3. Show familiarity with the treatment and prophylaxis of antipsychotic-induced acute dystonic reactions

1. Death by APs: Case 1 (Final Table of Contents)

1.2. Death by Antipsychotics Case 1: Final Conclusion

- Never give15 mg IM haloperidol without knowing the outcome after lower doses.
- If you use 5 mg IM haloperidol for agitation remember:
  - It is not very sedating.
  - Always add 50 mg IM diphenhydramine to:
    - ↑ sedation
    - ↓ risk for acute dystonic reaction
  - Adding 1 mg IM lorazepam may further ↑ sedation.

Questions

- Please review the 10 questions on the pdf entitled "Questions on the Presentation Antipsychotic Death Case 1".
- 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. B
2. D
3. D
4. B
5. A
6. D
7. D
8. D
9. D
10. A