Valproate Case 2: Safety 2-12-16

Jose de Leon, MD

(and an imaginary argumentative resident who argues in “red” letters)

2. Valproate Case 2

J Clin Psychopharmacology 2009;29:310-1

http://www.ncbi.nlm.nih.gov/pubmed/19440094

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 that, for understanding valproate drug response, one must consider
   - 2.1. Efficacy
   - 2.2. Safety
3. Show familiarity with the wide range of adverse drug reactions associated with valproate

Abbreviations

- AED: anti-epileptic drug
- ADR: adverse drug reaction
- C: concentration
- CNS: central nervous system
- D: dosage
- DDI: drug-drug interaction
- ER: extended-release
- GI: gastrointestinal
- ID: intellectual disability
- RCT: randomized clinical trial

ADR Definitions

- First, Dr. de Leon defines **Common** ADRs as occurring in >10% of patients in RCTs.
- Second, Dr. de Leon defines **Potentially Lethal** ADRs according to their risk of lethality. They are rarely found in RCTs. Most of the time they are found after being marketed (pharmacoepidemiologists call this “postmarketing surveillance”).
- Then the rest are: **Relatively Uncommon** ADRs
- Dr. de Leon always has a specific section on: **Metabolic** ADRs, due to their clinical relevance.

Valproate Case 2

2.1. Valproate Efficacy

2.2. Valproate Safety

2.3. Case Description

Valproate Case 2

2.1. Valproate Efficacy

2.2. Valproate Safety

- 2.2.1. Common ADRs
- 2.2.2. Relatively Uncommon ADRs
- 2.2.3. Potentially Lethal ADRs
- 2.2.4. Metabolic Syndrome
- 2.2.5. Teratogenicity

2.3. Case Description

- 2.3.1. Eosinophilic Pleural Effusion
- 2.3.2. Association with Valproate
- 2.3.3. Anticonvulsant Hypersensitivity Reaction
- 2.3.4. Other Drugs
- 2.3.5. Association with Clozapine
- 2.3.6. Pharmacokinetic DDI
- 2.3.7. Naranjo ADR Scale

2.1. Valproate Efficacy

http://link.springer.com/chapter/10.1007/978-1-4614-2012-5_21

Book Chapter 21: “A Practitioner’s Guide to Prescribing Valproate for Adults with Intellectual Disabilities.”

2.1. Case 2: Valproate Efficacy

What do you know about the efficacy of valproate?

2.1. Case 2: Valproate Efficacy

- Epilepsy: wide spectrum AED
- Bipolar disorder http://www.ncbi.nlm.nih.gov/pubmed/18752718
  - Acute mania: clear efficacy
  - Acute depression: reasonable data
  - Maintenance treatment: limited data, but guidelines generally agree that it is an alternative as monotherapy or an adjunctive agent
- Migraine prophylaxis
- Off-label:
  - Self- and hetero-aggressive behavior
  - Adjunct therapy in schizophrenia

2.2. Valproate Safety

http://link.springer.com/chapter/10.1007/978-1-4614-2012-5_21

Book Chapter 21: “A Practitioner’s Guide to Prescribing Valproate for Adults with Intellectual Disabilities.”

2.2. Case 2: Valproate Safety

What do you know about valproate ADRs?

2.2. Valproate Safety

2.2.1. Common ADRs
2.2.2. Relatively Uncommon ADRs
2.2.3. Potentially Lethal ADRs
2.2.4. Metabolic Syndrome
2.2.5. Teratogenicity

2.2.1. Valproate Common ADRs

2.2.1. Case 2: Valproate Common ADRs

- CNS symptoms
- GI symptoms
- Thrombocytopenia
- Alopecia

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

2.2.1. Valoproate Common ADRs

2.2.1.1. CNS symptoms

2.2.1.2. GI symptoms

2.2.1.3. Thrombocytopenia

2.2.1.4. Alopecia

2.2.1.1. Valproate Common CNS Symptoms

2.2.1.1. Case 2: Valproate Common CNS Symptoms

- Common CNS Symptoms (>10%):
  - Tremor (≤57%)
  - Headaches (≤31%)
  - Somnolence (≤30%)
  - Weakness (≤27%)
  - Dizziness (≤25%),
  - Diplopia (≤16%),
  - Insomnia (≤15%)
  - Blurred vision (≤12%)
  - Nervousness (≤11%)
  - Pain (≤11%)

2.2.1.1. Case 2: Valproate Common CNS Symptoms

- Tremor:
  - usually mild
  - usually looks like a benign essential tremor
  - possible interventions include:
    - D reduction
    - switching to divalproex ER
    - propranolol

2.2.1.1. Case 2: Valproate Common CNS Symptoms

- Cognitive ADRs:
  - Caution patients about performing tasks that require alertness (e.g., operating machinery) until they know how they are influenced by valproate.
  - Better profile than the average AED:
    In a study, the relevant subjective cognitive ADR rate averaged 13% in AEDs vs. 8% in valproate.

    http://www.ncbi.nlm.nih.gov/pubmed/19010446
  - In a neuropsychological study in bipolar patients:
    - best scores: oxcarbazepine and lamotrigine
    - intermediate scores: lithium
    - worst scores: valproate, carbamazepine and topiramate

    http://www.ncbi.nlm.nih.gov/pubmed/17406176

2.2.1.2. Valproate Common GI Symptoms

2.2.1.2. Case 2: Valproate Common GI Symptoms

- Common GI Symptoms (>10% in RCTs):
  - Nausea (≤48%)
  - Vomiting (≤27%)
  - Diarrhea (≤23%)
  - Abdominal pain (≤23%)
  - Dyspepsia (≤23%)
  - Anorexia (≤12%)
- Tend to ↓:
  - with time
  - when the drug is taken with food.
  - when changing to: ● enteric-coated or
    ● slow-release

2.2.1.3. Valproate-Induced Thrombocytopenia

2.2.1.3. Case 2: Valproate Thrombocytopenia

- Thrombocytopenia (≤24% in RCTs)
  - Risk Factors:
    - higher D or C
    - female gender
    - age > 65 years

2.2.1.4. Valproate-Induced Alopecia

2.2.1.4. Case 2: Valproate-Induced Alopecia

- Alopecia (≤14% in RCTs)
  - Treatment Recommendations:
    - Lower D
    - Take vitamins and supplements hours before or after valproate

2.2.2. Valproate
Relatively Uncommon ADRs

2.2.1. Case 2: Valproate Relatively Uncommon ADRs

- Parkinsonism http://www.ncbi.nlm.nih.gov/pubmed/17201721
- Interference in platelet aggregation and low fibrinogen levels http://www.ncbi.nlm.nih.gov/pubmed/10695824
- Neutropenia http://www.ncbi.nlm.nih.gov/pubmed/7864268
- Polycystic ovary syndrome: http://www.ncbi.nlm.nih.gov/pubmed/19012099
- Osteoporosis: http://www.ncbi.nlm.nih.gov/pubmed/16275821
  - less than AEDs with potent inducing properties
  - valproate may be a mild inducer: vitamin D inducer
- Edema http://www.ncbi.nlm.nih.gov/pubmed/10630841

2.2.3. Valproate
Potentially Lethal ADRs

2.2.3. Valproate Potentially Lethal ADRs

2.2.3.1. Stevens-Johnson Syndrome
2.2.3.2. Severe Hematological ADRs
2.2.3.3. Hepatotoxicity
2.2.3.4. Encephalopathy
2.2.3.5. Pancreatitis
2.2.3.6. Suicide

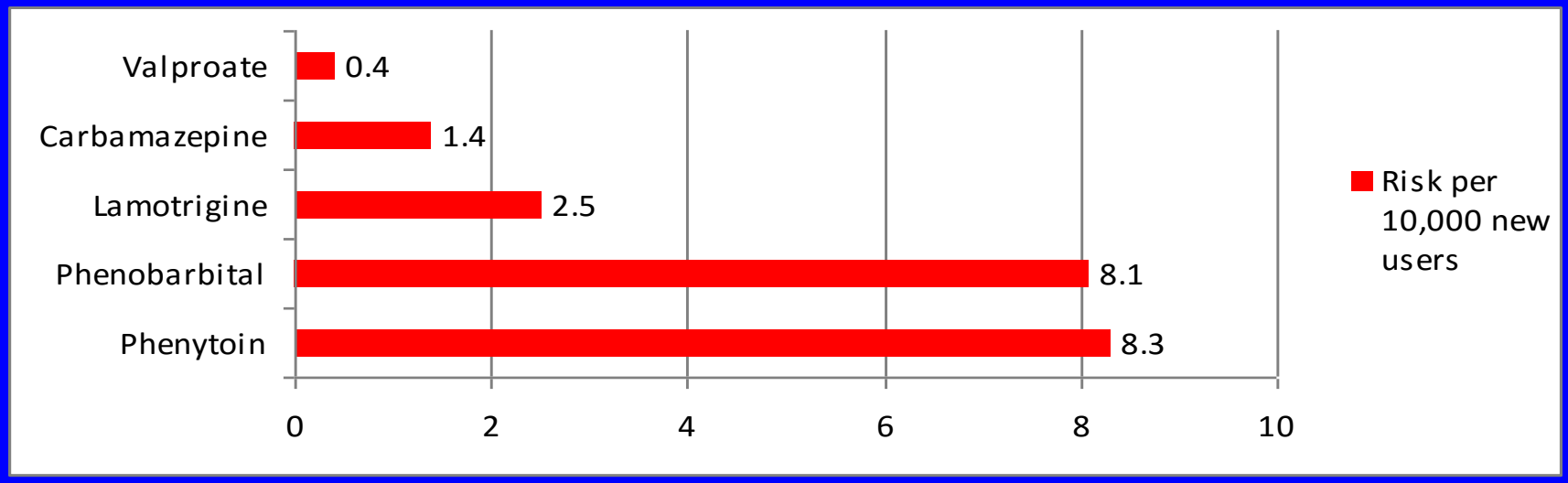
2.2.3.1. Valproate-Induced Stevens-Johnson Syndrome

2.2.3.1. Valproate Case 2: Stevens-Johnson Syndrome

- Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis is much less frequent with valproate than with other classic AEDs (see next slide).
  See the presentation on Lamotrigine Case 1: Stevens-Johnson Syndrome for details and pictures.
- Benign rashes are also less frequent than with other AEDs.
  http://www.ncbi.nlm.nih.gov/pubmed/17502552

2.2.3.1. Valproate Case 2: Stevens-Johnson Syndrome

Pharmacoepidemiology Study of Stevens-Johnson in Germany



http://www.ncbi.nlm.nih.gov/pubmed/15824335

2.2.3.1. Valproate Case 2: Stevens-Johnson Syndrome

- Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis is sometimes included in a large group of disorders called Anticonvulsant Hypersensitivity Reactions.
- Valproate is considered low risk for Anticonvulsant Hypersensitivity Reactions and safe for patients who have developed a hypersensitivity reaction to another AED.

http://www.ncbi.nlm.nih.gov/pubmed/17896897

2.2.3.2. Valproate-Induced Severe Hematological ADRs

2.2.3.1. Valproate Case 2: Severe Hematological ADRs

- Very rare
- The include:
  - aplastic anemia
  - pure red cell aplasia
  - myelodisplasia

2.2.3.2.Valproate Hepatotoxicity

2.2.3.2. Valproate Case 2: Valproate Hepatotoxicity

- Usually in young children
- Fatalities are rare in adults
- In individuals with ID:
  hepatotoxicity tends to be:
  - sudden and
  - unpredictable

http://www.ncbi.nlm.nih.gov/pubmed/17201699

2.2.3.3. Valproate Encephalopathy

2.2.3.2. Valproate Case 2: Encephalopathy

- Four forms of encephalopathy:
  http://www.ncbi.nlm.nih.gov/pubmed/16010067
  - encephalopathy as a direct toxic effect (high valproate Cs but normal ammonia)
  - hyperammonemic encephalopathy
  - encephalopathy with impaired liver function and hyperammonemia
  - encephalopathy with hepatopathy, but with normal ammonia
- With symptom encephalopathy, measure:
  - serum valproate C
  - serum ammonemia
  - liver function tests

2.2.3.4. Valproate-Induced Pancreatitis

2.2.3.4. Valproate Case 2: Pancreatitis

- Pancreatitis may be more frequent than the literature reports. http://www.ncbi.nlm.nih.gov/pubmed/17322992
- Mechanism: not well understood
- In adults with IDs, a study found a very high frequency of 7%. http://www.ncbi.nlm.nih.gov/pubmed/7592507
- It usually manifests with:
  - severe abdominal pain,
  - nausea and vomiting.
- Serum lipase appears to be more sensitive for diagnosing pancreatitis than serum amylase. http://www.ncbi.nlm.nih.gov/pubmed/17015559

2.2.3.5.Valproate and Suicide

2.2.3.5. Valproate Case 2: Suicide

- The FDA meta-analysis, which indicated that AEDs are associated with increased suicide risk, did not include valproate data.
- AED reviews indicate valproate may:
  - be associated with very low risk for depression http://www.ncbi.nlm.nih.gov/pubmed/17253878
  - have positive effects on mood stabilization, according to some limited studies http://www.ncbi.nlm.nih.gov/pubmed/17604407
- Valproate does not appear to have the anti-suicide properties in bipolar disorder that lithium does. http://www.ncbi.nlm.nih.gov/pubmed/14965852

2.2.4. Valproate and Metabolic Syndrome

2.2.4. Valproate Case 2: Metabolic Syndrome

- Valproate is associated with weight gain in:
  - Epilepsy: http://www.ncbi.nlm.nih.gov/pubmed/18201150
    - 20% of patients
    - worse in women
  - Bipolar disorder:
    - from 1.5-11 Kg in 3-12 months
    - occurs in 3-20% of patients

2.2.4. Valproate Case 2: Metabolic Syndrome

- Valproate contributes to hyperinsulinemia by:
  - stimulating pancreatic beta-cells
  - promoting insulin resistance

    http://www.ncbi.nlm.nih.gov/pubmed/19188736
- Valproate ↓ total cholesterol and HDL in patients with:
  - epilepsy http://www.ncbi.nlm.nih.gov/pubmed/16600693
  - migraines http://www.ncbi.nlm.nih.gov/pubmed/16109117
- In a 2-yr epilepsy prospective study, almost ½ of patients taking valproate developed the full metabolic syndrome.

  http://www.ncbi.nlm.nih.gov/pubmed/19682024

2.2.5. Valproate Teratogenicity

2.2.5. Valproate Case 2: Teratogenicity

- Exposure during the first 2-3 months: ↑ risk of anatomical defects:
  - neural tube
  - cardiac,
  - facial dysmorphic features
  - skeletal abnormalities

http://www.ncbi.nlm.nih.gov/pubmed/19369673

The relative risk of major congenital malformations:

- 3.8 vs. the general population
- 2.6 vs. other AEDs

http://www.ncbi.nlm.nih.gov/pubmed/16639967

- Exposure during the whole gestational period may explain the association with:
  - ↓ IQ http://www.ncbi.nlm.nih.gov/pubmed/19369666
  - autism http://www.ncbi.nlm.nih.gov/pubmed/19047565

2.3. Case

2.3. Case

2.3.1. Case Description
2.3.2. Eosinophilic Pleural Effusion
2.3.3. Association with Valproate
2.3.4. Anticonvulsant Hypersensitivity Reaction
2.3.5. Other Drugs
2.3.6. Association with Clozapine
2.3.7. Pharmacokinetic DDI
2.3.8. Naranjo ADR scale

2.3.1. Case Description

2.3.1. Valproate Case 2: Description

- 64-yo Spanish Caucasian ♀
  - disorganized schizophrenia
  - hospitalized in a long-term psychiatric hospital (25 years)
  - no history of allergies
  - smokes 1 pack/day
  - history of recurrent respiratory infections

2.3.1. Valproate Case 2: Description

- Treatment:
  - Clozapine started 11 years ago
    current D=600 mg/day
  - Haloperidol started 3 years ago
    current D=36 mg/day
  - Olanzapine started 1 year ago
    current D=30 mg/day
  - Anticholinergic: biperiden D=1.5 mg/day
  - Levomepromazine as a hypnotic (100 mg at night). It is a sedating antipsychotic.

2.3.1. Valproate Case 2: Description

- Sodium valproate (ER formulation) was added to try to control remaining symptoms:
  - starting D=300 mg/day
  - in 2 weeks D ↑ to 1500 mg/day (valproate C=78 µg/ml)
- Approximately 2 months after adding sodium valproate, the patient developed:
  - a productive cough
  - with no fever, dyspnea or skin reactions.

2.3.2. Eosinophilic Pleural Effusion

2.3.2. Valproate Case 2: Pleural Effusion

- Normal blood tests:
  - no leukocytosis or eosinophilia
  - normal coagulation tests
- Arterial gases:
  - pH 7.39
  - pCO2 59.1 mm Hg
  - pO2 86.8 mm Hg
- A chest X-ray:
  - left pleural effusion
    that was not present in the prior year's routine chest X-ray

2.3.2. Valproate Case 2: Pleural Effusion

- Treatment decisions:
  - Sodium valproate was discontinued.
  - The patient was transferred to the pulmonology department of a general hospital.

2.3.2. Valproate Case 2: Pleural Effusion

- Pleural Fluid Obtained by Thoracocentesis:
  - 50,000 erythrocytes/mm^3
  - 4,100 leukocytes/mm^3:
    - 5% neutrophils
    - 8% lymphocytes,
    - 42% macrophages, and
    - **35% eosinophils**
  - Glucose 88 mg/dL, triglycerides 26 mg/dL, and cholesterol 108 mg/dL
  - Enzymes:
    - amylase 24UI/L,
    - lactate dehydrogenase 376 UI/L
    - adenosine deaminase 21 UI/L
  - Proteins 3.6 g/dL and albumin 2 g/dL
  - pH 7.4
  - Negative cultures (including for mycobacterias)

2.3.2. Valproate Case 2: Pleural Effusion

- Thoracic CT Scan:
  - left pleural effusion of moderate significance
  - secondary left basal atelectasis
  - slight pericardia effusion
- Bronchoscopy:
  - diffuse inflammatory signs with thick mucous secretions
  - no malignant cells
  - negative microbiological results

2.3.2. Valproate Case 2: Pleural Effusion

- No apparent cause for the eosinophilic pleural effusion other than the addition of valproate
- It resolved with valproate discontinuation:
  Chest X-rays:
  - 38 days after the first one: residual mild pleural effusion with no symptoms
  - 4 months later: the effusion had completely disappeared

2.3.3. Association with Valproate

2.3.3. Valproate Case 2: Association with Valproate

So, Dr. de Leon, are you implying that the eosinophilic pleural effusion was caused by valproate?

2.3.3. Valproate Case 2: Association with Valproate

So, Dr. de Leon, are you implying that the eosinophilic pleural effusion was caused by valproate?

Yes.

2.3.3. Valproate Case 2: Association with Valproate

Dr. de Leon, how do you know the eosinophilic pleural effusion was caused by valproate?

2.3.3. Valproate Case 2: Association with Valproate

Dr. de Leon, how do you know the eosinophilic pleural effusion was caused by valproate?

That's a complex question.

2.3.3. Valproate Case 2: Association with Valproate

First, I looked in PubMed.

2.3.3. Valproate Case 2: Association with Valproate

- I searched for “valproate and pleural effusion”:
  - This search provided 18 articles on 2/04/16.
  - The title and abstracts indicated all were case reports.
    There was no study with a large series of cases.
    The first option is to review some of the case reports.
- The second option is to complete another search:
  - “Drug-induced pleural effusions” led to 123 articles.
  - This is too many articles.
    I clicked on “Review” below “Article types”.
    This provided 30 review articles.
  - I scanned the abstracts until I found a good review article:
    “Huggins JT, Sahn SA. Drug-induced pleural disease. Clin Chest Med. 2004;25:141-153.”
    http://www.ncbi.nlm.nih.gov/pubmed/15062606

2.3.3. Valproate Case 2: Association with Valproate

Dr. de Leon,
you seem to be familiar with PubMed searches.
Can you provide some general advice based on this specific search?

2.3.3. Valproate Case 2: Association with Valproate

Dr. de Leon,
you seem to be familiar with PubMed searches.
Can you provide some general advice based on this specific search?

Sure; see the next 4 slides.

2.3.3. Valproate Case 2: Association with Valproate

- **Advice for reviewing case reports and small studies (many have no abstracts):**
  - They may be biased or have idiosyncratic opinions. Try reviewing several of them.
  - Some may not be in English.
  - How many you read depends on how easily you can obtain the articles and read them.

2.3.3. Valproate Case 2: Association with Valproate

- **Advice for selecting review articles**:
  Drug-induced pleural disease. (Huggins JT, Sahn SA. Clin Chest Med. 2004;25:141-153) appears to be a good review article.
  - It includes information on valproate, but includes it in the context of other drugs.
  - Pleural effusions are usually handled by pulmonologists. This review was published in a pulmonology journal; the authors appear to have practical experience.

2.3.3. Valproate Case 2: Association with Valproate

- Please be aware that the review article by *Huggins et al.* was published in 2004 and describes one only valproate case.
- ***14 of the 18 case reports found in PubMed have been published since 2005 and thus were not reviewed by Huggins et al.***
- Good news: one of the case report articles includes a literature review: *"Kamenetsky Z, Da'as N, Esayag Y, Kleinman Y, Samuels N. Valproic acid-induced eosinophilic pleural effusion: a case report and review of the literature. Neurologist. 2012 Jan;18(1):39-40."*

http://www.ncbi.nlm.nih.gov/pubmed/22217614

2.3.3. Valproate Case 2: Association with Valproate

- **Summary of These Articles:** Our case is similar to prior published cases in which valproate was considered the possible cause of an eosinophilic pleural effusion.
- Supporting similarities include:
  - The absence of:
    - malignancies,
    - infections,
    - allergies or
    - systemic diseases
  - The effusion disappeared after valproate discontinuation.

2.3.3. Valproate Case 2: Association with Valproate

Do you have any remaining doubts about the case?

2.3.3. Valproate Case 2: Association with Valproate

Do you have any remaining doubts about the case?

Yes, Dr. de Leon.

2.3.3. Valproate Case 2: Association with Valproate

A prior slide described AEDs as associated with hypersensitivity reactions. Is this an anticonvulsant hypersensitivity reaction?

2.3.3. Valproate Case 2: Association with Valproate

A prior slide described AEDs as associated with hypersensitivity reactions. Is this an anticonvulsant hypersensitivity reaction?

No; see the next section.

2.3.4. Anticonvulsant Hypersensitivity Syndrome

2.3.4. Valproate Case 2: Anticonvulsant Hypersensitivity Syndrome

- The anticonvulsant hypersensitivity syndrome usually includes a triad of symptoms: http://www.ncbi.nlm.nih.gov/pubmed/17896897
  - rash
  - fever
  - evidence of organ involvement
- Our patient had:
  - no skin rash
  - no fever

Therefore, the case appears to fit better with a drug-induced pleural effusion.

2.3.4. Valproate Case 2: Anticonvulsant Hypersensitivity Syndrome

In summary,
as the patient was only taking one drug, valproate, we should conclude this is a valproate-induced pleural effusion.

2.3.4. Valproate Case 2: Anticonvulsant Hypersensitivity Syndrome

One moment, Dr. de Leon; the patient was taking 5 other drugs. Can they be ignored?

2.3.4. Valproate Case 2: Anticonvulsant Hypersensitivity Syndrome

One moment, Dr. de Leon; the patient was taking 5 other drugs. Can they be ignored?

No, you are right.

2.3.5. Other Drugs

2.3.5. Valproate Case 2: Other Drugs

- Valproate was added to:
  - clozapine: 600 mg/day
  - haloperidol: 36 mg/day
  - olanzapine: 30 mg/day
  - biperiden: 1.5 mg/day
  - levomepromazine: 100 mg at night

2.3.5. Valproate Case 2: Other Drugs

- *Huggins et al.'s* review article lists clozapine as a possible cause of pleural effusions.
- 2 titles out of 18 case reports found while searching for "valproate and pleural effusion" appear to blame clozapine as a possible cause of pleural effusions. These 2 titles list clozapine and not valproate.

2.3.6. Association with Clozapine

2.3.6. Valproate Case 2: Clozapine

Dr. de Leon,
how do you know the eosinophilic pleural effusion was not caused by clozapine?

2.3.6. Valproate Case 2: Clozapine

Dr. de Leon,
how do you know the eosinophilic pleural effusion was not caused by clozapine?

I do not know.

I looked in PubMed.

2.3.6. Valproate Case 2: Clozapine

- On 2/4/16 a search for “clozapine and pleural effusion” provided 16 articles. All described case reports except for *Huggins et al.’s* review.
- The presentation in those clozapine cases appears to differ from this case, since all of those cases were much more complicated. Their pleural effusions also involved:
  - skin reactions,
  - neuroleptic malignant syndrome,
  - multiple medical problems, or
  - polyserositis (generalized effusions).

The clozapine-induced pleural effusions were reviewed during the publication of our case report.

http://www.ncbi.nlm.nih.gov/pubmed/19440094

2.3.6. Valproate Case 2: Clozapine

- Moreover, this patient had been on clozapine for 11 years prior to the development of the pleural effusion.
- The chronology:
  - onset a few weeks after adding valproate and
  - slow disappearance after its discontinuation suggest that valproate may be the responsible agent.

2.3.6. Valproate Case 2: Clozapine

So, Dr. de Leon,
are you 100% sure that clozapine did not contribute to the eosinophilic pleural effusion?

2.3.6. Valproate Case 2: Clozapine

So, Dr. de Leon,
are you 100% sure that clozapine did not contribute to the eosinophilic pleural effusion?

No.

2.3.6. Valproate Case 2: Clozapine

Dr. de Leon,
is it possible that adding valproate has contributed to changing the metabolism of clozapine and then the metabolites have contributed to the eosinophilic pleural effusion?

2.3.6. Valproate Case 2: Clozapine

Dr. de Leon,
is it possible that adding valproate has contributed to changing the metabolism of clozapine and then the metabolites have contributed to the eosinophilic pleural effusion?

Yes, it is possible.

2.3.7. Pharmacokinetic DDIs

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon,
I have 2 hypotheses.
Are you willing to listen to them?

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon,
I have 2 hypotheses.
Are you willing to listen to them?

Sure; go ahead.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

First hypothesis:
adding valproate created
a new clozapine metabolite,
a “toxic” one that caused
the pleural effusion.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Second hypothesis: discontinuing valproate made the "toxic" clozapine metabolite disappear.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

What do you think of my two hypotheses?

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

What do you think of my two hypotheses?

They are possible, but it is not likely they are true.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon,

I am not sure

I agree with that.

See my next slide.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- Dr. de Leon, you have taught us that:
  - clozapine is metabolized by CYP1A2 and glucuronidation.
  - Valproate inhibits the glucuronidation of lamotrigine and lorazepam.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon,
is this information
correct?

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon,
is this information
correct?

Yes.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon,
I have resolved the case; valproate inhibited clozapine glucuronidation and caused a toxic metabolite!

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon,
I have resolved the case;
valproate inhibited clozapine glucuronidation and caused a toxic metabolite!

I doubt that.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

This time,

Dr. de Leon, you are not getting away easily.

Why do you doubt it?

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

This time,
Dr. de Leon, you are not getting away easily.
Why do you doubt it?

There is no support from PubMed articles.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- Dr. de Leon, my 2/4/16 search for "clozapine and valproate" provided 230 articles, too many of them irrelevant.
- As you, Dr. de Leon, have taught me:
  - I went to MeSh headings and selected "Clozapine/metabolism" [Mesh]. This provided 8894 articles focused on clozapine metabolism.
  - Then I added "and valproate". The search was "Clozapine/metabolism" [Mesh] AND valproate." This provided 17 articles. A reasonable number!

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Let's read the first article from the list.

http://www.ncbi.nlm.nih.gov/pubmed/24764199

Oh no, you Dr. de Leon, are the last author. You are probably biased.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- First title: “Can valproic acid be an inducer of clozapine metabolism?”
- The results section of the abstract says: “VPA appeared to be an inducer of clozapine metabolism since total plasma clozapine concentrations in subjects taking VPA were significantly lower (27% lower; 95% confidence interval, 14-39%) after controlling for confounding variables including smoking (35% lower, 28-56%).”

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Let's read the second article from the list.

http://www.ncbi.nlm.nih.gov/pubmed/24113673

Oh no, again, you Dr. de Leon, are the last author.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- Second article title: “A case report that suggested that aspirin's effects on valproic acid metabolism may contribute to valproic acid's inducer effects on clozapine metabolism.”
- There is no abstract.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Let's read the third article from the list.

http://www.ncbi.nlm.nih.gov/pubmed/23104241

Oh great,

Dr. de Leon, you are not an author.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- Third article title: “Clinical predictors of serum clozapine levels in patients with treatment-resistant schizophrenia.”
- Abstract: “While employing multivariate robust regression models, oral clozapine dose ($P<0.001$), caffeine intake ($P=0.04$) and Valproate comedication ($P=0.005$) were associated with serum clozapine levels”

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

This third article says valproate has a significant effect on clozapine concentration but it does not say direction. It can be an inhibitor or an inducer, correct?

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

This third article says valproate has a significant effect on clozapine concentration but it does not say direction. It can be an inhibitor or an inducer, correct?

Yes, this is a “bad” abstract. Valproate was an inhibitor.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Let's read the fourth article from the list.

http://www.ncbi.nlm.nih.gov/pubmed/18484549

Oh no, again, you Dr. de Leon, are the last author.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- Fourth article title: “Estimating the size of the effects of co-medications on plasma clozapine concentrations using a model that controls for clozapine doses and confounding variables.”
- Abstract: “Valproic acid appeared to inhibit clozapine metabolism in non-smokers (effect size, E=+16%), whereas it appeared to induce clozapine metabolism in smokers (E=-22%). ”

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

I give up; you seem to know about this subject. Dr. de Leon, can you summarize the subject for me?

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

I give up; you seem to know about this subject. Dr. de Leon, can you summarize the subject for me?

Yes; see the next slide.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- Changes in clozapine metabolism caused by valproate:
  - are likely to be small
  - There are descriptions of both
    - induction and
    - inhibition
  - In one case valproate caused potent induction of clozapine metabolism.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon, are these changes in drug metabolism relevant for this case?

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

Dr. de Leon, are these changes in drug metabolism relevant for this case?

I'm not sure; see the next slide.

2.3.7. Valproate Case 2: Pharmacokinetic DDIs

- In summary, although this case appears similar to prior cases of eosinophilic pleural effusions due to valproate, we cannot completely rule out the possibility that valproate changed:
  - clozapine metabolism, and
  - these changes may then have contributed to this ADR.
- We can use the Naranjo ADR scale to establish the relationship with valproate.

2.3.8. Naranjo ADR Scale

2.3.8. Valproate Case 2: Naranjo ADR Scale

- The literature review on valproate-induced pleural effusion by *"Kamenetsky et al."*

  http://www.ncbi.nlm.nih.gov/pubmed/22217614

  uses the Naranjo ADR scale to score cases of pleural effusion associated with valproate.

- The article describing the scale is *"Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther.1981 Aug;30(2):239-45."* http://www.ncbi.nlm.nih.gov/pubmed/7249508

2.3.8. Valproate Case 2: Naranjo ADR Scale

- The Naranjo ADR scale has 10 questions:
  - Each question can be answered:
    - yes
    - no
    - unknown
  - The total scoring can be:
    - ≥ 9: the ADR is “definite”
    - 5-8: the ADR is “probable”
    - 1-4: the ADR is “possible”
    - ≤0: the ADR is “doubtful”

http://www.ncbi.nlm.nih.gov/pubmed/7249508

2.3.8. Valproate Case 2: Naranjo ADR Scale

- *"Kamenetsky et al."* rated this case with the Naranjo ADR scale: "4" or "possible."

  http://www.ncbi.nlm.nih.gov/pubmed/22217614

- Dr. de Leon also rated this case with the Naranjo ADR scale as "4" or "possible". The next slide provides details.

2.3.8. Valproate Case 2: Naranjo ADR Scale

- Dr. de Leon's ratings:
  - 1. Are there previous conclusive reports on this reaction? **Yes (+1).**
  - 2. Did the adverse event appear after the suspected drug was administered? **Yes (+2).**
  - 3. Did the adverse reaction decrease when the drug was discontinued or a specific antagonist was administered? **Yes (+1).**
  - 4. Are there alternative causes (other than the drug) that could on their own have caused the reaction? **Yes, clozapine (-1).**
  - 10. Was the adverse event confirmed by any objective evidence? **Yes (+1).**

Total=1+2+1-1+1=**4**

Questions

- Please review the 10 questions on the pdf entitled "Questions on the Presentation Valproate Case 2: Safety".
- 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. C
4. A
5. B
6. D
7. D
8. C
9. A
10. A