Comparing Nonlinear Pharmacokinetic Properties of Therapeutic Drugs from 2000 to 2015

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Outline

☐ Background
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☐ Methods
☐ Results
☐ Conclusion
☐ Limitations
☐ Next Steps
What is nonlinear?

**Linear**

**Nonlinear**

Having to wait because saturation does NOT mean that you can do ANYTHING you want!!

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Background

What is nonlinear pharmacokinetics?

- Nonlinear pharmacokinetics can cause increases in drug concentrations that are disproportionately high or low relative to the change in dose. [1]
Background

Causes of nonlinear PK $^{[1]}$

- Reduced absorption
- Protein binding saturation
- Saturation of first pass metabolism
- Biotransformation saturation
- Target-mediated drug disposition (TMDD)
- Saturation of excretion
Background

Why did we choose to do this study?

- Nonlinear pharmacokinetic drugs pose a challenge in therapy management due to their complex nature.
- Presently, there are no known databases dedicated to drugs of this class despite the growing number on the market.
Goal

Our goal is to improve medication management and patient care by analyzing the trends in the approval, use, mechanism of action, and formulation of nonlinear drugs.
Objective

- Using the FDA database, search for new drugs approved with nonlinear pharmacokinetic characteristics
- Analyze trends specific to this group of nonlinear drugs
Methods

- We chose which drugs to analyze for nonlinear pharmacokinetics by searching for new drug approvals on the FDA website from the years 2000-2015.
- We recorded the generic names, brand names, mechanism of action, metabolic pathway, dosing regimen, bioavailability and indications of all drugs approved in this time period.
Methods

The information on the package insert was used to determine which drugs exhibited nonlinear kinetics and the mechanism of the nonlinear kinetics

- If the kinetics weren’t clear from the package insert, we searched for additional resources in PubMed
Methods

Key words that can indicate a drug exhibits nonlinear pharmacokinetics -
- Nonlinear
- Non-proportional/not proportional
- Saturable
- Michaelis-Menten kinetics
Methods - Statistical Analysis

1. Student $t$-Test: Examine the comparison between the amount of linear vs. nonlinear drugs approved from 2000-2015

1. Fisher’s Exact Test: Comparison of drug classes between linear and nonlinear drugs approved from 2000-2015
Results

- From 2000-2015, the FDA approved 439 drugs in total
  - 96 (21%) are nonlinear drugs
  - 74 (77.1%) are small molecules, 22 (22.9%) are large molecules/biologics
Number of linear and nonlinear drugs approved from 2000-2015

Number of linear and nonlinear drugs approved from 2000-2015

p<0.0001

Non-linear drugs (N=94)  Linear drugs (N=345)
Comparison of number of biologics and nonlinear biologics from 2000-2015

Number of Biologics
Number of nonlinear Biologics
DISTRIBUTION OF NONLINEAR MECHANISM

- Absorption: 32%
- Metabolism: 43%
- Distribution: 7%
- TMDD: 15%
- Poor solubility: 3%
DISTRIBUTION OF NONLINEAR DRUGS ACCORDING TO TREATMENT CLASSIFICATION

- Oncology: 26%
- Endocrines: 15%
- GI: 8%
- Hypercholesterol: 3%
- Hypertension: 2%
- Hypoalimentation: 2%
- Immune suppressant: 5%
- Enzyme deficiencies: 4%
- Electolyte problems: 3%
- CNS agents: 13%
- Anti-infectives: 15%
- Others: 4%

Macular degeneration: 2%

Oncology 26%
Treatment classification of nonlinear drugs every year from 2000 to 2015

- anti-infectives
- CNS agents
- Electrolyte problems
- Endocrines
- Enzyme deficiencies
- GI
- Hypercholesterol
- Hypertension
- Immune suppressant
- Macular degeneration
- oncology
- Others
Comparison of nonlinear vs linear drug in treatment classification from 2000-2015

- Others
- Oncology
- Macular degeneration
- Immune suppressant
- Hypertension
- Hypercholesterol
- GI
- Enzyme deficiencies
- Endocrines
- Electrolyte problems
- CNS agents
- Anti-infectives

Total number

- Linear drug
- Nonlinear drug
Fisher’s Exact Test:

Odds ratio:  
(drugs onco-logic-linear / drugs onco-logic - non-linear)  
(drugs non-onco-logic-linear / drugs non-onco-logic-non-linear)
## Table 1. Treatment classification of nonlinear and linear drugs

<table>
<thead>
<tr>
<th>Drug indication</th>
<th>Number of agents with non-linear PK approved from 2000-2015</th>
<th>Number of agents with linear PK approved from 2000-2015</th>
<th>Odds ratio (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-infective</td>
<td>14</td>
<td>56</td>
<td>0.907 (0.444, 1.75), 0.874</td>
</tr>
<tr>
<td>CNS agents</td>
<td>13</td>
<td>76</td>
<td>0.573 (0.278, 1.10), 0.086</td>
</tr>
<tr>
<td>Electrolyte problems</td>
<td>3</td>
<td>5</td>
<td>2.24 (0.342, 11.7), 0.376</td>
</tr>
<tr>
<td>Endocrines</td>
<td>14</td>
<td>43</td>
<td>1.23 (0.593, 2.43), 0.495</td>
</tr>
<tr>
<td>Enzyme deficiencies</td>
<td>4</td>
<td>7</td>
<td>2.15 (0.451, 8.65), 0.259</td>
</tr>
<tr>
<td>GI</td>
<td>8</td>
<td>16</td>
<td>1.91 (0.686, 4.92), 0.196</td>
</tr>
<tr>
<td>Hypercholesterol</td>
<td>3</td>
<td>10</td>
<td>1.11 (0.192, 4.42), 1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>17</td>
<td>0.422 (0.046, 1.83), 0.390</td>
</tr>
<tr>
<td>Immune suppressants</td>
<td>5</td>
<td>50</td>
<td>0.334 (0.101, 0.869), 0.021</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>2</td>
<td>5</td>
<td>1.48 (0.139, 9.21), 0.645</td>
</tr>
<tr>
<td>Oncology</td>
<td>25</td>
<td>52</td>
<td>2.03 (1.13, 3.60), 0.014</td>
</tr>
<tr>
<td>Others (Nutrition supplements, NSAIDs, osteoporosis, Gaucher’s disease)</td>
<td>4</td>
<td>20</td>
<td>0.725 (0.176, 2.24), 0.798</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>97</strong></td>
<td><strong>357</strong></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion:

It was determined that there were no significant differences on comparing the nonlinear vs. linear drugs in each class against the remaining total, hence accepting the null hypothesis (p<0.0024, CI=95%).
Results (cont)

- Nonlinear drug is a component of therapeutic monitoring
- Only 13 out of 96 drugs actually made into guideline
  - 2 out of 14 are biologics
Table 2. List of nonlinear drugs mentioned in clinical TDM guidelines.

<table>
<thead>
<tr>
<th>Clinical guideline(s) examined</th>
<th>Nonlinear drugs listed for TDM</th>
<th>Type of nonlinear drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao et al(^9)</td>
<td>Erlotinib, Gefitinib, Sunitinib, Nilotinib, Sorafenib</td>
<td>Oncology (N=5)</td>
</tr>
<tr>
<td>Medina et al(^{10})</td>
<td>Tocilizumab</td>
<td>Immune suppressant (N=1)</td>
</tr>
<tr>
<td>Heimke et al(^{11})</td>
<td>Rivastigmine, Paroxetine, Iloperidone, Lamotrigine, Fluvoxamine</td>
<td>CNS agent (N=5)</td>
</tr>
<tr>
<td>Casteele et al(^{12})</td>
<td>Natalizumab, Temsirolimus</td>
<td>Immune suppressant (N=2)</td>
</tr>
</tbody>
</table>
Conclusion

- On average, one in five approved drugs have nonlinear pharmacokinetic properties
- Nonlinear pharmacokinetics are independent from molecular weight, treatment classification, and other drug properties
- Most nonlinear mechanisms come from changes in metabolism and absorption
  - A significant portion of nonlinear drugs exhibit TMDD
Conclusion

- Very few nonlinear drugs have specific guidelines or clinical monitoring instructions.
  - Some of these drugs patients may use on an “as needed” basis at home, increasing the risk of sub- or supra-therapeutic levels.

→ There is a need to include monitoring guides for these drugs for patients to take home.
Limitations

- Database isn’t complete - only 15 years have been analyzed, there could be additional or extended trends we didn’t see
- Drug classes were based on indication
- Drugs with multiple uses were only placed into one category
Next Steps

- Continue to search for nonlinear drugs as new drugs are approved, and search through drugs approved before 2000 to complete the database.
- Optimize the complete database for use in the clinical/acute setting to improve drug monitoring and patient management.
ANY QUESTIONS?

Your project is to look at the shed Her2 antigen from a patient dataset.

Most literature said that HER2 antigen.

I need to think of a good question to ask.

THINK OF A QUESTION ANY QUESTIONS?

Any questions?

Yes. What are we looking at again?

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References


Drugs@FDA: FDA Approved Drug Products. Retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm


Survey Link
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