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Apr 6th, 10:00 AM - 11:00 AM

N-acetylcysteine (NAC) and Ondansetron (Zofran) Intravenous Compatibility Determination via RP-HPLC and LC-MS/MS

Methods

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N-acetylcysteine (NAC) and Ondansetron (Zofran) Intravenous Compatibility Determination via RP-HPLC and LC-MS/MS Methods

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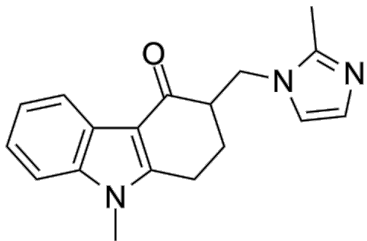
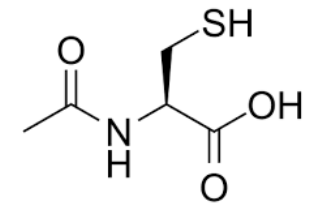
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Background



Acetaminophen toxicity accounts for approximately 56,000 emergency room visits yearly

Standard of care (SOC) is a 21-hour NAC intravenous (IV) infusion



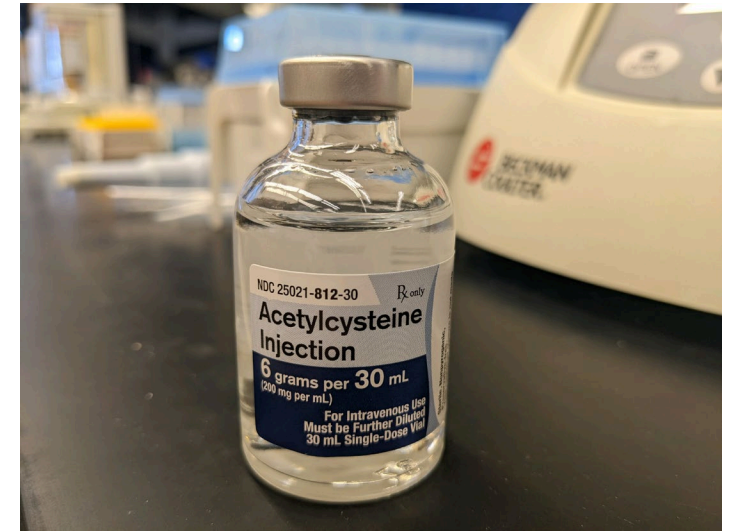
NAC administration often leads to nausea/vomiting warranting ondansetron, a 5-HT₃ receptor antagonist

IV infusion of NAC must be interrupted for ondansetron treatment increasing unnecessary risk of liver complications

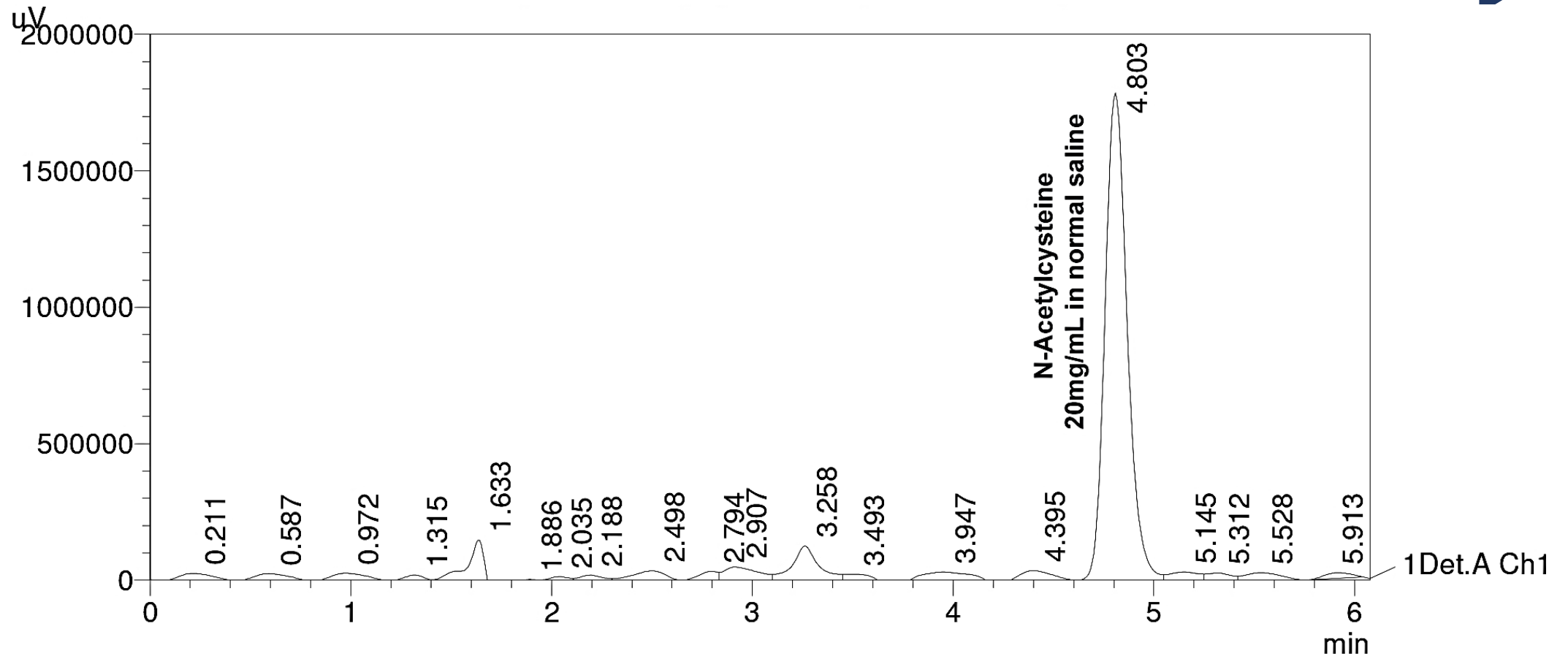


Quantification of N-Acetylcysteine

- Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC)
 - Detection: UV (212nm)
 - Separation: C18 column + isocratic mobile phase
 - Agilent Eclipse XDB-C18 (3.5 micron, 4.6 X 150 mm)
 - Acetonitrile (ACN) + water (10:90 v/v) + 0.1 % trifluoroacetic acid (TFA)
 - Flow Rate: 0.500 mL/min
 - Injection Volume: 10 microliters
 - Temperature: 50°C

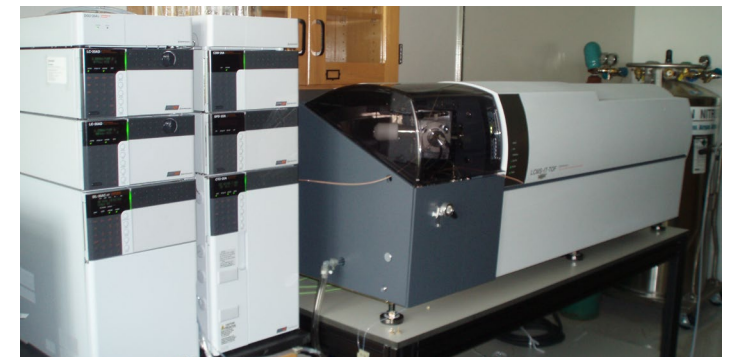
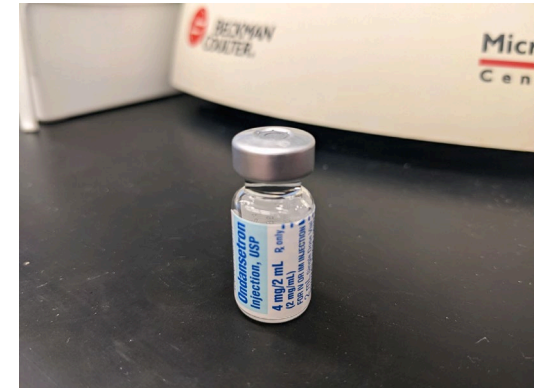


NAC RP-HPLC Chromatogram

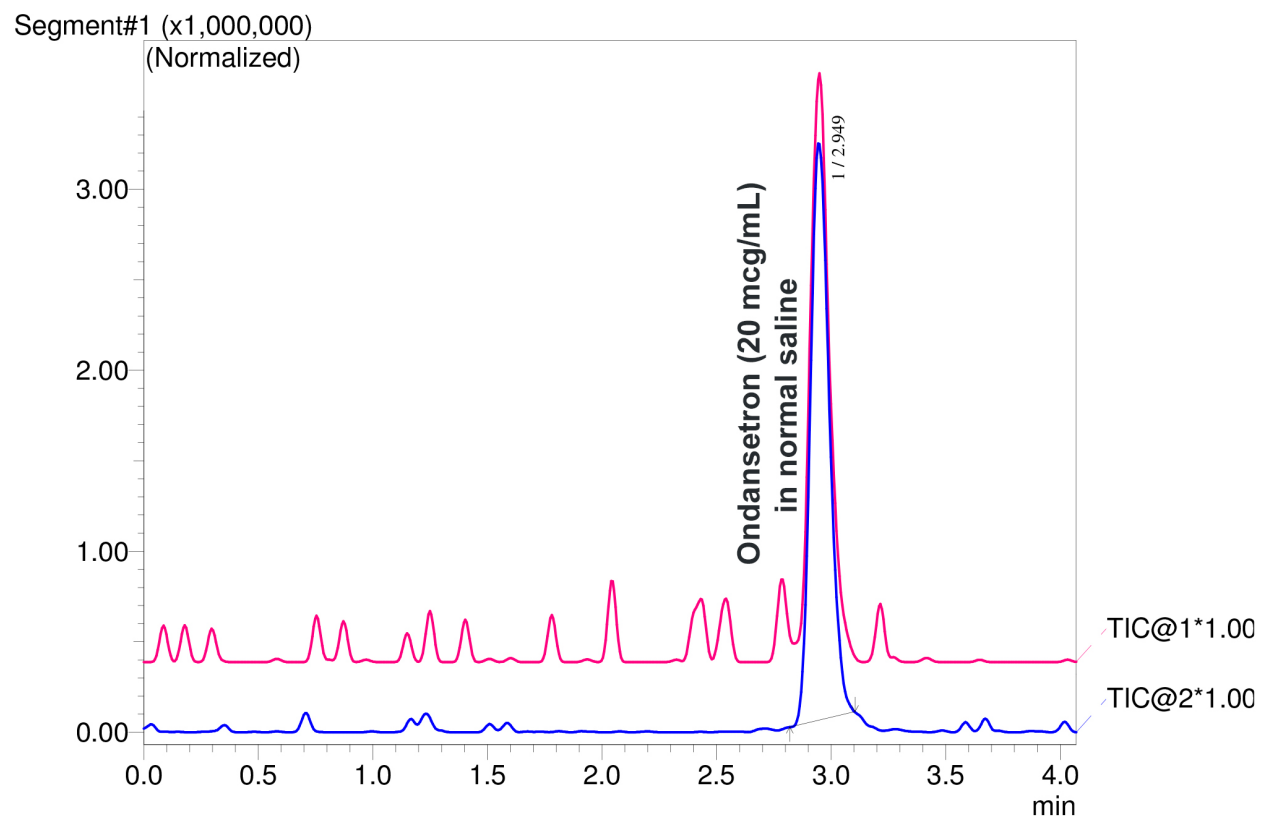


Quantification of Ondansetron

- Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)
 - Detection: +ESI-MS (Precursor ion = m/z 294)
 - Separation: C18 column + isocratic mobile phase
 - Waters XBridge C18 (3.5 micron, 4.6 mm x 150 mm)
 - Ammonium formate buffer (pH = 3.0, 5 mM) + acetonitrile (15:85 v/v)
 - Flow Rate: 0.500 mL/min
 - Injection Volume: 1 microliter
 - Temperature: 50°C



Ondansetron LC-MS/MS Chromatograph

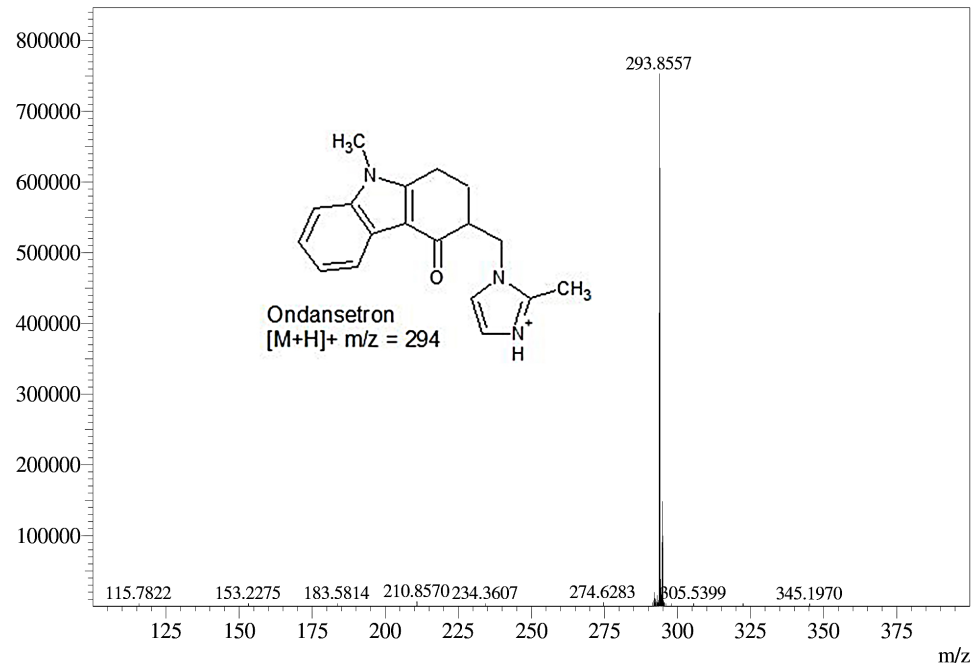


TIC1 = precursor ion (m/z = 294)

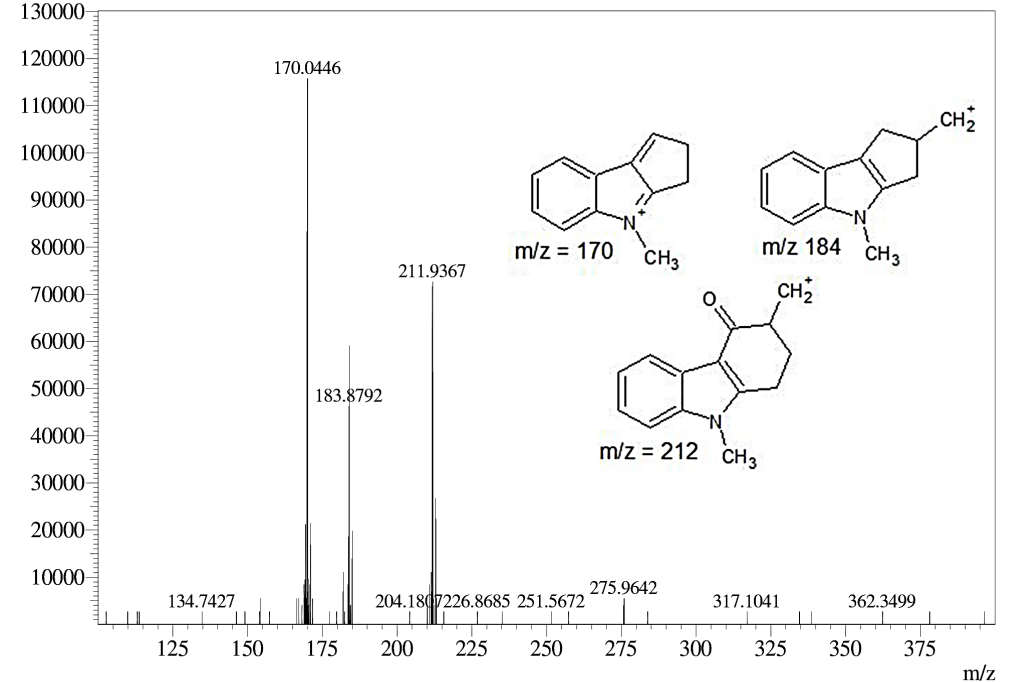
TIC2 - product ion (m/z = 170)

Ondansetron LC-MS/MS Spectrum

MSMS/MS: Precursor m/z 294.02 +/- Base Peak 293.86(753148)



MSMS/MS: Precursor m/z 294.02 +/- Base Peak 170.04(73176)



Why different methods?

Literature illustrates NAC does not perform well with LC-MS

- Small molecular weight difficult to distinguish from noise
- Amphoteric molecule (absence of strong ions in + or – mode)

Concentration of NAC and Ondansetron has order of magnitude difference

- Large, dynamic range would be hard to accommodate

Ondansetron will work via HPLC-UV, but LC-MS creates opportunity to evaluate possible NAC-ondansetron adducts

Experimental Setup

- Pump contains 5 channels ported by medical grade tubing
 - Channel 1 – NAC only
 - Channel 2 – Ondansetron only
 - Channel 3-5 – NAC/Ondansetron combinations
- Goal is to compare single drug channels with combination drug channels
- Combinations have ondansetron introduced to NAC via γ -site



Expected Results

- Selected methods are validated for linearity, precision, and accuracy to ensure accurate quantification of NAC and ondansetron
- Methods will allow us to evaluate the chemical compatibility of NAC and ondansetron for simultaneous IV administration
 - Warnings exist on hospital formularies to avoid administration of medications simultaneously with NAC
 - Trissel's IV Compatibility via LexiComp provides not information on NAC/Ondansetron compatibility

References

- Gaurav Ninama, Rashmin Patel, Mrunali Patel, Gaurang Shah, Solid phase extraction liquid chromatography mass spectrometry method with electrospray ionization for the determination of Ondansetron in human plasma: Development and validation consideration, Arabian Journal of Chemistry, Volume 10, Supplement 2, 2017, Pages S3135-S3141, ISSN 1878-5352, <https://doi.org/10.1016/j.arabjc.2013.12.004>.
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- Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (Paracetomal)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf. 2006 Jun;15(6):398-405. doi: 10.1002/pds.1191. PMID: 16294364.