SEVOFLURANE AND DESFLURANE HEPATOTOXICITY

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DISCLOSURES

• MCGRAW – HILL EDUCATION
  • ON-LINE PODCASTS/LECTURES

AT THE COMPLETION OF THIS LECTURE

• **COMPREHEND** THE PREVALENCE OF HEPATOTOXICITY ASSOCIATED WITH SEVOFLURANE AND OTHER HALOGENATED ANESTHETICS.

• **REVIEW** ACCEPTED MECHANISMS OF HEPATOTOXICITY FROM SEVOFLURANE AND DESFLURANE AS WELL AS METHODS FOR CONFIRMATION OF THE DIAGNOSIS.

• **RECOGNIZE** GAPS IN KNOWLEDGE SURROUNDING THE PREVALENCE AND MECHANISMS OF SEVOFLURANE AND DESFLURANE HEPATOTOXICITY AND BEGIN TO DISCUSS HOW THESE GAPS MAY BE ADDRESSED.
BACKGROUND
LIVER DISEASE

• LIVER DISEASE AND CIRRHOSIS ARE THE SIXTH MOST COMMON CAUSE OF DEATH IN ADULTS BETWEEN THE AGES OF 25 AND 64 (NATIONAL CENTER FOR HEALTH STATISTICS, 2014).

• LIVER-RELATED MORTALITY IN THE UNITED STATES MAY BE UNDERESTIMATED (ASRANI ET AL., 2013).
LIVER DISEASE

• DRUG-INDUCED HEPATITIS IS A LEADING CAUSE OF LIVER FAILURE AND IS THE MOST COMMON REASON AN APPROVED MEDICATION IS REMOVED FROM THE CONSUMER MARKET (BELL AND CHALASANI, 2009).

• MANY TYPES OF DRUG-INDUCED HEPATITIS ARE BELIEVED TO BE IMMUNE-MEDIATED.
BOTH OF THE MODERN HALOGENATED ANESTHETICS HAVE BEEN ASSOCIATED WITH HEPATOTOXICITY

BACKGROUND SUMMARY

• LIVER-RELATED MORTALITY IS AT AN ALL TIME HIGH IN THE US

• THE BURDEN OF DISEASE ASSOCIATED WITH THE LIVER MAY BE UNDERESTIMATED

• IMMUNE-MEDIATED HEPATITIS IS A FINAL COMMON MECHANISM THAT FOLLOWS MANY FORMS OF LIVER INJURY

• DESFLURANE AND SEVOFLURANE HAVE BEEN ASSOCIATED WITH HEPATOTOXICITY
WHAT IS THE INCIDENCE OR PREVALENCE OF HEPATOTOXICITY ASSOCIATED WITH DESFLURANE OR SEVOFLURANE?
DESFLURANE

• INTRODUCED IN 1993

• PREVALENCE OF HEPATOTOXICITY: 1 IN 10 MILLION

• REPORTED CASES OF HEPATOTOXICITY: FIVE
<table>
<thead>
<tr>
<th>Year</th>
<th>Age/Sex</th>
<th>Procedure</th>
<th>Prior exposure</th>
<th>POD Onset</th>
<th>Elevated LFTs</th>
<th>Infectious rule out</th>
<th>CYP2E1 or TFA testing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>65y/o F</td>
<td>Thyroidectomy</td>
<td>Yes</td>
<td>14</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>survival</td>
</tr>
<tr>
<td>1999</td>
<td>37y/o F</td>
<td>Tibial fx</td>
<td>Yes</td>
<td>12</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>survival</td>
</tr>
<tr>
<td>2005</td>
<td>81 y/o F</td>
<td>Hemi-colectomy</td>
<td>Yes</td>
<td>6</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>survival</td>
</tr>
<tr>
<td>2007</td>
<td>15 mo M</td>
<td>Nissen</td>
<td>Yes</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>survival</td>
</tr>
<tr>
<td>2018</td>
<td>54y/o F</td>
<td>Sleeve gastrectomy</td>
<td>Yes</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>survival</td>
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</table>
SEVOFLURANE

• INTRODUCED IN 1999

• INCIDENCE OR PREVALENCE OF HEPATOTOXICITY: UNKNOWN

• REPORTED CASES: NINE
<table>
<thead>
<tr>
<th>Year</th>
<th>Age/Sex</th>
<th>Procedure</th>
<th>Prior exposure</th>
<th>POD Onset</th>
<th>Elevated LFTs</th>
<th>Infectious rule out</th>
<th>CYP2E1 or TFA testing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>infant</td>
<td>Extra digit</td>
<td>No</td>
<td>15</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unk</td>
</tr>
<tr>
<td>2007</td>
<td>75 y/o F</td>
<td>AVR</td>
<td>Yes (4)</td>
<td>2</td>
<td>Yes</td>
<td>Unk</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>2007</td>
<td>69 y/o M</td>
<td>vascular</td>
<td>Yes (twice in 2 days)</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>2010</td>
<td>66 y/o F</td>
<td>Lymph node 2 weeks after mastectomy</td>
<td>Yes (twice in 2 days)</td>
<td>15</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>2010</td>
<td>37 y/o M</td>
<td>abdominal</td>
<td>Unk</td>
<td>3</td>
<td>Yes</td>
<td>EBV</td>
<td>No</td>
<td>survival</td>
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<tr>
<td>2010</td>
<td>47 y/o F</td>
<td>Renal transplant</td>
<td>Unk</td>
<td>2</td>
<td>Yes</td>
<td>Unk</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>2012</td>
<td>24 y/o F</td>
<td>colectomy</td>
<td>Weeks apart</td>
<td>8wks</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>survival</td>
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<tr>
<td>2012</td>
<td>38 y/o M</td>
<td>Hand reconstruction</td>
<td>No</td>
<td>8mos.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>survival</td>
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<tr>
<td>2012</td>
<td>30 y/o F</td>
<td>crani</td>
<td>No</td>
<td>8wks</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>survival</td>
</tr>
</tbody>
</table>
SUMMARY:
THE INCIDENCE OR PREVALENCE OF DESFLURANE HEPATOTOXICITY IS 1 IN 10 MILLION

• DESFLURANE HEPATOTOXICITY HAS BEEN REPORTED AT LEAST 5 TIMES
  • 80% OF CASES WERE IN FEMALE PATIENTS
  • 20% OF CASES WERE IN MALE PATIENTS
  • ALL REPORTED CASES HAVE SURVIVED
SUMMARY:
THE INCIDENCE OR PREVALENCE OF SEVOFLURANE HEPATOTOXICITY IS UNCLEAR

- Sevoflurane hepatotoxicity has been reported at least 9 times.
- 55% of cases were in female patients.
- 33% of cases were in male patients.
- In 11% of cases, the sex was unknown.
- Death occurred in 44% of patients, and of the patients that died, all were female.
SUMMARY: IF METABOLISM IS THE KEY....

• WHY DID HEPATOTOXICITY OCCUR WITH DESFLURANE AND SEVOFLURANE?

• ARE THERE SUSCEPTIBLE PERSONS OR CONDITIONS THAT INCREASE SUSCEPTIBILITY DESFLURANE OR SEVOFLURANE HEPATOTOXICITY?
WHAT ARE THE ACCEPTED MECHANISMS OF HEPATOTOXICITY FROM SEVOFLURANE AND METHODS FOR CONFIRMATION OF THE DIAGNOSIS.
CHARACTERISTICS OF IMMUNE-MEDIATED HEPATOTOXICITY FROM ANESTHETICS

- FEMALE
- URTICARIA OR SKIN RASH, SUGGESTING A DRUG ALLERGY
- EOSINOPHILIA
- SERUM AUTOANTIBODIES TO CYTOCHROME P450 2E1 (CYP2E1)
- SERUM ANTI-DRUG METABOLITE (TFA)
- LIVER INFLAMMATION ± FULMINANT LIVER FAILURE
- MILD OR MODERATE INCREASES IN LIVER ENZYMES
- FAMILY HISTORY OF AUTOIMMUNE DISEASE
WE NOW KNOW THIS......
CFA (viral Mimic)

S100 (liver Proteins)

CFA + TFA-S100
WE ALSO KNOW THIS......

CYP2E1

McCarthy E, et al., mSphere, 2018
PATIENTS WITH ANESTHETIC HEPATOTOXICITY DEVELOP ANTIBODIES TO ONE IMMUNOGENIC PIECE OF CYP2E1

McCarthy E, et al., mSphere, 2018
SUMMARY: IMMUNE-MEDIATED HEPATOTOXICITY

Stress

Chemical Antigens/
Drug Metabolites

Viruses

Activation of the Immune System

Cytokine, Chemokine or Other Tissue Factor Release

End Organ Inflammation/Immune dysregulation
COULD REGULATORY CELLS BE UTILIZED TO REDUCE IMMUNE RESPONSES IN SEVOFLURANE OR DESFLURANE HEPATOTOXICITY?

T regs
B regs
Natural Killer Cells
Macrophages
Cottagiri M, et al., Cellular and Molecular Immunology, 2018
IN ANESTHETIC HEPATOTOXICITY, IL-33 IS UPREGULATED WHILE IPEX IS DOWN-REGULATED

Cottagiri M, et al., Cellular and Molecular Immunology, 2018
DYSREGULATED IL-33- IPEX EXPRESSION PROMOTES ANESTHETIC HEPATOTOXICITY

Cottagiri M, et al., Cellular and Molecular Immunology, 2018
SUMMARY:
DEFICIENCY OF REGULATORY T CELLS INCREASES HEPATOTOXICITY SEVERITY IN FEMALES
WHAT ARE THE GAPS IN KNOWLEDGE SURROUNDING THE PREVALENCE AND MECHANISMS OF SEVOFLURANE HEPATOTOXICITY AND CAN WE BEGIN TO DISCUSS HOW THEY MAY BE ADDRESSED
WHAT IS THE INCIDENCE OR PREVALENCE OF PERIOPERATIVE LIVER INJURY?

WHAT IS THE INCIDENCE OR PREVALENCE OF SEVOFLURANE HEPATOTOXICITY?

IS SEVOFLURANE HEPATOTOXICITY MORE SEVERE IN FEMALES?

COULD T REGULATORY CELL MARKERS BE DEVELOPED AS CHECKPOINTS FOR SEVOFLURANE OR DESFLURANE HEPATOTOXICITY?
Drug-induced hepatotoxicity: incidence of abnormal liver function tests consistent with volatile anaesthetic hepatitis in trauma patients

Jonathan Lin, David Moore, Brad Hockey, Rachel Di Lernia, Alexandra Gorelik, Danny Liew and Amanda Nicoll

Forty-seven (3%) of 1556 patients had abnormal post-operative liver biochemistry potentially attributable to volatile anaesthetic.

Liver Int. 2014 Apr;34(4):576-82
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