Drug Safety and Anesthesia

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Drug Safety (1)

- Current state of the pharmaceutical industry
- The drug approval process
- My experiences at the FDA
Drug Safety (2)

- Drug shortages
- Limits on pharma interactions with physicians
- Conflict-of-interest rules for academic physicians
Drug Safety (3)

- Some controversial stories:
  - Succinylcholine
  - Sevoflurane
  - Droperidol
  - Aprotinin
  - Heparin
  - Suggamadex
Drug approval process

http://www.nature.com/embor/journal/v5/n9/images/7400236-f1.jpg
Drug approval process

http://www.chemcases.com/cisplat/images/fdadevelop.gif
Consolidation

THE WALL STREET JOURNAL
WSJ.com

JANUARY 24, 2009

Pfizer Nears Giant Drug Deal

By MATTHEW KARNITSCHNIG and SARAH RUBENSTEIN

Pfizer Inc. is expected to pay between $65 billion and $70 billion to acquire rival Wyeth, people familiar with the matter say, as the drug maker makes a risky effort to shore itself up ahead of huge disruptions in the next few years.
Consolidation

• “Pipeline” problems
  ○ Losing patent protection of Lipitor

• Allows Pfizer access to biologics
  ○ Vaccines
  ○ Large molecules
    ■ Difficult to make as generics
Ellis opines

- Pharma interested in two types of drugs:
  - Drugs that patients take every day for the rest of their lives
    - e.g., antihypertensives
  - Drugs for niche uses that command high prices
    - e.g., recombinant Factor VII
January 13, 2009

F.D.A. Eases Off-Label Drug Rules

By REUTERS

WASHINGTON (Reuters) — Health officials completed guidelines that allow pharmaceutical companies to tell doctors about unapproved uses of their medicines, a practice opposed by critics of industry marketing.

Under the guidelines, established by the Food and Drug Administration, manufacturers are allowed to distribute copies of medical journal articles that describe unapproved uses. The action could help companies expand the markets for medicines and medical devices.

The move puts in place a policy that drew objections from Congressional Democrats and critics of the drug industry when it was proposed last year.
Roughly half of drug use is “off-label.”
Which study would you cite?

SPECIAL ARTICLE

Alpha-2 Adrenergic Agonists to Prevent Perioperative Cardiovascular Complications: A Meta-analysis

Duminda N. Wijeysundera, MD, Jennifer S. Naik, MD, W. Scott Beattie, MD, PhD

Figure 4. Effect of \( \alpha_2 \)-agonists on myocardial ischemia during all types of surgery

The American Journal of Medicine Volume 114, Issue 9, 15 June 2003
Premedication with Oral and Transdermal Clonidine Provides Safe and Efficacious Postoperative Sympatholysis

John E. Ellis, MD*, Greet Drijvers, MD*, Steven Pedlow, MS†, Scott P. Laff, MD*, Matthew J. Sorrentino, MD‡, Joseph F. Foss, MD*, Manish Shah, BS*, J. R. Busse, MD*, Srinivas Mantha, MD*, James F. McKinsey, MD§, Joachim Osinski, MS*, Ronald A. Thisted, PhD*, Michael F. Roizen, MD*

Departments of *Anesthesia and Critical Care, †Statistics, ‡Medicine (Section of Cardiology), and §Surgery, The University of Chicago, Chicago, Illinois
Which study would you cite?

Figure 4. Effect of $\alpha_2$-agonists on myocardial ischemia during all types of surgery.

*The American Journal of Medicine, Volume 114, Issue 9, 15 June 2003.*
Which study would you cite?

Figure 4. Effect of α2-agonists on myocardial ischemia during all types of surgery

*The American Journal of Medicine, Volume 114, Issue 9, 15 June 2003*
How best to sell the drug?

![Graph showing cumulative risk over time for Aspirin and Clopidogrel with p = 0.043]

| Time since randomisation (months) | Patients A: 9586 9190 8087 6139 3979 2143 542 | Patients C: 9599 9247 8131 6160 4053 2170 539 |
|----------------------------------|-----------------------------------------------|

Lancet Volume 348, Issue 9038, 16 November 1996, Pages 1329-1339
How best to sell the drug?

- Clopidogrel reduces CV events by 8.7% compared to aspirin

- You need to treat (NNT) 200 patients with plavix to have 1 patient do better than if you’d used aspirin

Lancet Volume 348, Issue 9038, 16 November 1996, Pages 1329-1339
Cleveland Clinic's Dr. Steven Nissen, shortlisted for U.S. Food and Drug Administration commissioner, talks about the agency

Tuesday, January 20, 2009
Sarah Jane Tribble
Plain Dealer Reporter

Dr. Steven Nissen rose to national prominence as a drug-industry watchdog by exposing the diabetes drug Avandia for increasing the risk of heart attack and for sounding early warnings about the painkiller Vioxx.
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.
Conclusions

- Rosiglitazone was associated with a significant increase in the risk of MI and with an increase in the risk of death from CV causes that had borderline significance.
- Our study was limited by a lack of access to original source data...
- Despite these limitations, .... consider the potential for serious adverse CV effects of treatment with rosiglitazone for type 2 DM.
Lawyers love drug recalls!

Sample Of Harmful Recalled Drug Cases

If you do not see a particular drug listed here or on the left, this means we have not added it to the website yet. Please contact us for information on any drug. CLICK HERE TO CONTACT US NOW

We specialize in drug cases!

- **OxyContin**
  - OxyContin is a prescription painkiller used for moderate to high pain relief associated with injuries, bursitis, dislocations, fractures, neuralgia, arthritis, lower back pain, and pain associated with cancer.

- **Permax**
  - Permax

- **Zyprexa**
Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.
Glaxo's Emails on Avandia Reveal Concern

By ALICIA MUNDY and JARED FAVOLE

(See Correction & Amplification below.)

When a study linking GlaxoSmithKline PLC's diabetes treatment Avandia to increased heart-attack risk was published in 2007, the pharmaceutical giant publicly responded by denouncing the researchers' conclusions. But internal emails indicate some of the company's own scientists were concerned that Glaxo's data were showing the same thing.
• The study by Dr. Nissen for NEJM was supposed to be kept under wraps until its release on May 21, but Glaxo obtained a copy on May 3 from a doctor, Steven Haffner of the University of Texas, who was reviewing it for the medical journal.
Dr. Haffner had been a Glaxo consultant on Avandia and received $433,000 from Glaxo between 2000 and 2007.

He confirms giving Glaxo the study, though saying it was "a terrible mistake."

http://online.wsj.com/article/SB123190610976680477.html?mod=googlenews_wsj
Ethics?

- Sharing the article is clearly unethical
- What about $61,000 annually???
  - What is difference is average annual compensation between academic and private practice ???
Dr. Nissen says that when he was visited by top Glaxo scientists, including the chief medical officer, just days before publication, they tried to get him to rethink his concerns.

http://online.wsj.com/article/SB123190610976680477.html?mod=googlenews-wsj
"They never revealed that they had obtained a copy of our manuscript and had concluded that our findings were irrefutable," he says.

"Instead, they attacked the ... study and ... the authors and the NEJM."
Academic medical centers respond

U of I to bar free drug samples, gifts

By ERIN JORDAN
ejordan@dmreg.com

Iowa City, Ia. — A new University of Iowa policy would prohibit physicians from giving free drug samples to patients, a long-standing practice that hospital leaders and consumer advocates say contributes to the ballooning cost of health care.

Other changes include barring U of I Health Care employees from accepting gifts and meals from private companies and requiring all doctors who do industry consulting to report who they work for and how much they are paid.
VOTE
Time to vote!

- There shouldn’t be limits on interactions?
- Researchers should not own stock in companies affected by their research?
- We don’t care how much the pharma pays Dr. X, but the $$ should be public knowledge?
- Professionalism requires no such financial arrangements.
• Even though publication bias, and overly enthusiastic early studies may exist
Drug Companies & Doctors: A Story of Corruption

By Marcia Angell

*Side Effects: A Prosecutor, a Whistleblower, and a Bestselling Antidepressant on Trial*
by Alison Bass
Algonquin Books of Chapel Hill, 260 pp., $24.95

*Our Daily Meds: How the Pharmaceutical Companies Transformed Themselves into Slick Marketing Machines and Hooked the Nation on Prescription Drugs*
by Melody Petersen
Sarah Crichton/Farrar, Straus and Giroux, 432 pp., $26.00

*Shyness: How Normal Behavior Became a Sickness*
by Christopher Lane
Yale University Press, 263 pp., $27.50; $18.00 (paper)
How pervasive is this?

- A recent survey found that about two thirds of academic medical centers hold equity interest in companies that sponsor research within the same institution.
- A study of medical school department chairs found that two thirds received departmental income from drug companies and three fifths received personal income.

Can medical schools police this?

- “Surely you remember that SKB donated an endowed chair to the department and there is some reasonable likelihood that Janssen Pharmaceuticals will do so as well.
- …In addition, Wyeth-Ayerst Pharmaceuticals has funded a Research Career Development Award program in the department, and I have asked both AstraZeneca and BMS to do the same.
- …Part of the rationale for their funding our faculty in such a manner would be my service on these boards.”
"The problems I've discussed are not limited to psychiatry, although they reach their most florid form there.

Similar conflicts of interest and biases exist in virtually every field of medicine, particularly those that rely heavily on drugs or devices."

Former NEJM editor
Former NEJM editor

• “It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines.

• I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of The New England Journal.
OIG Key Findings (Jan 2009)

- 1% of clinical investigators (206 of 29,691) disclosed a financial interest.
- FDA does not have a complete list of clinical investigators and does not use on-site inspections to confirm that submitted financial information is complete, meaning that reviewers cannot determine whether sponsors have submitted financial information for all clinical investigators.

OIG Key Findings (Jan 2009)

- 42% of FDA-approved marketing applications were missing financial information,
- 23% of approved marketing applications were missing a certification or disclosure form or required attachments,
- 28% of applications, sponsors used the due-diligence exemption to indicate that they were unable to provide complete financial information.

OIG Key Findings (2009)

- FDA did not document a review of any financial information for 31% of marketing applications. Reviewers who followed a review template were more likely to include financial information than those who did not.

- In 20% of applications with disclosed financial conflicts, neither the FDA nor sponsors took action.

Drug Safety Issues in Anesthesia Practice

How does this impact daily life?
Some controversies

- Succinylcholine
- Sevoflurane
- Droperidol
- COX2 inhibitors
- Aprotinin
- Heparin
- Suggamadex
Succinylcholine

- From 1990 to 1993, 36 cases of cardiac arrest (> 1/2 proceeding to death) were reported associated with the use of Sch.
- Most occurred in Duchenne's muscular dystrophy (occurs exclusively in males) and all but one of the children were under 8 years old.
Succinylcholine

• Nonetheless, routine use of Sch in children was banned except to emergently intubate or secure an airway.

• This provoked an uproar in the pediatric anesthesia community.
Succinylcholine

- The effects of a ban on routine use could result in increased respiratory and airway misadventures in other patients in whom succinylcholine might have been uniquely efficacious (quick on, quick off) in facilitation airway management, were its use allowed.
Succinylcholine

• Current package insert more liberal:
  ○ Succinylcholine in children should be reserved for emergency intubation or instances where immediate securing of the airway is necessary, e.g. laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible.
Rapicuronium

- Rapicuronium was felt to be a potential replacement for succinylcholine.
- It was approved August 1999.
- **Bronchospasm** was identified during Phase 3 trials as a potential problem
  - its prevalence and severity appeared even greater after it was released.
- It was withdrawn from the market in March 2001.
Succinylcholine

- Rapicuronium was later introduced in hopes of replacing Sch, but it had its own problems with bronchospasm that led to its recall.
Sevoflurane

When initially approved, there were concerns that fluoride ion and compound A production (from interaction with soda lyme in CO2 absorbents) might cause renal toxicity in humans.
Sevoflurane was approved with a limitation on its use with low fresh gas flows; package insert now states:

- "Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest that there is a potential for renal injury which is presumed due to Compound A."
Sevoflurane

- Animal and human studies demonstrate that sevoflurane administered for more than 2 MAC•hours and at fresh gas flow rates of <2 L/min may be associated with proteinuria and glycosuria."
VIOXX® 25 mg
(Rofecoxib Tablets)

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

Each tablet contains 25 mg rofecoxib.
Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

30 Tablets
Lot N2432 EXP 04-2005
Vioxx and CV events

http://content.nejm.org/content/vol352/issue11/images/large/07f2.jpeg
Vioxx and CV events

![Graph showing cumulative incidence of CHF, PE, or CF over time for Rofecoxib and Placebo groups.](http://content.nejm.org/content/vol352/issue11/images/large/07f2.jpeg)
Parecoxib and valdecoxib in CABG

<table>
<thead>
<tr>
<th>SAE</th>
<th>Standard care, N = 151 (%)</th>
<th>Current study parecoxib/valdecoxib, N = 311 (%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>15 (9.9)</td>
<td>59 (19.0)</td>
<td>.015</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>4 (1.3)</td>
<td>.309</td>
</tr>
<tr>
<td>Cerebrovascular disorder</td>
<td>1 (0.7)</td>
<td>9 (2.9)</td>
<td>.177</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.7)</td>
<td>5 (1.6)</td>
<td>.669</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (1.3)</td>
<td>3 (1.0)</td>
<td>.664</td>
</tr>
<tr>
<td>Abnormal renal function or increased creatinine level</td>
<td>0</td>
<td>6 (1.9)</td>
<td>.184</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>0</td>
<td>3 (1.0)</td>
<td>.554</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (0.7)</td>
<td>7 (2.3)</td>
<td>.283</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (2.0)</td>
<td>4 (1.3)</td>
<td>.688</td>
</tr>
<tr>
<td>Sternal wound infection</td>
<td>0</td>
<td>10 (3.2)†</td>
<td>.035</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>0</td>
<td>3 (1.0)</td>
<td>.554</td>
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But, wouldn’t that analgesia be nice for a few days in a sleep apneic?
Droperidol
Prolonged QT and Torsades de Pointes

- In 2001, the FDA issued a new “black box” warning on droperidol because of concerns of serious cardiac arrhythmias secondary to QT prolongation.
  - 273 cases reported for a 4-year period
  - 127 cases with serious adverse outcomes.
  - A possible cardiac event occurred in 74 cases.
Prolonged QT and Torsades de Pointes

- There were 89 deaths reported, but the dose of droperidol was $\leq 2.5$ mg in only two deaths.

*Journal of Clinical Anesthesia* Volume 20, Issue 1, February 2008, Pages 35-39
Black box warning changed practice

<table>
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<tr>
<th>1st choice antiemetic</th>
<th>Before black box warning</th>
<th>After black box warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Droperidol</td>
<td>47%</td>
<td>5%</td>
</tr>
<tr>
<td>5-HT₃ receptor antagonist</td>
<td>25%</td>
<td>42%</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>5%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Does Low-dose Droperidol Administration Increase the Risk of Drug-induced QT Prolongation and Torsade de Pointes in the General Surgical Population?

Pre- and post- black box warning

Before the warning

● 2,321 patients (1.66%) had QT prolongation, TdP, or death within 48 h after surgery

● 12% rec’d droperidol

After the warning

● 2,207 patients (1.46%) had documented QT prolongation, TdP, or death within 48 h after surgery

● 0% rec’d droperidol

Anesthesiology 2007; 107: 531–6
“Conclusions: This indicates that the Food and Drug Administration black box warning for low dose droperidol is excessive and unnecessary.”
FDA response to calls for change

• "The droperidol boxed warning applies to the approved doses of this product as delineated in the product label..."

FDA response to calls for change

• “...The FDA has received no data to support or dispute any speculation that lower, unapproved doses of droperidol might or might not be sufficiently cardiotoxic so as to merit an equal level of concern as the approved doses...”

FDA response to calls for change

“…Although we are aware of the literature describing the use of lower, unapproved doses of droperidol, these data have not been submitted to the FDA for review.”

Typical problem
No one will pay to do studies of old (off-patent) drugs
Outbreak of Adverse Reactions Associated with Contaminated Heparin

David B. Blossom, M.D., Alexander J. Kallen, M.D., M.P.H.,
Ganpan Gao, Ph.D., Robert Langer, Sc.D., Kiran M. Perkins, M.D.,
Jennifer L. Jaeger, M.D., Katie M. Kurkjian, D.V.M., M.P.H.,
Marilyn Jones, R.N., M.P.H., Sarah F. Schillie, M.D., M.P.H.,
Nadine Shehab, Pharm.D., Daniel Ketterer, M.D., Ganesh Venkataraman, Ph.D.,
Takashi Kei Kishimoto, Ph.D., Zachary Shriver, Ph.D., Ann W. McMahon, M.D.,
K. Frank Austen, M.D., Steven Kozlowski, M.D., Arjun Srinivasan, M.D.,
George Turabelidze, M.D., Ph.D., Carolyn V. Gould, M.D.,
Matthew J. Arduino, Dr.P.H., and Ram Sasisekharan, Ph.D.
WEDNESDAY, Dec. 3 (HealthDay News) -- A final report on the deadly contamination of the blood thinner heparin confirms that the problem was caused by a man-made chemical that was added to batches of the drug imported from China, U.S. investigators report.
Contaminated Heparin releases Kallikrein

NEJM 359;25 www.nejm.org
december 18, 2008
Toxins, injury, inflammation, ischemia, viral infections, etc.

Factor XIIa → Prekallikrein → Kallikrein

C1-Inh → Kallikrein

HMW-Kininogen → Bradykinin

ACE → des-8,9-Bradykinin inactive

(Aprotinin) DX-88

Icatibant

Microvascular leakage, vasodilatation, pain

http://www.hae-network.info/site/en/int/01_all_about_hae/01_15_disease-causes/bradykinin.php
Mechanisms

Although hypotension was the most common, a large proportion of case patients had nausea, shortness of breath, vomiting, tingling, flushing, and diaphoresis. Urticaria was not a prominent feature among the case patients.
Mechanisms

Urticaria was not a prominent feature among the case patients. This finding is consistent with reactions that are not mediated by mast cells and supports the role of bradykinin and other mediators instead.
Drug Making’s Move Abroad Stirs Concerns

By GARDINER HARRIS

WASHINGTON — In 2004, when Bristol-Myers Squibb said it would close its factory in East Syracuse, N.Y. — the last plant in the United States to manufacture the key ingredients for crucial antibiotics like penicillin — few people worried about the consequences for national security.

“If tomorrow China stopped supplying pharmaceutical ingredients, the worldwide pharmaceutical industry would collapse”
Suggamadex
Reversal of Profound Rocuronium-induced Blockade with Sugammadex

A Randomized Comparison with Neostigmine

R. Kevin Jones, M.D.,* James E. Caldwell, M.B., Ch.B.,† Sorin J. Brull, M.D.,‡ Roy G. Soto, M.D.§
Suggamadex vs. neostigmine

Anesthesiology 2008; 109:816–24
Suggamadex vs. neostigmine

Anesthesiology 2008; 109:816–24
And, residual block is bad

<table>
<thead>
<tr>
<th></th>
<th>TOF &lt; 0.7</th>
<th>Postop Pulmonary Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancuronium</td>
<td>26%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Atrac / Vecur</td>
<td>5.3%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

EU says “yes”
FDA Advisory Panel says “yes”
FDA says “no”!
FDA concerns

- Anaphylaxis with repeat exposure?
- Patients with abnormal end-organ function
- Enamel formation in children
- “Some analysts have speculated that FDA has become more cautious about putting new drugs on the market following the safety concerns around drugs like ... Vioxx and ... Avandia. In both cases, there were older medications on the market with more established safety profiles.”

http://groups.google.com/group/anesthesiologyig/web/fda-delays-release-of-sugammadex?pli=1
Will patients suffer in the meantime?

Slow reversal with neostigmine?

Tachycardia, arrhythmias?
Conclusions

- Pharmaceutical industry is huge and powerful
- FDA likely underfunded to regulate all this
- Conflict-of-interest scandals in the news
- Recent drug recalls have made FDA cautious
- Specific instances in anesthesia highlighted