Clinical investigation

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Clinical investigation

• How to develop a study
• Case studies
• Review
Clinical investigation
Methods

• Ask a question about a patient or series of cases
• Has anyone answered this question?
• Literature search
• How can we answer the question?
• Devise a study
• Review by Research Committee and Human Use Committee
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Possible problems

- Funding
- Manpower
- Time
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Money

• Grants from the government
  – U.S.: NIH
• Grants from Pharmaceutical companies
• Grants from organizations
  – American Cancer Society; Professional societies
  – Large companies who have a stake (?) JAL ?
• Private donations
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Manpower

• If there is outside funding it often pays the salaries of the personnel

• Medical students
  – Will need some training

• Other students
  – Will need more training
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Time Management

• Always a difficult problem to find time
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• EXAMPLES
Case 1
Observation

- Two patients with neurofibromatosis were seen in the liver clinic on the same day
- Both had abnormal liver tests
Case 1

• **Question:** Has it ever been observed that patients with neurofibromatosis have abnormal liver findings?

• **Literature Review:** There were no published cases of patients with neurofibromatosis and abnormal liver tests (1976)

• **Chart review:**
  - All charts from the neurofibromatosis clinic at UCSF were reviewed
  - 3-4 cases had abnormal liver tests
  - Charts reviewed in depth
Case 1

- Discussion (informal) with colleagues in other cities about similar cases
- Single case report published in JAMA
- Collecting 4 cases with good information lead to final publication


- Time from observation to publication: 6 years
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Case 1

MONEY: no additional money required

MANPOWER: lead author did everything

TIME: lead author made time from his daily and weekend schedule
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Case 2

QUESTION: Does topical anesthesia improve GIF outcomes?

LITERATURE REVIEW: not clear

STUDY PROTOCOL:
- Study patients who have GIF
- Patients with and patients without topical lidocaine to the pharynx
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Case 2

RESULTS:
- Topical lidocaine did not change the examiner’s ability to complete the exam
- Patients report less gagging and fewer sore throats
- Not statistically significant

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Case 2

**MONEY:** no additional money required

**MANPOWER:** lead author did almost everything but the GIF procedures

**TIME:** lead author made time from his daily and weekend schedule
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Case 3

**QUESTION:** Does atropine improve GIF outcomes?

**LITERATURE REVIEW:** no study published

**STUDY PROTOCOL:**
- Study patients who have GIF
- Patients with and patients without intramuscular atropine 30 minutes before GIF
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Case 3

RESULTS:
- atropine decreases oral secretions
- atropine somewhat decreased gastric motility
- no difference in patient acceptance of GIF

Clinical Research
Case 3

MONEY: no additional money required

MANPOWER: lead author did almost everything, performing half of the GIF procedures

TIME: lead author made time from his daily and weekend schedule
Clinical Research
Case 4

**QUESTION:** Does GIF cause a change in gastrin levels?

**LITERATURE REVIEW:** studies disagree on effect of gastric distention on serum gastrin

**STUDY PROTOCOL:**
- Study patients who have GIF
- Gastrin levels before and 30 minutes after premedication; and immediately after GIF
RESULTS:
- gastric distention from GIF does not significantly raise gastrin levels

CONCLUSION: there is no false positive gastrin elevation following GIF

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Case 4

**MONEY:**
- no additional money required
- gastrins performed in clinical lab (military hospital)

**MANPOWER:** lead author did almost everything and half of the GIF procedures

**TIME:** lead author made time from his daily and weekend schedule
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Lessons learned

• One question answered leads to many more questions
• Not all research requires extra funding
• Not all research requires extra manpower
• Most research requires extra time by the investigator
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Case 5

• 19 year old 36 Kg woman with SLE nephritis developed *Cryptococcus neoformans* septicemia

• 50 mg IV AMB given over 30 minutes
  – First infusion: Transient hyperkalemia noted
  – Later infusion:
    • ventricular fibrillation noted and resuscitated
    • K+: 8.4 and 8.0 mEq/dL

• Why did a patient receiving IV amphotericin B develop hyperkalemia and ventricular fibrillation?
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Case 5

• Literature Search:
  No apparent information about hyperkalemia or ventricular fibrillation in the literature nor in the drug handout for physicians

Study Methods:
- Compare serum AMB concentration and K+ levels
  • in index patient
  • Two anuric patients receiving 4 hour infusions
  • Eight patients with normal renal function receiving rapid infusions
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Case 5 Results

• Patient:
  – Without concurrent dialysis:
    • K+ rose 2.8 +/- 0.6 mEq/L falling to preinfusion levels within 1-2 hours;
    • Ventricular fibrillation occurred
  – With dialysis and/or slower infusions
    • K+ remained stable
    • No ventricular fibrillation
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Case 5

• RESULTS:
  – Anuric patients on dialysis and/or slower infusions:
    • K+ levels and EKG remained normal
  – Normal renal function/rapid infusion
    • K+ rose from 3.9 +/- 0.9 mEq/dL to 4.4 +/-0.6 mEq/dL
    • AMB levels rose slightly
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Case 5 Conclusion

• High levels of AMB in serum, caused by high initial dose or rapid infusion, pose a risk of serious hyperkalemia in patients with impaired renal function

• We recommend that
  – Anuric patients receive AMB during dialysis
  – Azotemic patients not being dialysed receive slow infusions and have K+ levels monitored
  – Doses > 1 mg/Kg for patients with normal renal function be administered over 4-6 hours or with K+ monitoring

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Drug Warnings

• Rapid IV infusion of AMB has been associated with hypotension, hyperkalemia, arrhythmias, and shock and should, therefore, be avoided

• AMB should be used with care in patients with reduced renal function; frequent monitoring of renal function is recommended
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Conclusions

• Clinical investigation can be done anywhere
• Keen observation is necessary
• Has this been seen before?
• Plan a study to answer the question
• Get funding if necessary
• KISS (KEEP IT SIMPLE!!!!)
• Start again
Thank you for your attention