



Matsuyama castle 4-1-2009

Clinical investigation

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11 April 2009

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

Clinical investigation

Possible problems

- Funding
- Manpower
- Time

Clinical investigation 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

Clinical investigation 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

- Meyer, GW et al. Hepatobiliary Involvement in von Recklinghausen's Disease. [Annals of Internal Medicine](#) 1982; 97:722-723.

- Time from observation to publication: 6 years

Clinical Research

Case 1

MONEY: no additional money required

MANPOWER: lead author did everything

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

Clinical Research

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

Gordon, MJ et al. Meperidine and topical lidocaine in pre-endoscopic medication. *Gastro Endosc* 1977;24:14-16

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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

Clinical Research

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

Cattau EL et al Efficacy of atropine as an endoscopic premedication.
Gastro Endosc 1983; 29:285-288

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

Clinical Research

Case 4

RESULTS:

- gastric distention from GIF does not significantly raise gastrin levels

CONCLUSION: there is no false positive gastrin elevation following GIF

Cattau EL et al. Effect of Atropine and Upper Gastrointestinal endoscopy on Serum Gastrin. J Clin Gastro 1983; 5:311-313

Clinical Research

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

Craven PC and Gremillion DH. Risk factors of ventricular fibrillation during rapid amphotericin B infusion. Antimicrob Agents Chemother 1985; 27:868-71

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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

Clinical investigation

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

