The management of adverse drug reactions

I Ralph Edwards

- Diagnosis
- Procedures
- Management
- Therapy
  - Often no clear separation…

The management of adverse drug reactions

- To Start!

Is the patient taking drugs?

- OTC
- OC
- Herbal/traditional
- Abused drugs
- Long term prescription
- Check with medical history

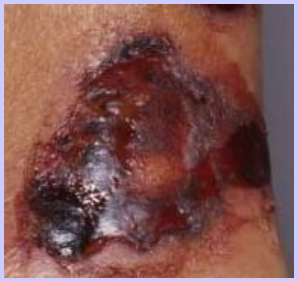
A patient

- An 81 year old man with an old valve replacement and recent heart failure.

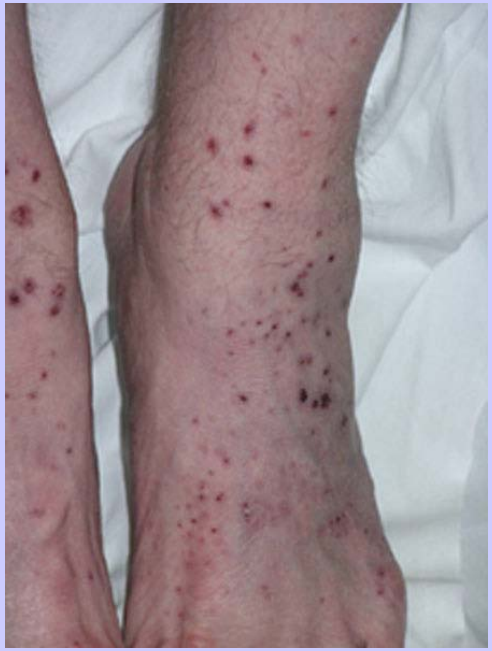
- Digoxin 0.25 mg daily
- Warfarin 4mg daily
- Frusemide 80 mg daily
- Potassium supplements

The patient

- Develops a deep bleeding ulcer and other red patches



–Eventually looks like this:



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- Q2. Could the symptoms and signs be due to drugs?
  - Yes!
- When there is polypharmacy, this becomes difficult
- Q3. WHICH DRUG?!

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- Q4. Diagnosis and causality

Time relationships

- Do they make sense?
  - Drug before disease?
  - Timing of drug and reaction?
    - Kinetics-steady state
      - Withdrawal reaction?
    - Allergy type
      - Previous exposure?
    - Pregnancy stages
    - Neoplasia kinetics

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- Q5. YES,BUT WHICH DRUG?
  - Known pharmacology
    - Of single drug
    - Of class
  - Known idiosyncracy
    - Of single drug
    - Of class

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- Q6. Are there any special tests which may help?
- Blood levels of medicines (therapeutic monitoring)
- Other clinical tests to help establish
  - The disease entity eg. allergy testing, skin biopsy
  - Baseline state eg. liver and kidney function
  - Follow up of response following discontinuation of medicine or reduction of dose

Patient

- Diagnosis
  - Possible bleeding tendency: over-anticoagulated

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- Q6. How serious is the patient's clinical state?
- If very serious:
  - Stop all drugs which may POSSIBLY cause condition
  - Treat, as necessary
  - Consider step-wise re-introduction, later
- If not serious:
  - Look at one drug at a time

Patient

- Action
  - Stop warfarin
  - Check prothrombin ratio

Patient

Prothrombin ratio normal and patient has been stabilised for a long time

Oh Dear!!

- New diagnosis
  - Possible coumarin necrosis
    - During chronic treatment?

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- Q7. What if the patient depends on some drugs?
- Try some options:
  - Stop non essential drugs
  - Consider dose - reduce where suitable
  - Consider interactions
  - Stop those likely to be causing serious reactions and whose benefit/risk balance in this situation is not good

Patient

- Consider skin biopsy
  - Result likely to be available in two weeks !

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- Q7. Reconsider the likelihood of patients condition being drug related
  - Frequency, related to drug(s) versus background
  - With sound clinical benefit/risk judgement decide to stop any other relevant drug(s)

Patient

- Could these be emboli with infarction and ulcer due to failed anticoagulation ?
  - Septic emboli ?
  - Both unlikely explanations

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- Q8. NOW WHAT?
  - Wait (dechallenge)
    - Is it plausible in onset and duration?
      - Patient is improving/well
        - Start alternative therapy if necessary
        - Report your suspected ADR, if 'interesting'

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Q9. What if the Patient is getting worse?

Sorry, wrong diagnosis, wrong drug, or patient cannot manage without this drug!

- Try the next most likely drug(s)
- Try a suitable substitute
  - *Watch cross reaction of any sort!*
  - *Could try re-instituting same drug*
    - *At lower dose?*

- There is a need to manage the patient clinically !!

Patient

- Patient needs anti-coagulation, so start heparin until biopsy result available

- *N.B. Patient stays in hospital because he cannot manage injections and no short term support can be arranged*

Patient

- Patient is certainly NOT well. He develops several more very painful bleeding ulcers

Patient

- Start paracetamol for pain

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Q10. When treating an ADR doesn't this add more drugs and confusion?

- Do not confuse the picture unnecessarily!
- Have a clear objective
- Do not treat for longer than is necessary
- Review patient regularly for response

Patient

- Pain very severe
  - Start morphine

Biopsy result surprisingly quickly available and shows vasculitis with much bleeding

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Finally

- Reconsider interactions
- Consider rechallenge for drugs which are or will be important to the patient
  - Ethics
  - Same dose? Same route?Same preparations?
  - Safeguards!

Send in report

Patient

- Frusemide considered as cause of vasculitis with bleeding super-imposed because of anti-coagulation
  - But consider long ½ life of Warfarin
- Frusemide stopped

- *Pain continues*

Patient

- The dose of morphine is increased and mild heart failure occurs
- This is followed by bronchopneumonia

- And the patient dies in a few days
  - of a morphine adverse reaction?

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THE END