Stronger Together

London North West Healthcare NHS
NHS Trust

Drug Absorption in patients with Short Bowel

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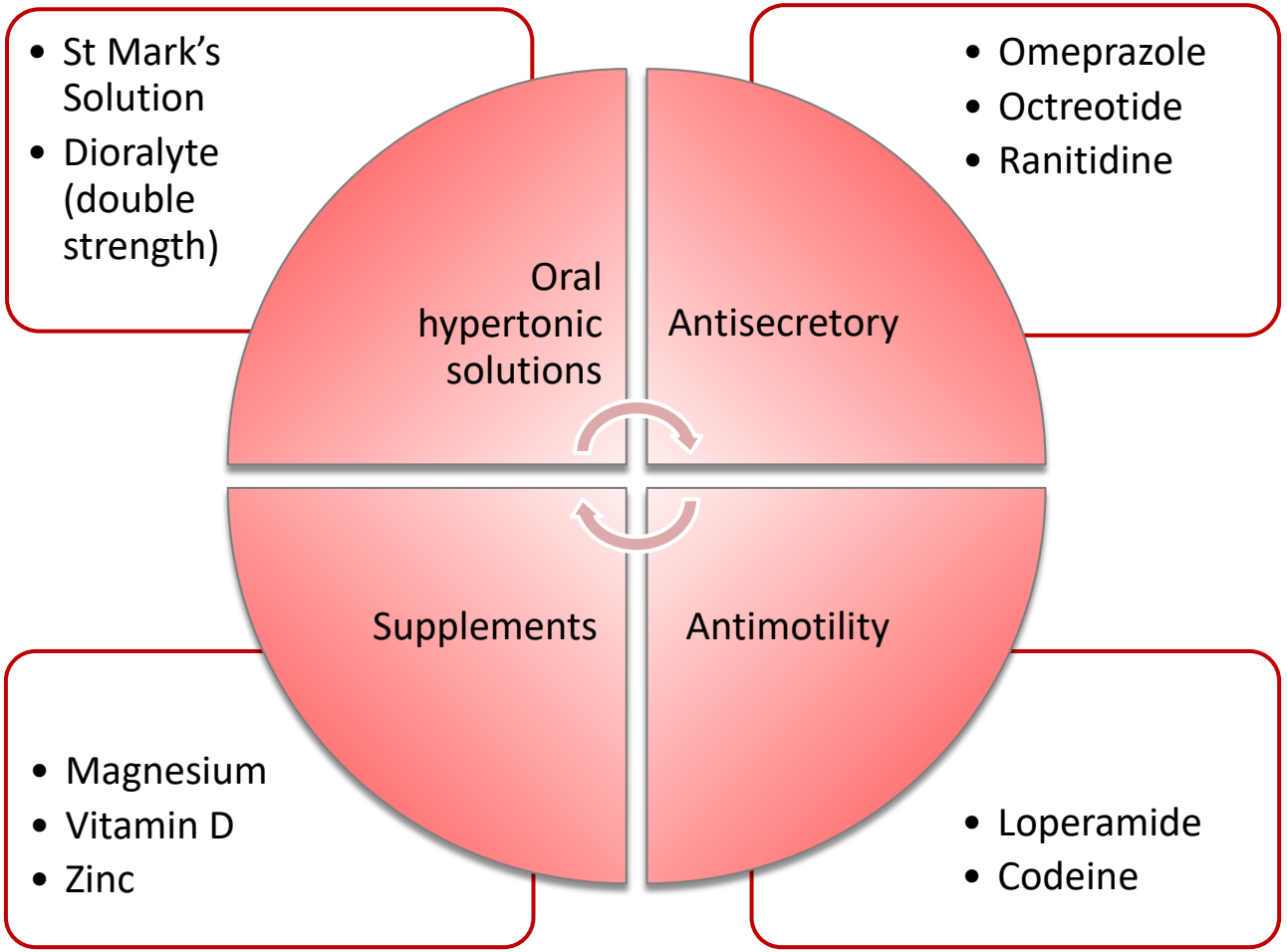
Declarations

- Richard Ng Kwet Shing
  - Employee of Norgine Ltd
- Jackie Eastwood
  - Market research for various companies
  - Hospitality from BBraun
  - ITH Pharma

Background

- Average length of the adult small intestine is ~ 600 cm (range 260 to 800 cm).[1]
- The common etiologic factor in all causes of short bowel syndrome (SBS) is the functional or anatomic loss of extensive segments of small intestine so that absorptive capacity is severely compromised.
- Any situation leaving <200 cm of viable small bowel or a loss of >50% of small intestine places the patient at risk of SBS.
- SBS is clinically defined by malabsorption, diarrhoea, steatorrhoea, fluid and electrolyte disturbances, and malnutrition.

Drugs used in SBS



What about other drugs?

- Patients with SBS may also suffer from other conditions that require medication(s).
- Many patients report that medications are passed virtually intact/whole.
- Some common tips

• Avoid modified release oral preparations	• High osmolality • May contain sorbitol • Will increase stomal output	• If comes out of stoma bag then crush tablet or open capsules
Oral medicines 	Caution with liquids/syrups 	Use capsules/tablets 

Oral medication in SBS

Lack of absorption	• Reduced efficacy
Variability of absorption	• Unpredictable effects
Increased side effects	• If higher doses used

Prediction of efficacy

Minimal evidence of oral absorption in IF

- Warfarin
- Tacrolimus
- Amitriptyline
- Nortriptyline
- Digoxin
- Amiloride
- Paracetamol
- Fluoxetine

Inter-patient variability

hard to extrapolate with differing intestinal anatomy

Therapeutic drug monitoring

Availability of drug level testing may be limited

Questions to ask ...

Is the medication essential?

Is there another form of medication that is suitable?

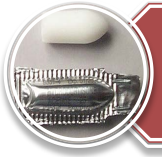
Is there another route of administration?

Routes of administration

Sublingual

Buccal

Topical



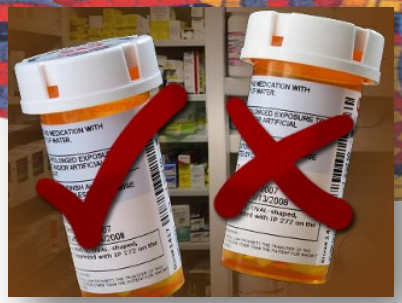
Rectal

Subcutaneous

Intravenous

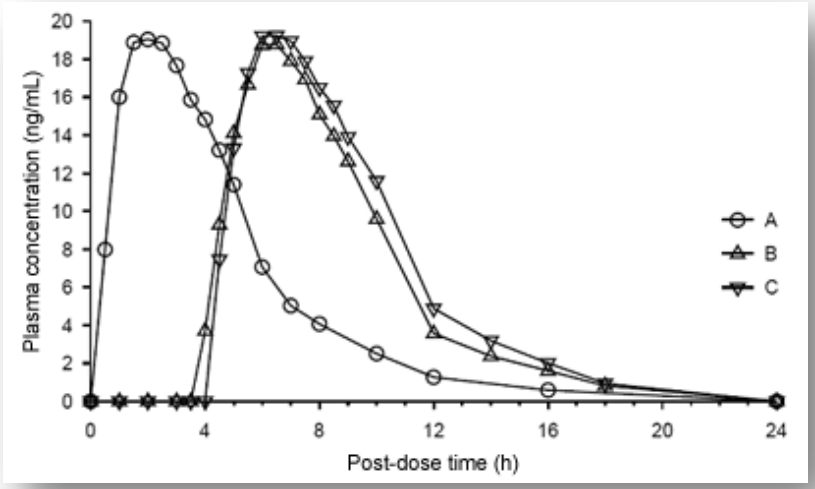
Avoid unless benefit > risk

Questions to ask …



- Is the medication essential?
- Is there another form of medication that is suitable?
- Is there another route of administration?
- Is there another medication that could be used?
- Contact pharmaceutical company for absorption information
- Review pharmacokinetics of medication

Pharmacokinetics



Bioavailability	• What is the bioavailability of the medication?
C_{max} and T_{max}	• What is the time to C_{max}?
Interactions	• Drug-drug & drug-nutrient interactions?

Is there another way?

- Can we use other standard pharmacokinetic factors to help predict those drugs that may be better suited to a SBS patient?
- Pharmacokinetics (ADME; A = Absorption)

- **The Biopharmaceutics Classification System (BCS)**[2,3,4]
- The BCS was developed to differentiate between immediate release (IR) solid oral dosage drug formulations on the basis of their solubility and permeability.
- It is a guide for predicting intestinal drug absorption.
- 3 major factors that govern the rate and extent of absorption of a drug in the GI tract.

Permeability

- A medicine is considered of high permeability if:
  - It is completely absorbed during a limited transit time in the intestine
  - In the EU this needs to be >85%[2] of medicine absorbed, in the USA this is >90%[3]

Solubility and dissolution

- A medicine is considered to be highly soluble if:
  - The solubility is not likely to limit dissolution and therefore absorption
  - The measure is the highest dose that is soluble in <250ml water in a pH range 1 - 7.5
- A medicine is classed with very rapid or rapid dissolution to ensure that in vivo dissolution will not be the rate determining step
  - Very rapid - dissolves in 15 minutes
  - Rapid – dissolves in 30 minutes

BCS Classification System

- According to the BCS, drug substances are classified as follows:

Solubility / Permeability	High	Low
High	Class I	Class II
Low	Class III	Class IV

BCS – Lists

- **International Pharmaceutical Federation (FIP)**
  http://www.fip.org/bcs_monographs

News and Publications
Programmes and Projects
Statements and Guidelines
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Activities
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SIG on Drug Design and Discovery
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Biowaiver monographs

Under the leadership of Dr Dirk Barends of the Dutch National Institute for Public Health and the Environment (RIVM) the FIP-BPS Special Interest Group (SIG) Biopharmaceutics Classification System (BCS) and Biowaiver started to collect publicly available information for Essential Medical Drug Products based on the Biopharmaceutical Classification System (BCS). This activity now continues under the leadership of the current Chair of the Focus Group "BCS and Biowaiver", Prof. Jennifer Dressman of the Goethe University in Frankfurt am Main, Germany. This project is supported by WHO and takes published guidances of the WHO, FDA and EMA into consideration as well as scientific developments in this field. The collected information is critically reviewed and published as monographs in Journal of Pharmaceutical Sciences. They are also made available on the FIP Website below. Up till now, more than 30 monographs have been published and more will follow. The selection of drug candidates for future biowaiver monographs is primarily based on the "Essential Drug List"of WHO, in order to assist approval of generic drug products in a facile and objective manner, with the aim of improving access to reliable medicines, especially developing countries. Other drugs that are widely used can also be considered for Biowaiver Monographs.

Although the monographs have no formal regulatory status, they represent the best scientific opinion currently available. They are published in the Journal of Pharmaceutical Science but can also be downloaded free of charge by clicking on the link in the list below. It is foreseen to update the monographs with addenda if new data becomes available.

1. Acetaminophen = Paracetamol (click here)
2. Acetazolamide (click here)
3. Acetylsalicylic acid (click here)
4. Aciclovir (click here)
5. Amitriptyline Hydrochloride (click here)
6. Amodiaquine Hydrochloride (click here)
7. Atenolol (click here)
8. Bisoprolol fumarate (click here)
9. Chloroquine Phosphate (click here)
10. Chloroquine Sulfate (click here)
11. Chloroquine Hydrochloride (click here)
12. Cimetidine (click here)
13. Ciprofloxacin Hydrochloride (click here)
14. Codeine phosphate (early preview: click here)
15. Diclofenac Potassium (click here)
16. Diclofenac Sodium (click here)

Biowaiver Monographs 2004-2012

Bringing essential medicines to those who need them most

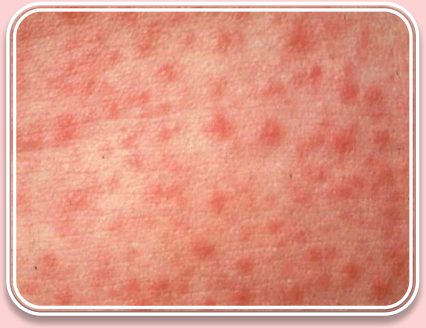
Fédération Internationale Pharmaceutique
International Pharmaceutical Federation

BCS – Class 1 List

- Abacavir
- Acetaminophen
- Acyclovir
- Amiloride
- Amitriptyline
- Antipyrine
- Atropine
- Buspirone
- Caffeine
- Captopril
- Chloroquine
- Chlorpheniramine
- Cyclophosphamide
- Desipramine
- Diazepam
- Diltiazem
- Diphenhydramine
- Disopyramide
- Doxepin
- Doxycycline
- Enalapril
- Ephedrine
- Ergonovine
- Ethambutol
- Ethinyl Estradiol
- Fluoxetine
- Glucose
- Imipramine
- Ketorolac
- Ketoprofen
- Labetolol
- Levodopa
- Levofloxacin
- Lidocaine
- Lomefloxacin
- Meperidine
- Metoprolol
- Metronidazole
- Midazolam
- Minocycline
- Misoprostol
- Nifedipine
- Phenobarbital
- Phenylalanine
- Prednisolone
- Primaquine
- Promazine
- Propranolol
- Quinidine
- Rosiglitazone
- Salicylic acid
- Theophylline
- Valproic acid
- Verapamil
- Zidovudine

Monitoring

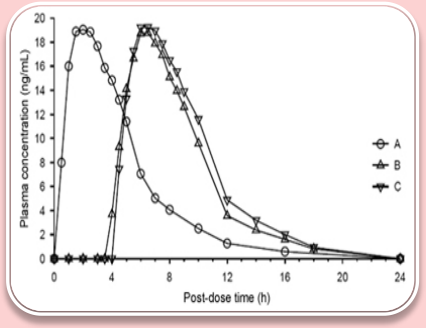
Clinical effect



Side effects

- especially if high dose

Therapeutic drug monitoring



Watch for variability of effect

Making changes

Patient

- Work with the patient in order to change medication

MDT

- Work as a MDT to achieve the outcomes that you want

Small changes

- Make changes one step at a time

Reassure

- Persuade the patient & relatives that you are doing the right thing

References

1. Weser E. Nutritional aspects of malabsorption: short gut adaptation. *Clin Gastroenterol*. May 1983;12(2):443-61.
2. EMA; Guideline on the investigation of bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1
3. FDA; Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations
4. WHO Technical Report Series, No. 937, 2006; Annex 8: Proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms.