Bioavailability와 서방성제제의 개발

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Bioavailability and Development of Sustained Release Dosage Formss

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사람에게 투여된 약물이 치료효과를 발휘하기 위해서는 投藥→吸收→體內循環→作用點에의 到達→生體의 應答反應과 같은 과정을 거치지 않으면 안된다. 이 과정을 지배하는 因子로서는 pharmacodynamic한 因子, pharmacokinetic한 因子 및 患者側의 生理的 因子의 3가지를 들 수 있다. 最適의 치료효과는 이 3가지 因子가 적절히 배합되어야 얻을 수 있다. 이 中 pharmacokinetic한 因子의 指標의 하나가 bioavailability이다.

製劑의 bioavailability를 지배하는 要因에는 藥物의 物性面, 製劑의 특성과 같은 製劑側의 要因, 患者側의 諸要因이 있는데 이들을 고려하여 製劑를 개발해 나가야 할 것이다. 특히 經口劑의 개발에 있어서는 消化管內에서의 약물吸收에 큰 영향을 주며 bioavailability에도 영향을 미치는 gastric emptying(胃內容物排出), intestinal transit(腸內체류), water flux, 藥物吸收機構 등을 고려해야 한다.

이러한 生理的因子까지 고려하면서 徐放性製劑의 開發을 시도한 一例로서 「metoprolol의 胃腸管內 擧動과 bioavailability의 變動」에 관한 硏究를 간단히 소개하고자 한다.

醫藥品의 品質과 Bioavailability에 關한 심포지움 (1985. 4. 26 코리아나 호텔)에서 발표되었음

Objectives of an optimised oral drug delivery system

1. Prolong and control duration of drug action
2. Control of rate and site of release in the gastrointestinal tract
3. Complete and reliable absorption
4. Minimal irritant or unwanted local effects
5. Minimal effects of physiological variables on drug absorption
6. Maximal chemical and physical stability
7. Minimal systemic side effects through precise control of tissue concentrations

Ideal design attributes and principles of oral controlled drug delivery systems

1. Lack of sensitivity to physiological variables
2. Drug release determined by physicochemical principles
3. Drug release not keyed to a single physiological variable
4. A high order of drug dispersion (molecular scale optimum)
5. A flexible system capable of incorporating a wide variety of drugs, doses, and release rates
6. Physical and chemical stability

Ecological windows for drug absorption

Gastrointestinal tract absorption sites	Prevailing conditions	Route of drug removal	Drug presentation	Methods of monitoring absorption
Mouth	pH 6.2-7.0 Much fluid	Non-portal	Solution Suspension	
Stomach	pH 1.0-5.0 Fluidity varies with ingestion of food and drink	Portal	SR pellets Tablet, disintegrating	Directly Indirectly, by measuring drugs and metabolites in: blood plasma saliva urine faeces
Upper gastrointestinal tract	pH increases towards 7.5 Fluidity decreases Transit rate decreases	Portal	Tablet, keeps integrity (i.e. OROS) SR tablet (i.e. matrix) Enteric-coated tablet	
Lower gastrointestinal tract	pH about 7.5 Fluidity as Transit rate very slow	Portal	Hard capsule (disintegrates quickly) Soft capsule (disintegrates quickly) Enteric capsule	
Rectum	pH 6.8-7.0 Fluidity, mucus at membrane Transit depends on defaecation	Portal, upper Non-portal, lower	Solution Suspension Suppository SR pellets	

Factors influencing drug absorption and response

Dosage Form and Regimen

Drug form
Excipients
Compounding
Coating
Drug amount
Administration schedule
Route of administration

Physiological Factors

Age
Sex
Body weight
Genetic
Nutritional state
Disease
Pregnancy
Gut flora
Gastrointestinal motility
Renal function
Physical activity

Dietry Factors

Effect on:
- drug absorption
- drug metabolism
- drug excretion
- drug-receptor site interactions

Pharmacological Factors

Effect of other drugs and food constituents on:
- enzyme induction
- enzyme inhibition
- protein binding
- stomach emptying time
- intestinal motility
- biliary flow
- local blood flow
- gut flora
- urinary pH
- drug receptor interactions

Tolerance
Environmental factors

Factors influencing gastric emptying rate

a) Physiological
- Food
- Gastric distension
- Osmotic pressure
- Posture
- Sleep
- Personality trait

b) Pathological
- Trauma and pain
- Myocardial infarction
- Gastrointestinal disease
  - pyloric stenosis
  - Crohn's disease
  - coeliac disease
- Gastric surgery
- Metabolic disease

c) Pharmacological
- Anticholinergics
- Narcotic analgesics
- Antihistamines
- Tricyclic antidepressants
- Aluminium hydroxide
- Metoclopramide
- Anticholinesterases
- Alcohol

Factors affecting gastrointestinal drug absorption

1. Gastric motility and emptying
2. pH of the gut contents
3. Enzyme activity
4. Food
5. Fluid volume, composition and viscosity
6. Posture and activity
7. Mental state
8. Individual variability
9. Disease

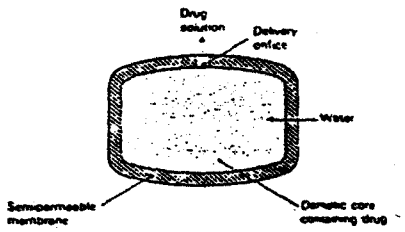
Factors involved in drug interactions with food and drink

1. Drug dissolution
2. Binding of drug to food constituents
3. Intraluminal decomposition of drug
4. Gastrointestinal transit time
5. Interference with mucosal transport
6. Net water flux
7. First-pass metabolism

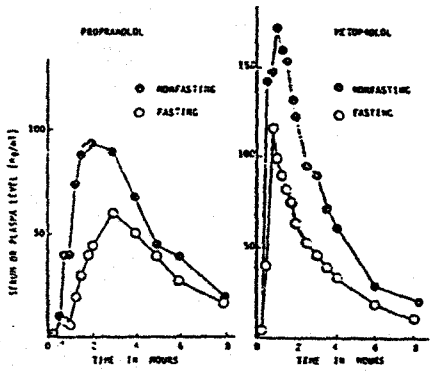
Age-related changes in gastrointestinal physiology

Process	Abnormality in infancy	Abnormality in elderly
Gastric acid secretion	Decreased	Decreased
Gastric emptying time	Prolonged	Generally prolonged but may also be reduced due to increased pH
Intestinal blood flow	Variable	Reduced
Mucosal absorbing area	Increased	Reduced
Bacterial colonisation	Low but increases progressively	Increased

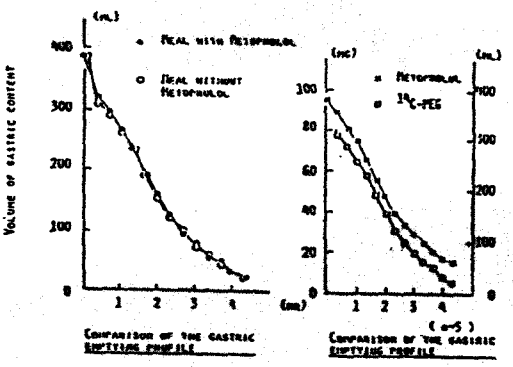
Elementary osmotic pump cross-section



PHYSIOLOGICAL FACTORS AFFECTING ORAL BIOAVAILABILITY

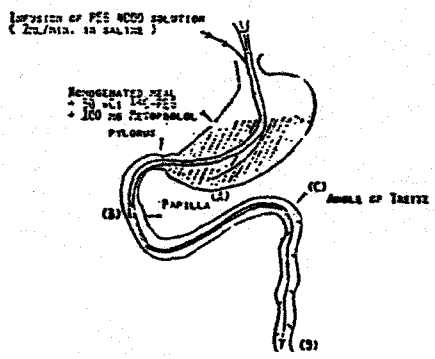


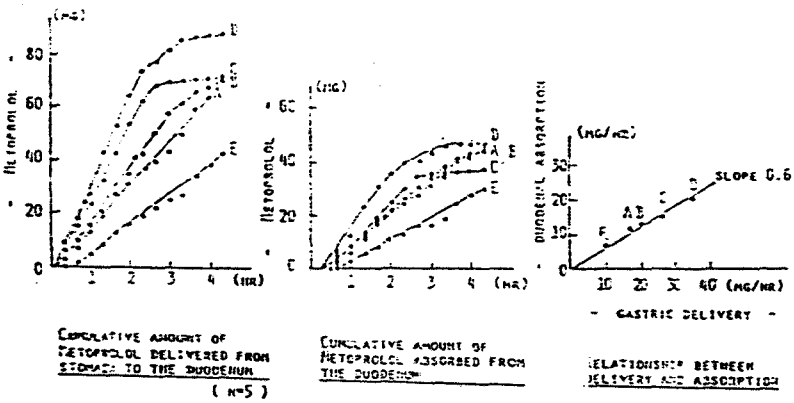
STOMACH



SCHEMATIC REPRESENTATION OF THE GI TRACT WITH THE LOCATIONS OF THE DIFFERENT TUBES

COLLECTION OF FLUIDS

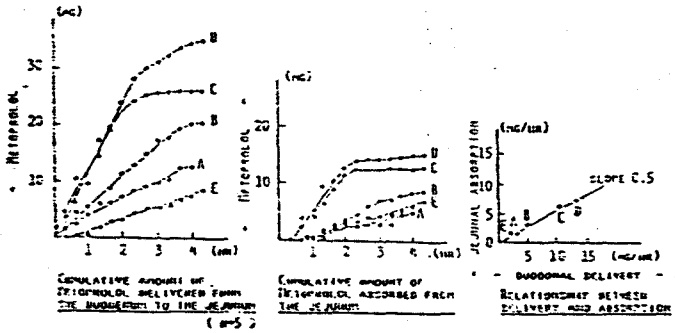




Cumulative amount of metoprolol delivered from stomach to the duodenum (n=5)

Cumulative amount of metoprolol absorbed from the duodenum

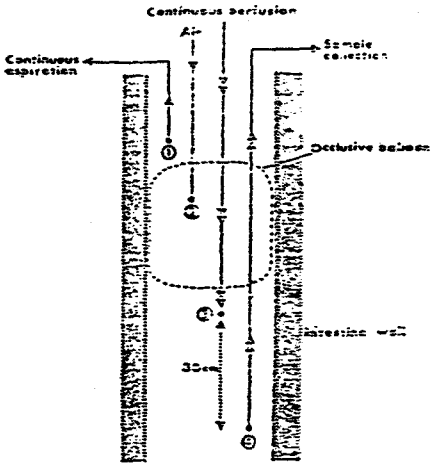
Relationship between delivery and absorption

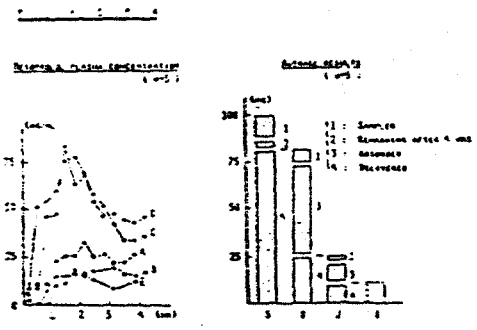


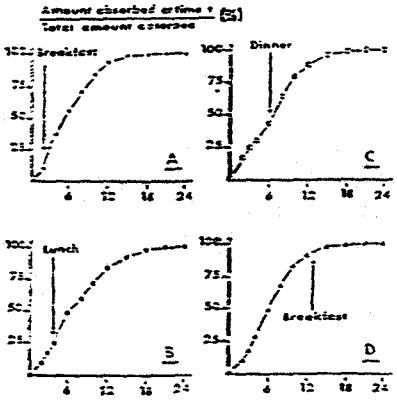
Cumulative amount of metoprolol delivered from the duodenum to the jejunum (n=5)

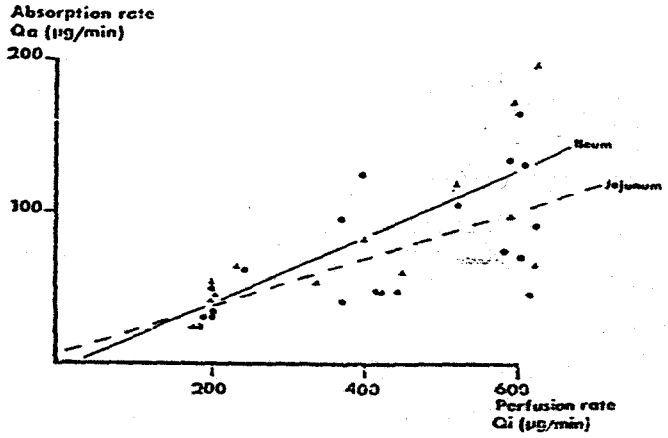
Cumulative amount of metoprolol absorbed from the jejunum

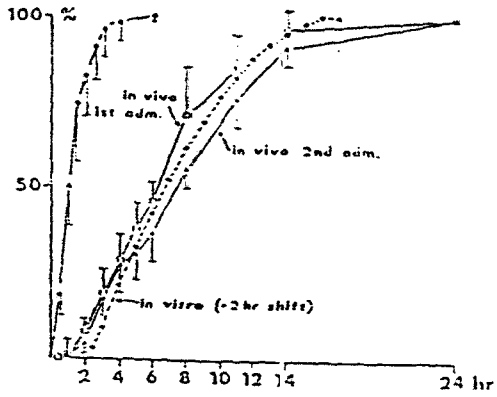
Relationship between delivery and absorption

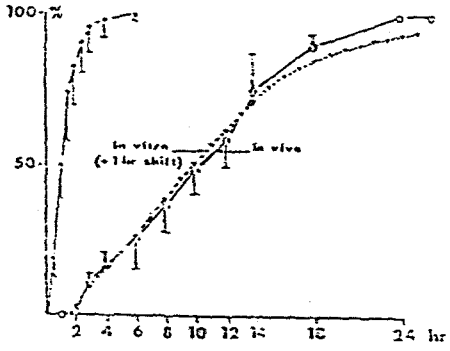

Continuous perfusion
Air
Continuous aspiration
Sample collection
Occlusive balloon
Intestine wall
30cm




Breakfast
Dinner
Lunch
Breakfast
A
C
B
D


Absorption rate
Qa (μg/min)
200
100
Ileum
Jejunum
200
400
600
Perfusion rate
Qi (μg/min)


100
%
50
in vivo
1st adm.
in vivo 2nd adm.
in vitro (+2 hr shift)
2 4 6 8 10 12 14
24 hr


100
%
50
in vitro
(+1 hr shift)
in vivo
2 4 6 8 10 12
24 hr